Priority Setting for Expensive Biopharmaceuticals: An Analysis of Six Drug Case Studies

by

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ABSTRACT

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Priority setting for expensive biopharmaceuticals is one of the most important challenges for publicly funded health systems. One of the drivers of rising healthcare expenditures is pharmaceuticals (i.e., drugs). Moreover, people are living longer and their expectation of, and demand for, health care, drugs, and services are continually increasing. The overall aim of this research was to describe and evaluate reimbursement decisions for six expensive biopharmaceuticals across five countries in order to ascertain if the processes were legitimate and fair.

I conducted qualitative case studies of six expensive biopharmaceuticals in order to describe and evaluate the priority setting activities of eight
committees across five countries, including Canada, England and Wales, Australia, Israel and the United States. Data sources included: 1) 32 documents and 2) 56 interviews with informants. The recommendations process of each committee partially met the four conditions of ‘accountability for reasonableness’.

My main finding is that, while a number of values were considered by committees when making reimbursement decisions, committees tended to focus on values of evidence, effectiveness and efficiency, but not the full range of relevant values. Thus, these contexts did not fully meet the conditions of legitimacy and fairness.

I have provided an in-depth description of the eight committees’ priority setting activities regarding the study drugs, as well as committee members’, patients’ and industry representatives’ views regarding the process. I developed practical guidance for leaders for improving reimbursement decisions for expensive biopharmaceuticals, the implementation of which would enhance the fairness and legitimacy of priority setting. This study has demonstrated that in order to create a fair and legitimate drug reimbursement process, we need to ensure the incorporation of a wide range of values, and the involvement of multiple stakeholder groups within the deliberative and appeals/revisions processes.
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# TABLE OF CONTENTS

## 1.0 INTRODUCTION

1.1 AIMS AND OBJECTIVES ........................................................................... 3
1.2 THESIS OVERVIEW .............................................................................. 4

## 2.0 BACKGROUND AND SIGNIFICANCE

2.1 PRIORITY SETTING OVERVIEW .......................................................... 8
2.2 PRIORITY SETTING IN HEALTH INNOVATIONS AND BIOPHARMACEUTICALS .......................................................... 27
2.3 THE ROLE OF VALUES IN PRIORITY SETTING ................................... 37
2.4 DRUG REIMBURSEMENT SYSTEMS .................................................... 44
2.5 GAPS IN KNOWLEDGE ........................................................................ 67

## 3.0 METHODS

3.1 DESIGN .................................................................................................... 69
3.2 SETTING .................................................................................................. 71
3.3 SAMPLING ............................................................................................. 78
3.4 DATA COLLECTION ................................................................................ 90
3.5 DATA ANALYSIS ................................................................................... 92
3.6 CONCEPTUAL FRAMEWORK .................................................................. 94
3.7 RESEARCH ETHICS ................................................................................ 95

## 4.0 RESULTS

4.1 DESCRIPTION OF DECISIONS FOR EACH DRUG BY COUNTRY .......... 98
  CANADA ..................................................................................................... 98
  ENGLAND & WALES ............................................................................. 108
  AUSTRALIA ............................................................................................ 114
  ISRAEL .................................................................................................... 118
  UNITED STATES .................................................................................... 121
4.2 COMPARISON OF DECISIONS, EVIDENCE AND VALUES ACROSS COUNTRIES ......................................................... 125
4.3 COMPARISON OF VALUES COUNTRIES USED BY DRUG TYPE BASED ON PUBLISHED RATIONALES ............................................................... 138
4.4 VALUES USED BY EACH COMMITTEE AND PARTICIPANTS’ PERCEPTIONS BASED ON INTERVIEWS .................................................................. 138
4.5 EVALUATION OF DECISION MAKING FOR EACH DRUG ACCORDING TO AFR CONDITIONS .......................................................... 157
  RELEVANCE .......................................................................................... 158
  PUBLICITY .............................................................................................. 162
  REVISIONS AND APPEALS ................................................................... 164
  LEADERSHIP ........................................................................................ 167
4.6 THE ROLE OF INNOVATION ............................................................... 170
List of Tables

TABLE 1. CONDITIONS OF ‘ACCOUNTABILITY FOR REASONABLENESS’ ..................41
TABLE 2. GENERAL INFORMATION ABOUT COMMITTEES........................................73
TABLE 3. STAKEHOLDERS INVOLVED IN DECISION MAKING.................................78
TABLE 4. STAKEHOLDERS AS RELATED TO EACH DRUG CASE ..............................89
TABLE 5. REIMBURSEMENT OF CEREZYME AND FABRAZYME IN
CANADA ........................................................................................................101
TABLE 6. CANCER FUNDING MECHANISMS FOR GLIVEC ACROSS
CANADA .........................................................................................................104
TABLE 7. REIMBURSEMENT OF REMICADE FOR RA IN CANADA ..................107
TABLE 8. COMPARISON OF DRUG LISTING DECISIONS ACROSS COUNTRIES .......126
TABLE 9. EVIDENCE USED TO ASSESS COST-EFFECTIVENESS AND EFFECTIVENESS BY
COUNTRY .........................................................................................................128
TABLE 10. THRESHOLD PER QALY BY COUNTRY ..............................................129
TABLE 11. DEFINITIONS OF COMMON VALUES USED IN RECOMMENDATIONS BY
COUNTRY ........................................................................................................132
TABLE 12. VALUES APPLIED TO CEREZYME RECOMMENDATIONS AND COUNTRIES
SUBSEQUENT ASSESSMENT ........................................................................135
TABLE 13. VALUES APPLIED TO FABRAZYME RECOMMENDATIONS AND COUNTRIES
SUBSEQUENT ASSESSMENT ........................................................................136
TABLE 14. VALUES APPLIED TO XIGRIS RECOMMENDATIONS AND COUNTRIES
SUBSEQUENT ASSESSMENT ........................................................................137
TABLE 15. VALUES APPLIED TO GLIVEC RECOMMENDATIONS AND COUNTRIES
SUBSEQUENT ASSESSMENT ........................................................................137
TABLE 16. VALUES APPLIED TO REMICADE RECOMMENDATIONS AND COUNTRIES
SUBSEQUENT ASSESSMENT ........................................................................138
TABLE 17. STAKEHOLDERS WITH ACCESS TO THE APPEALS MECHANISM ........166
TABLE 18. FILLING THE GAPS IN KNOWLEDGE ..............................................189
TABLE 19. RECOMMENDATIONS FOR DRUG RECOMMENDATION COMMITTEES .......213
List of Diagrams

DIAGRAM 1. CANADIAN DRUG LISTING PROCESS ..............................................48
DIAGRAM 2. CANCER DRUGS AND THE CED ...........................................50
DIAGRAM 3. UK DRUG LISTING ....................................................................55
DIAGRAM 4. AUSTRALIAN DRUG LISTING .............................................60
DIAGRAM 5. ISRAELI DRUG LISTING ..........................................................63
DIAGRAM 6. US MEDICAID DRUG ACCESS ..............................................66
List of Appendices

APPENDIX 1. COMPARISON OF INTERNATIONAL SPENDING ON DRUGS ...............217
APPENDIX 2. SAMPLING TABLE ........................................................................218
APPENDIX 3. DOCUMENTS COLLECTED ..............................................................219
APPENDIX 4. INTERVIEW GUIDE ........................................................................220
APPENDIX 5. PUBLISHED ARTICLE IN HEALTH POLICY 87(2008):359-368........222
APPENDIX 6. FORTHCOMING ARTICLE IN CPHS WORKING PAPER ..................245
APPENDIX 7. DRAFT ARTICLE ON STAKEHOLDER INVOLVEMENT .................269
1.0 INTRODUCTION

Priority setting (PS) in healthcare, also known as rationing, or resource allocation, can be defined as the distribution of goods and services among competing programs and people [1]. This ethical process challenges many health systems [2]. Healthcare PS is necessary because the current demands for healthcare coverage outweigh the available resources [3]. This situation is made more difficult by the increasing cost of healthcare, including drugs, devices and services. One of the leading drivers of rising healthcare expenditures is pharmaceuticals (i.e., drugs) [4]. Moreover, people are living longer and their expectations of, and demands for, healthcare, drugs, and services are continuously increasing. Providing healthcare services that are paid for by public (i.e., government) funding sources is a source of considerable economic pressure in most Organization for Economic Cooperation & Development (OECD) countries [5].

The Romanow and Kirby reports are examples of the numerous reports that have focused on increases in health expenditure and on health systems’ ability to sustain future cost increases [6, 7]. The sustainability of health systems is affected by a number of factors. However, the rise of the pharmaceutical-based therapies is emerging as a particular challenge to sustainability for three reasons: 1) public spending on drugs is increasing at a higher rate than spending in other sectors, 2) actual spending on drugs is the second highest area of spending [5, 8, 9], (see Appendix 1) and 3) the impact of PS pharmaceutical funding decisions on investment in pharmaceutical
innovations i.e., drugs [10]. While pharmaceutical innovations are associated with the possibility of improving health and boosting the national economy [4, 11, 12], they are also associated with driving drug prices [12, 13]. Governments face a dilemma between ensuring a sustainable health system and investing in pharmaceutical innovations [14].

There are a number of methods used by decision makers in health systems to set priorities and determine which pharmaceuticals will ultimately be reimbursed (e.g., health technology assessment, cost-effectiveness analysis and program budgeting and marginal analysis, accountability for reasonableness). However, there is no consensus on how to set priorities for publicly funded drugs because these decisions typically involve value judgments about which there is no consensus [15]. In the absence of consensus about how to set priorities for drugs, it is extremely problematic to establish a climate in which it is acceptable to deny funding for some drugs. Key elements of establishing such a climate are legitimacy and fairness. Central components of a legitimate and fair priority setting process are transparency, the inclusion of pertinent values, and the involvement of stakeholders in decision making [16].

My research describes biopharmaceutical reimbursement decisions for six expensive drugs, across five countries. Specifically, I examined reimbursement recommendations regarding Cerezyme, Fabrazyme, Xigris, Glivec, Remicade and Gonal F across eight committees located in Canada, England and Wales,
Australia, Israel and the United States. My research is innovative because this is the first time, to my knowledge, that case study research has been conducted using a drug as the case, which allows for a more in-depth study of drug reimbursement priority setting. The use of the drug as the case not only expanded the scope of this study over a number of jurisdictions, but also allowed for the inclusion of more stakeholder perspectives such as the perspectives of government, patient and industry groups. My research evaluated reimbursement decisions for six specific expensive and innovative biopharmaceuticals using the ethical framework of ‘accountability for reasonableness’.

1.1 Aims and Objectives

The overall aim of this research was to examine priority setting for expensive biopharmaceuticals. This work was guided by a conceptual framework for ethical priority setting, ‘accountability for reasonableness’. The examination resulted in the identification and discussion of eight themes related to the priority setting of expensive biopharmaceuticals. These themes explored values related to drug priority setting (e.g., rule of rescue, access, cost, medical necessity, evidence and publicity), potential for an alternative drug priority setting mechanism, and the impact of technology and innovation on drug priority setting. There were three specific research objectives:

1) To describe priority setting decisions surrounding the reimbursement of expensive biopharmaceuticals.
2) To evaluate whether governmental decision making with regards to the reimbursement of these biopharmaceuticals was legitimate and fair using accountability for reasonableness as a conceptual framework.

3) To understand the relationship, if any, between drug priority setting and innovation in the area of biopharmaceuticals.

1.2 Thesis Overview

Chapter 2 Background & Significance

This chapter provides the context for my research in priority setting of expensive biopharmaceuticals, providing an analysis of the academic literature and its relevance to my thesis, as well as identifying the current gaps in knowledge.

Chapter 3 Methods

This chapter describes the methods used for the six case studies of expensive biopharmaceuticals: Cerezyme, Fabrazyme, Xigris, Glivec, Remicade and Gonal-F.

To describe the views of various stakeholders, interviews were conducted with drug recommendation committee members, industry representatives, patient representatives and academics. Additionally, documents related to each of the study drugs were analyzed.
Chapter 4  Results

This chapter describes findings from my six case studies and was divided into seven sections:

1) A description of decisions for each drug by each country.

2) A comparison of final funding recommendations, evidence used to assess cost-effectiveness and effectiveness, and definitions of values used by committees in their recommendations.

3) A comparison of the values used by each committee based on published rationales.

4) A discussion of the values and participants’ perceptions based on the interviews.

5) An evaluation of the decision making using the framework of ‘accountability for reasonableness.’

6) The role of innovation in healthcare sustainability.

7) Results section recapitulation.

Reflections text boxes which identified areas to be further discussed in Chapter 5 were included throughout these sections.

Main Findings

My main finding is that, while a number of values were considered by committees when making reimbursement decisions, committees tended to focus on values of evidence, effectiveness and efficiency, and not on the full range of relevant values. Thus, these contexts did not fully meet the
conditions of legitimacy and fairness. These values were recognized by committee members, patient representatives, and industry representatives. However, committee members tended to focus on the values of evidence based medicine and economics, while the patient and industry representatives discussed the importance of additional values, such lack of alternative treatments, life saving ability and quality of life.

Participants identified five improvements to the decision making process, which are not currently included in decision making and published rationales but that they believed to be important and which should be considered when making drug reimbursement decisions: 1) Consider other values (e.g., life saving ability) when decisions are made in the absence of evidence. 2) Incorporate more inclusive cost considerations when using cost-effectiveness analysis. 3) Consider the lack of alternative treatments when making reimbursement recommendations. 4) Acknowledge current notions of medical necessity and its role in the reimbursement process. 5) Consider increases to quality of life (QOL) when making drug reimbursement recommendations.

Chapter 5 Discussion

This chapter includes the following six sections:

1) *Filling the Gaps in Knowledge*, which identifies how my research fills some of the gaps in knowledge described in Chapter 2 and discusses how the findings of my research advances the background literature.
2) Lessons Learned, which elaborates on the Reflection textboxes which appeared throughout the Results Section.

3) Implications for Policy & Practice, which elaborates on policy and practice perspectives based on this thesis research.

4) Study Limitations, which describes the methodological and other limitations of this study and discusses some ways in which this project could be improved.

5) Future Research, which identifies areas for future research.

6) Concluding Remarks, which reflects upon the study and its findings by pointing to directions for improved PS in the reimbursement of expensive biopharmaceuticals.
2.0 BACKGROUND AND SIGNIFICANCE

This Chapter contains five sections which describe the state of knowledge in the following areas:

1) **Priority Setting Overview**, which defines priority setting, presents an overview of different levels of priority setting research, as well as describes and presents the limitations of some disciplinary-specific approaches to priority setting.

2) **Priority Setting in Health Innovation and Biopharmaceuticals**, which examines priority setting as it pertains to health innovation and biopharmaceuticals.

3) **The Role of Values in Priority Setting**, which discusses the role of values in priority setting through an examination of a legitimate and fair process and the application of an ethical framework to evaluate such a process.

4) **Drug Reimbursement Systems**, which describes the five health systems, Canadian, English and Welsh, Australian, Israeli and American, as well as access to and policies regarding orphan drugs and fertility treatment.

5) **Gaps in Knowledge**, which lists the gaps in knowledge which this thesis attempts to fill.

2.1 Priority Setting Overview

PS, also known as rationing or resource allocation, can be defined as the distribution of goods and services among competing programs and people [1]. This ethical process challenges many health systems [2]. PS is required because no public health system has sufficient funds to provide all healthcare services that may be desired. This is, in part, due to cost increases in the provision of healthcare,
including drugs, devices and services, as well as increases in the current demands for healthcare coverage [3]. Pharmaceuticals (i.e., drugs) are one of the leading drivers of rising public healthcare expenditure [4]. Public healthcare expenditure is a source of considerable economic pressure in most Organization for Economic Cooperation & Development (OECD) countries; the cost of delivering healthcare services and the limits on government resources challenges the sustainability of such health systems [5]. Health system sustainability involves ensuring that sufficient resources exist for the provision of quality services which address the changing needs of its users over time [6]. It is essential to establish limits, through priority setting, to what will be publicly covered in order to maintain and sustain public health systems. Ultimately, the establishment of priorities will determine the sustainability of the health system, regardless of the funding source (i.e., public or private) [17-19].

PS is ubiquitous in the provision of health care [20] occurring at the macro (i.e., government), meso (i.e. regional or institutional), and micro (i.e., bedside/clinical programs) levels. To date, only one study has focused on PS within and between all three levels [21]. Additionally, there exist different kinds of PS such as those related to health technologies and drugs, bed management, hospital budgets and wait list management. This thesis focuses on the PS of expensive biopharmaceuticals, mainly at the macro level, across five health systems: Canadian, English and Welsh, Australian, Israeli and American. It also discusses meso level decision making within hospitals and Primary Care Trusts (PCTs). Below is a discussion of both
Macro and meso level PS research. A discussion of micro level PS research was not included because it is not relevant to my thesis.

**Macro-level Priority Setting Research**

At the macro level, there has been PS research conducted on centralized agencies [22-27] and pharmacy benefit management organizations (typically in the USA). Centralized agencies may be national agencies established to assess, prioritize and recommend new pharmaceutical products for reimbursement [28]. The research conducted on centralized agencies can be further subdivided into two categories: comparative and single case studies.

Within the comparative case studies research, Sabik et. al., examined PS across eight countries (including Norway, Sweden, Israel, the Netherlands, Denmark, New Zealand, the United Kingdom and the state of Oregon in the US) and concluded that the establishment of a values framework for PS had little impact on health policy and that there is little evidence that supports the notion that PS exercises lead to the ideal of “an open and participatory public involvement in decision making” [29]. Mitton et. al. presented an international comparison of the fairness of four centralized drug review agencies (including Canada, Australia, New Zealand, and the UK) based on perspective of stakeholders. The authors concluded that transparency was crucial to both the legitimacy and fairness of the PS process. Furthermore, a fair process should promote stakeholder engagement [26]. McMahon
et. al., compared Canada’s Common Drug Review (CDR) to England & Wales’ National Institute for Health and Clinical Excellence (NICE). The authors concluded that there are three important issues that have to be considered in the PS process and review of pharmaceuticals: the selection of drugs for review, centralized versus decentralized decision making, and the presence of local receptors for knowledge/recommendation uptake [27]. Kapriri et. al., examined PS across three countries (specifically Canada, Norway and Uganda) and concluded that PS decisions are influenced by politics, public pressure, and advocacy [17]. Lexchin and Mintzes examined drug reimbursement decisions across three countries (including Canada’s Common Drug Review (CDR), Australia’s Pharmaceutical Benefits Advisory Committee (PBAC), and Scottish Medicines Consortium) and concluded that the CDR did not differ from the other agencies studied in terms of the number of drugs recommended. However, this finding may be a result of the small number of drugs the countries commonly reviewed [30]. Raftery compared reimbursement of costly pharmaceuticals across three agencies (including England and Wales’ NICE, Australia’s PBAC, and the Pharmaceutical Management Agency in New Zealand). He concluded that all three agencies made funding exceptions for drugs used in the treatment of severe diseases despite their inability to sufficiently meet the cost-effectiveness criteria [31].

Within the single case studies, PS research has been conducted on a number of specific agencies. A few studies have focused on the Canadian experience. For example, Pauss Jenssen’s study described the process of listing drugs on the
Ontario provincial drug formulary and concluded that decision making was based on the clinical merit of the product [32]. Laupacis described the organization and decision-making processes of Ontario’s (former) Drug Quality and Therapeutics Committee (DQTC) and the Canadian Expert Drug Assessment Committee (CEDAC) [33]. He described some challenges that the agency must address, including: interpreting the significance of surrogate markers and quality of life, the rising cost of new drugs, interpreting complex pharmacoeconomic evaluations, considering the real life cost-effectiveness for drugs used in populations who were initially studied, and the reimbursement of costly drugs for rare disorders [34]. Tierney et. al., focused on the CDR process and discussed the agency’s contribution to effective decision making and maintaining a sustainable health system through their assessment of pharmaceuticals [35].

Numerous studies have been conducted on England and Wales’ NICE. For instance, Raftery’s article reviewed NICE’s recommendations over five years. He concluded that while the rapid process is likely less intensive, NICE’s current appeals process has created consistency. NICE “continues to be best characterized not by saying no, but by saying yes but...” [24]. Another article by Cookson et. al., considered whether multiple agencies across the NHS are distorting PS decisions. They concluded that NICE should be developed into “a national healthcare rationing agency” and other agencies, such as the Health Technology Board for Scotland and the Scottish Inter-collegiate Guidelines Network (SIGN), need to complement NICE [28]. A study by Sheldon et. al., assessed the implementation of NICE guidance
across England and Wales. The authors concluded that implementation of NICE guidance is variable and more successful when there is strong professional support, credible evidence, and no increased costs [36]. A study by Pearson and Rawlins described NICE’s response to the inclusion of both clinical and cost considerations in their recommendations and concluded that despite criticisms of NICE, it does play an important role within the NHS; lessons learned from this agency are useful to the US case [25]. An article by Steinbrook presents an overview of NICE and suggested that one difficulty such agencies face is “saying no,” as this “takes courage — and inevitably provokes outrage” [37]. Walker et. al., focused on the cost-effective methods used by NICE for their technology appraisals. They concluded that NICE has the most “visible approach to introducing economic considerations” into their appraisals. However, disparities exist because of geographic variations as Primary Care Trusts (PCTs) ultimately make the final decision. One area of improvement is the establishment of programmes focused on disinvestment opportunities [38].

Some studies have also been conducted on the Australian experience. For instance, a paper by Stiller discussed her personal experience with PBAC in attempting to access the drug *infliximab*. She believed that PBAC decisions are based on the particular way they apply evidence [39]. A study by Harris et. al., analyzed the evidence used by PBAC to make coverage recommendations. They concluded that PBAC has provided coherence in decision making based on their use of evidence based coverage, clinical effectiveness and need, and value for money [40]. A study by Wonder et. al., examined the time it took to list medicines on the Pharmaceutical Benefit Scheme (PBS) once PBAC made a positive
recommendation. They concluded that from 1999 to 2003, recommendations for new listings and indications took longer [41]. Hailey examined PBAC decisions regarding pharmaceuticals compared to decisions of other health technologies. He concluded that PBAC used cost-effectiveness analysis in decision making for drugs, which contrasted its less frequent use in decisions regarding other technologies [22].

A few studies have been written regarding the Israeli experience. For example, Shani et. al., looked at the Israeli Ministry of Health (IMH) and suggested a national PS model for the inclusion of health technologies based on health technology assessment and explicit PS [42]. Another study by Shemer et. al., focused on the IMH’s experience using economic evaluation of medical technologies (EEMT) to assist in PS decisions [43]. A recent study by Chinitz et. al., demonstrated a shift in the Israeli public’s PS preference for treatments which increase quality of life over those treatments which extend life [44].

Few studies have been written about PS and the US Medicaid system. One article by Grannemann examined the application of PS to the US Medicaid program. He argued that it is more dependent on the system used to deliver care rather than on PS itself [45]. Another article by Blumstein examined the role of cost-benefit analysis in PS of Medicaid funds using the example of the US state of Oregon and concluded that Oregon avoided many of its cost-benefit analyses. Moreover, the Americans with Disabilities Act constrained the use of quality-of-life judgments in Medicaid PS decision-making [46]. A few studies have also been written about pharmacy benefit management organizations in the United States. Daniels et. al., proposed an ethical
template for pharmacy benefits and distinguishes between four levels of pharmacy coverage. This template called for transparency and relevance of rationales for PS and the ability to revise decisions. Another article by Daniels et. al., on pharmacy benefits, discussed the importance of fairness and consistency in PS decision making [47, 48].

**Meso-level Priority Setting Research**

At the meso level, studies have been conducted in a number of areas, including regional/district health authorities and hospitals. These studies have shown the importance of the process in attaining fair and legitimate PS decision making. For example, Ham examined PS across six different health authorities in the United Kingdom. He argued that because there is no one correct method to establish priorities, the justification for PS should focus on a fair process [49]. Another author, Teng, considered PS within a Canadian health authority. His study concluded that decision makers believed that the PS process should be more transparent, explicit and focused on fairness [50]. A study by Mitton, on PS within a Canadian health authority, discovered that collaboration between decision makers and researchers, as well as the establishment of an explicit and transparent process, can result in improved legitimacy of the PS decision making process [51].

The application of Program Based and Marginal Analysis (PBMA) to PS has been explored by Donaldson and Mitton within the context of regional health
authorities [52-57]. PBMA will be discussed in greater detail in section 3.3 below. PMBA is considered to be a useful and appropriate framework for PS decision makers because it allows for a process that is structured, evidenced-based and transparent [52-54]. Nonetheless, PMBA can be improved when used alongside an ethical framework for PS, namely ‘accountability for reasonableness’ (see Table 1 for the four conditions of ‘accountability for reasonableness’). The combination of both approaches results in a fairer process, as it will likely include a communication plan, a review mechanism, and formal appeals [58].

Hospitals and long-term care facilities are another important locus of PS. For example, Martin et. al., described and evaluated PS for the strategic plan of a Toronto tertiary care hospital [59]. The authors identified areas of good practice, including basing PS decisions on reasons considered relevant by participants in the hospital, such as a significant and robust number of participants, communicating decisions and rationales within the organization, and evaluating the PS process using an ethical framework [59].

Gibson et. al., examined hospitals and regional health associations. They identified PS criteria, process elements, and parameters of success which Board members and senior managers believed could enhance the fairness of PS [60]. Madden et. al. evaluated the appeals process of hospital PS. The authors found that the appeals process was a critical part of perceived fairness of the PS process. Moreover, it improved the overall satisfaction of participants [61].
Reeleder et. al., focused on the significance of leadership in hospital PS. They concluded that leadership was the area of PS most in need of improvement [62, 63]. Furthermore, a fair PS process is characterized by a number of criteria, such as multiple stakeholders, transparency, a communication strategy, an appeals process, and a monitoring and evaluating process. Such a process, which includes the aforementioned criteria, is more likely to be accepted by its stakeholders.

In regard to technologies, Hope et. al., discuss three concepts related to PS for drugs. They are effectiveness of treatment, patient choice and equity [64]. In his study, Foy et. al., discussed PS for new cancer drugs in the UK. Some challenges he highlighted were the persistent lack of national guidance, as well as conflicting values pertaining to the methods and outcomes of research [65]. Another study by Singer et. al., examining PS for new cancer and cardiac technologies, identified six interrelated domains, including institutions, people, factors (i.e. benefit, evidence), reasons, process and appeals [66]. Likewise, Martin et. al., described PS for cancer drugs and found that rationales for the listing of new cancer drugs were complex and multi-faceted.

Another study on new technologies in Canada, by Martin et. al., identified elements of a fair priority setting process based on decision makers’ perspectives. The authors concluded that the inclusion of all stakeholders was the most important element of fair PS [67]. Similarly, McKie et. al., described the views of the public
and health care professionals and concluded that the inclusion of a broad range of stakeholders was integral to legitimate and fair PS [68].

Two studies by Gallego et. al., focused on the PS of high cost drugs (HCDs) in hospitals. They concluded that decisions were not only based on effectiveness and cost, but on other factors such as 'clinical need' and the lack of alternative treatment [69]. A second study focused on public views regarding HCDs and priority setting within public hospitals. The authors discovered that participants considered factors such as treatment outcomes, quality of life and current health status when determining who should have access to high cost medicines. Moreover, participants wanted resources to be allocated to provide the "greatest benefit to the greatest number of people" [70].

As demonstrated above, PS setting research has tended to focus on particular levels. This approach allows for the analysis of a particular piece of the story. It does not provide the complete story. My study attempts to fill this methodological gap by using the drug as the case. The drug becomes a device which illuminates decision making for six specific, expensive biopharmaceuticals and facilitates comparison of PS within eight committees across five countries.

Additionally, while PS research has been conducted on drugs, only four studies have focused on high cost drugs (i.e., two aforementioned studies by Gallego et. al., Singer et. al., and Martin et. al.). My study exclusively compared and evaluated six expensive biopharmaceuticals across multiple jurisdictions.
Finally, PS research has identified the importance of stakeholder involvement in decision making. However, no PS studies have compared the views of drug recommendation committee members, patient groups and industry representatives on expensive drug reimbursement decisions. As a result, I decided to include these multiple stakeholder perspectives in my study. The inclusion of these groups allowed for a greater understanding of the reimbursement recommendation process for expensive biopharmaceuticals.

**Discipline-Specific Approaches to Priority Setting**

The ensuing sections describe four disciplinary approaches to PS, including philosophical, medical, economic, and policy.

**A Philosophical Approach**

Theories of distributive justice are all based on Aristotle’s principle of justice; i.e., equals should be treated equally and unequals should be treated unequally [71]. However, these theories differ in what constitutes material criteria and how to measure and distribute these criteria to result in justice. A number of theories of distributive justice, including Utilitarian, Egalitarian, Libertarian, and Communitarian, may be applicable to health care priority setting, and attempt to address the debate regarding how to distribute benefits and burdens. Utilitarian theories posit that an action is deemed right if it can promote the greatest overall good for humanity in comparison to other potential actions [72, 73]. Egalitarian theories focus on issues of need and equality of opportunity; i.e., that all individuals should have an equal level of material goods and services [74]. Libertarian theories concentrate on the fairness
of the process (rather than the outcomes) in order to make decisions [75]. According to Libertarian theories, the distribution of resources is considered just only when it is a free choice made by all those participating [73]. Communitarian theories focus on community-based principles, which are derived from specific community practices and traditions [73].

These theories are helpful because they can identify specific principles that may be used in PS. The limitations of these philosophical theories of distributive justice are that they are too abstract to provide guidance for actual decisions in specific drug contexts. Moreover, the philosophical theories conflict and there exists no consensus regarding which of the above theories is correct.

Traditionally, distributive justice theories are used by drug reimbursement recommendation committees. However, establishing criteria to determine whether equals are being treated equally is difficult, as committees are making decisions within and across multiple disease groups. In addition, even within the same disease group, there are individuals manifesting different degrees of severity; the tools needed to assess the severity and evidence regarding treatments are often insufficient to categorize equals and unequals.

A Medical Approach

*Evidence-Based Medicine*
Evidence-based medicine (EBM) has been frequently defined as “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients” [76]. There are different types of techniques used to assess the evidence, including meta-analysis, medical literature, risk-benefit analysis and randomized controlled trials. Systematic review of published studies is commonly used to evaluate specific treatments, such as the Cochrane Collaboration [77].

The qualification of evidence is measured according to degree of freedom from biases. As such, a randomized, double-blind, placebo-controlled trial with a homogeneous population and condition is considered the strongest type of evidence for a given therapeutic intervention. The value of effectiveness is emphasized in EBM regarding drug decision making and must be balanced by benefits and harms [78]. A number of countries have developed methods to assess the evidence of effectiveness for particular treatments. For instance, the US Preventive Services Task Force ranks evidence of effectiveness according to five levels, the strongest being randomized controlled trials and the weakest being expert opinions [79].

The strength of EBM lies in its ability to promote consistency and establish medical standards, as well as create principles to measure and assess medical performance [80]. Nonetheless, EBM is associated with a number of weaknesses. First, EBM does not incorporate the values of the very people it
affects - i.e., the patients [81,82, 83,84, 85]. Second, ‘evidence’ has multiple meanings and definitions, and is dependant on particular contexts [76,83, 86-88]. Drug recommendations are often grounded in principles of EBM [89]. However, recommendations are often made despite the lack of what is believed to be sufficient evidence [90].

**An Economic Approach**

Health economics is the assessment of all the significant costs, benefits and outcomes with regards to a medical intervention. It determines the most efficient manner to use the available resources in terms of costs and outcomes [91]. It places value on efficiency [78] and has been used for PS in various contexts, including pharmaceutical reimbursement. There are a number of methods used to assess the economics of a health intervention, including cost-effectiveness analysis (CEA) and program budgeting and marginal analysis (PBMA) [92].

*Cost-effectiveness Analysis (CEA)*

CEA is a tool in which costs and benefits are presented as a ratio of incremental costs per unit of benefit. Costs and benefits are measured in cost per year life saved and presented as either quality adjusted life years (QALYs) or disability adjusted life years (DALYs) [93]. Cost utility analysis (CUA) is a type of CEA which estimates the ratio between the cost of a health-related intervention and the benefit it produces in terms of the number of years lived in full health by the beneficiaries
During the 1990’s, there was an increasing interest and use of economic assessments of new therapies and explicit rationing in decision making [94-97].

Limitations of the economic approach include that it cannot objectively place a numeric value on a health outcome and is dependant on the person conducting the evaluation [71, 98]. Consequently, certain factors will always be ignored in the analysis, e.g., benefits which extend beyond the patient, such as family [99,100]. Also, placing an emphasis on meeting economic criteria, such as cost-effectiveness, places the value of efficiency above other values that are also important in decision making [101]. Additionally, the use of QALYs tends to discriminate against those with a disability, illness, and the elderly [102] and does not allow for comparison between different disease states [100].

Despite these limitations, evaluation committees continue to use economic assessments. For example, the Canadian Agency for Drugs in Technology and Health (CADTH) and the Drug Reimbursement System of The Netherlands focus on a single objective: cost-effectiveness [103]. However, within the Canadian system, oncology drugs seem to be adopted despite their inability to meet cost-effectiveness criteria. Other examples, not specific to drugs, include the Oregon Health Services Commission’s creation of a list of services to be funded by Medicaid, and New Zealand’s Core Service Committee (now the National Health Committee) priority funding recommendations for new treatments [104].
Program Budgeting and Marginal Analysis (PBMA)

Program budgeting and marginal analysis (PBMA) is based on two economic principles: opportunity cost and the margin [55]. This method allows for the comparison of different approaches through the assessment of their cost and benefits. PBMA attempts to improve overall benefit, while reducing opportunity cost [55]. Generally, PBMA requires the establishment of a panel of experts who assess and compare the use of resources within and across programs. Program budgeting requires programs to have clearly defined health objectives. The experts then use the best available data to estimate the costs and outputs for each program. Evaluation of the program is conducted through marginal analysis which determines what benefits would be gained and what would be lost if resources were shifted from one program to another. The process of marginal analysis is not simple because not all benefits can be measured in the same units of health gain. PBMA allows for an explicit discussion surrounding the two often conflicting values of efficiency and equity [105].

One advantage of PBMA over CEA is that it takes into account the issues of equity. The main limitation of this approach is that economic evaluations are generally extremely time consuming and costly [55]. Additionally, it requires that all objectives (i.e., equity, efficiency, etc.) be made explicit, which is sometimes not possible. Moreover, it does not help in identifying appropriate values to guide PS.
A Policy Approach

Health technology assessment (HTA) combines EBM and Health Economics. HTA considers “the effectiveness, appropriateness and cost of technologies.” The main purpose of HTA is to support and inform decision and policy makers at all levels – macro, meso and micro- regarding the implementation of any given technology through investigating the impacts of the health technology as related to its: technical properties, safety, efficacy and/or effectiveness, economic impacts, and social, legal, ethical and/or political impacts [106]. HTA attempts to maximize the value of effectiveness. HTA has become a tool used in PS to assess the value for money associated with a particular health technology [107-109].

The limitations of HTA include that it does not sufficiently address or incorporate values such as political, social, equity, and ethical considerations. Additionally, it is challenged by the quality of evidence, which often varies, resulting in coverage decisions that are often based on fair or poor quality evidence [110, 111].

Despite its limitations, HTA is used because of cost pressures internationally in the drug recommendation process. In the UK, the Labour Government’s support of national standards has resulted in numerous cases of HTA-based guidance. For example, the establishment of NICE, which was created to provide national guidance based on evidence of effectiveness and cost-effectiveness based on HTA, in order to overcome differences in geographic access to healthcare [107]. HTA is also used by CADTH. CADTH, specifically, looks at the following questions: How will this health technology affect the health of the population? How does it compare
with alternative technologies? Does it provide value for the investment? And are there other health service implications to consider? [112]

**Limitations of Discipline-Specific Approaches to Priority Setting**

Each of the above discipline-specific approaches to priority setting has limitations. The problems with using any discipline specific approach are that different approaches lead to different decisions; there is no consensus about which approach is correct; without consensus, it is very difficult for decision-makers to make consistent decisions (and decisions may be more easily subjected to government influence) [113, 114, 115]. Moreover, each approach tends to focus on a limited range of values, and there are few connections between the approaches. A number of values should be considered by decision makers when setting priorities, including (though not limited to) innovation, economic growth, equity and improved patient health [78, 113]. An interdisciplinary approach is needed to fully address priority setting issues [75].

The discipline-specific approaches listed above contribute an important perspective to priority setting of drugs. However, according to Norman Daniels, they are insufficient in providing guidance for specific PS challenges, including such problems as the *fair choices/best outcomes* challenge, which asks whether preference should be given to those who will derive the best outcomes, or rather to provide equal opportunity for deriving benefit to all; the *priorities problem*, which questions how much priority should be given to the person in greatest
need; the *aggregation problem*, which asks whether to prioritize an intervention that provides modest benefits to many people or one that provides significant benefits to a few; the *values vs. technical process conflict*, which presents the challenge raised by technical analysis, which is insufficient to solve allocation problems [116]. Ultimately multiple values are involved in decision making. In the absence of guidance for making value choices when faced with these challenges, it is crucial to create an environment which supports legitimate and fair decision making [117].

2.2 Priority Setting in Health Innovations and Biopharmaceuticals

**Priority Setting in Health Innovations**

Innovation is any advancement that results in the creation of a new product, reduces the production cost of a current product, or improves a current product’s therapeutic value [118]. Innovation is necessary because there are still health problems that need treatment options. Moreover, innovation can improve quality of life and has the potential to contribute to economic growth. The pursuit of innovation, including health biotechnology, has been identified as necessary and beneficial for both the industrial and health systems [112]. Innovation is essential to the successful growth of the health sector (i.e., all industry related to the production and service of health), which is one of the largest growing economies [119, 120]. For example, in 2006, Canada spent $148 billion on health care services and per capita spending reached $4548 [121]. The need to encourage innovation is acknowledged by many of the Organization for Economic Cooperation and Development (OECD) countries. At a January 2004 meeting, the OECD “reaffirmed that knowledge creation and diffusion
are increasingly important drivers of innovation, sustainable economic growth and social well-being” [122]. Health system sustainability is related to the promotion of health innovation and biotechnology in that health care fundors make PS reimbursement decisions about health innovations, such as biopharmaceuticals [14].

A number of factors are attributed to influencing science- and technology- based innovation in the health sector. They include the extent of scientific progress, governmental policies, funding, types of intellectual property rights, role of universities, clustering of firms, demands from the health system on innovation, and more [123]. Several governments are beginning to recognize some of these factors in promoting innovation in biotechnology and are taking steps toward enhancing this industry. While these government initiatives are not specific to health innovation, they do impact the health system, as some innovations and biotechnologies are applicable to the health sector.

Primarily, governments have focused on increasing government investment in innovation and establishing policies which motivate innovation [10]. However, no studies have been conducted on the effectiveness of these innovation strategies on the operation of health systems. Such an evaluation would be complex as the study intersects multiple sectors and governmental departments. The ensuing paragraphs will describe some innovation initiatives undertaken by the five countries in this study: Canada, the UK, Australia, Israel and the US.
In Canada, the federal Ministry of Industry is promoting the growth of biotechnology and innovation through policy and funding. In 2007, Industry Canada put forth an innovation strategy entitled “Mobilizing Science and Technology to Canada’s Advantage”. This report highlighted challenges and made recommendations for establishing Canada as an innovation leader. The document identified three areas that affect innovation: strong private sector commitment to science and technology, increase knowledge performance, and attract skilled workers [124]. The Canadian government also supports the biotechnology industry through funding. In 2003, CAD 1.7 billion in new funds was budgeted for research and development (R&D) and innovation. These were divided among the following eight areas: university research granting councils, universities and hospitals, indirect costs of federally supported R&D, health research facilities, new diagnostic equipment, Genome Canada, new graduate scholarship programs, skill improvement and education, and promotion of sustainable development [125]. From 1997 to 2003-04, expenditure on biotechnology grew an average of 18% per year, and in 2003, the human health sector had the most biotechnology products/processes, totaling 63% of all biotechnology [126]. Additionally, Canada established policies that aid in creating and sustaining innovative biotechnological firms. For example, Canada has generous R&D tax incentives compared to those in the US [127]. Moreover, Canada has been creating collaborative institutional structures to help with technology transfer of innovations. One example is the establishment of the National Biotechnology Strategy (NBS) in 1983 [128].
In the UK, the Department of Trade and Industry’s goal is to become an integral part of the global knowledge economy. Accordingly, they have identified innovation as a key element for their success. In the past decade, the chemicals sector (including pharmaceuticals) has grown faster than the economy as a whole. [129]

A report entitled “Competing in the Global Economy: The Innovation Challenge” identified the government as key in the successful pursuit of innovation. The government can create an environment that fosters growth through incentives and policy. For example, the government can aid in creating an improved relationship between the university and industry sector, and improved patenting policies.

Government funding has also been provided for the pursuit of innovation. In addition to the GPB 2.3 billion of R&D funded by the Office of Science and Technology (OST), and the Higher Education Funding Councils, Government Departments including the National Health Services (NHS) funded over GPB 4.5 billion of R&D in 2003 [129]. Another initiative, the UK Foresight, was launched in 1994 and again in 1998, and attempted to guide policy through identifying future market opportunities and threats in science and technology [130]. In 2003, 53% of the firms in the UK were in the human health sector, and the UK government spent GBP 211.8 million on biotechnology R&D (i.e., 1.6% of total government R &D expenditure) [126].

In Australia, the government developed a National Biotechnology Strategy in 2000, which is highlighted in a 2001 report entitled Backing Australia’s Ability and Backing Australia’s Ability – Building Our Future through Science and Innovation. At the
time, this government initiative was the largest financial contribution towards science and innovation (including health) by the Australian government, and amounted to AUD 3 million. Currently, the government contribution is 75 percent larger, in the amount of AUD 8.3 million for the years 2001 through 2011[131]. This initiative focuses on three areas: ability to generate ideas and pursue research, accelerating commercialization of ideas, and developing and retaining skills [132]. Additionally, in 2007, the State of Victoria put forth a plan entitled “Action in Partnership: Building Our Biotechnology Future,” which highlighted the importance of ensuring sustainable industry through commitment to the development of skills and investment in the biotechnology sector [133]. According to the OECD 2006 Report on Biotechnology, 47% of Australian firms consider themselves to be active in the human bio-industry sector, and 69% of their expenditure was spent on the human bio-industry sector [126].

In Israel, the government allocation of USD 22 million in 1995 and USD 24 million in 1996 to R&D in the life sciences has resulted in flourishing innovation. The health sciences sector contributes approximately 35% of research activity [134]. Additionally, Israel has numerous skilled workers, including numerous graduates in mathematics, physics and computer sciences [134]. There has been a substantial increase in biotechnology companies, from 30 in 1990, to 160 in 2000 [134]. Currently, Israel contributes 2.5% of the world's biotech sales [134]. The Office of the Chief Scientist (OCS) annually contributes USD $400 million in grants to life sciences companies showing promise [134]. The OCS has also created a 24 hour
technology incubator network, which promotes technology transfer from academic institutions to industry. However, there is a lack of experienced managers to aid in the commercialization process. Israel is currently partnering with the US in order to facilitate the commercialization of products and to gain access to new markets [134]. Expenditure on biotechnology R & D in 2002 was USD 251.1 million (i.e., 4.9% of total business R&D expenditure) [126].

The USA has the largest biotechnology sector in the world, with a total of 2196 firms undertaking biotechnology R& D in 2003 [126]. In 2002, the Department of Commerce’s Bureau of Industry and Security (BIS), Office of Strategic Industries and Economic Security, and the Technology Administration’s Office of Technology Policy (OTP) initiated a government assessment of the development and adoption of biotechnology in industry (based on a survey of 3000 biotechnology firms) [135]. The purpose of their assessment was to assist policy makers’ understanding of this sector. They found that in the US, 72% of biotechnology is focused on human health. Within this area, therapeutics has the greatest concentration. Biotechnology-related R&D expenditures amounted to USD 16.4 billion in 2001, which is approximately 10% of all US industry R&D for that year. Some major impediments to the commercialization of biotechnology products (as identified by biotech companies) include regulatory approval process and costs (59%), research costs and access to start-up capital (53% each). Additionally, unfair laws and regulations were also identified (but not specified) [135]. However, a report entitled “The Knowledge Economy: Is the United States Losing its Competitive Edge?” recognizes
that as other countries invest more resources into innovation, the US advantage will quickly dissipate [136]. The US Government is currently working on an Economic Recovery Plan. In January 2009, the Democrats’ plan included the allocation of $10 billion towards research and instrumentation and $6 billion towards the modernization of academic laboratories in order to “put scientists to work looking for the next great discovery, creating jobs…and making smart investments that will help business in every community succeed in a global economy” [137].

Internationally, governments are pursuing similar initiatives. For example, financial investments are made to improve the uptake of the science and innovation sector. Biopharmaceutical innovation is one area within this science and innovation sector. Nonetheless, financial investment in the promotion of innovation and biotechnology may negatively impact on the sustainability of the health system by creating biopharmaceuticals that the health system cannot afford. However, it is important to consider that innovation often involves research that results in unpredictable outcomes and differentiated returns that are difficult to see, such as jobs created, which cannot be easily quantified. Moreover, human health is complex and most drug candidates fail the clinical trial phase of innovation [12]. Furthermore, it is difficult to create a causal connection between government financial investment in innovation across all sectors and the subsequent adoption of pharmaceutical innovation within the health sector. Ultimately, successful uptake of biopharmaceuticals requires that appropriate receptors be established within the health system [14].
**Priority Setting in Biopharmaceuticals**

Biotechnology is "the application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services" [138]. Biotechnology drugs developed using biological molecules i.e., biopharmaceuticals [139], have been used for the treatment of health conditions such as rheumatoid arthritis. Currently, there are 253 biopharmaceutical products available in the US market, and more than 25 percent of new drugs approved by the US Food and Drug Administration (FDA) since 2000 have been biopharmaceuticals [139]. Global sales of biopharmaceuticals were USD 30 billion in 2004 [140]. In 2004, the top three selling biopharmaceuticals were: *filgrastim* (Neupogen, at a cost of USD 15 000 per patient, per year), *epoetin alfa* (Epogen, at a cost of USD 10 000 per patient, per year), and *interferon alfa-2b* (Intron A, at a cost of USD 22 000 per patient, per year) [140].

Biopharmaceuticals are often (though not necessarily) very expensive. Since the prices of biopharmaceuticals are generally higher than the prices of chemical drugs, fundors are becoming increasingly concerned with the PS of biopharmaceuticals [4]. Between 1998 and 2003, Kaiser Permanente, the US’ largest not-for-profit Health Maintenance Organization (HMO), tripled its expenditures on biopharmaceuticals [140]. PS of expensive biopharmaceuticals that benefit patients while simultaneously ensuring a sustainable healthcare system is complex and difficult. According to the OECD, increases in health care expenditures can be attributed to a number of factors, including technology/medical treatments such as biopharmaceuticals. Additionally, their “impact on expenditure will depend on the price elasticity of the
demand for health care” [5]. Moreover, even when new technologies are not expensive in unit costs, they may amplify demand by increasing the selection and quality of medical products on the market. The high cost of biopharmaceuticals may be associated with R&D, which “confronts levels of risk and uncertainty well beyond what is entailed in 'normal' R&D” [12]. According to Drews, the cost of bringing a new compound to market is between USD 50 million and USD 500 million, and the development time is between five to twelve years. His estimated costs include the cost incurred from pre-clinical research, testing and governmental approvals (it takes a minimum of one year to prepare for drug approval) [141]. DiMasi has estimated the average cost of bringing a drug to market at USD 802 million spread over 12 years [13], while the Boston Consulting Group estimated the cost at USD 880 million over 15 years [142]. Pisano believes that the high costs associated with R & D, coupled with low success rates of taking a drug to market account for the likely high cost of such drugs [12]. Hoffman et. al., noted the following factors as influencing drug costs: drug prices, drugs in development, and generic drugs [143].

It is important to note that some new drugs can be cost saving [4]. Some biopharmaceuticals have the potential to increase life expectancy, improve quality of life, enhance workplace productivity, decrease burden of disease, and reduce health care spending. Moreover, the application of pharmacogenomics to biopharmaceuticals holds the promise of improving drug effectiveness, reducing adverse side effects, and providing cost-effective pharmaceutical care [11].
According to Sullivan, evidence suggests that specialty drugs, when used in appropriate patient populations, may represent good health care value [144]. Further, the emergence of generic biopharmaceuticals will result in a decrease in current biopharmaceutical prices by 20 to 30 percent [140].

In addition to the high cost associated with biopharmaceuticals, PS of biopharmaceuticals is difficult because some of these drugs serve smaller populations and it is hard to measure their incremental therapeutic value and their societal value [145].

A major challenge facing health systems is providing users access to healthcare technologies while maintaining sustainability of the system [146]. If countries had unlimited resources, all beneficial treatments within a public system would be funded publicly. However, even wealthy countries have financial limits and rationing occurs both between different government responsibilities, e.g., money allocated for healthcare versus other socially valued services, and within government departments, e.g., the department of health’s allocation of funds towards drugs versus diagnostics versus services.

Ultimately, health system fundors may be forced to refuse reimbursement of beneficial, yet expensive treatments. Their refusal to reimburse beneficial innovative therapeutics may in turn have an impact on their industrial pursuits, and with that,
the promotion of innovation. Additionally, these decisions become complicated when treatments that have a potential for great benefit are coupled with great cost [147].

2.3 The Role of Values in Priority Setting

Traditionally, PS drug funding decisions are made by civil servants and experts, using evidence-based medicine and cost-effectiveness analysis. Moreover, patients, for whom the system exists, and members of the public, who fund the system through their taxes or insurance premiums, do not know how these decisions will be made or have a formal way of influencing the prioritization. As Wiktorowicz and Deber noted, decisions regarding drug funding involve value choices about which there is no consensus [15].

Value frameworks have been promoted internationally as a tool for healthcare reforms [148-151]. Despite recognition of the importance of values in decision making, much controversy exists regarding which values should be considered. As Giacomini et. al., pointed out,

“Some consider values to be ethical principles... while others see values as preferences revealed through choices or the willingness to pay for goods and services. Some seek values in collective beliefs (e.g. as expressed through social institutions), while others seek values in individual convictions (e.g. as represented by opinion polls)” [151].

Specific guiding values that are found within Canadian and American health reform proposals include: health, equity, economic viability, and good relationships [151].
In England and Wales, NICE considered the use of health states value in cost-effectiveness analysis (which values efficiency) in their technology appraisals. The use of the health state values allowed them to reflect on how to describe health, how to value health and who should provide the values for health. As Brazier noted, utility values can come from a variety of sources. As such, of utmost importance is the manner in which utility value literature reviews and synthesis of the evidence are conducted [152]. Mooney et. al., have argued that many economists view the UK’s National Health Service (NHS) as placing great value on health maximization of the population. However, they noted that many people do not believe that health maximization is the only goal of public health services, and that another consideration is the value of equity [153]. According to an industry perspective on NICE’s Guide to the Methods of Technology Appraisal, there is a need to consider society’s willingness to pay, and to establish clearer definitions of values [154].

Another value often considered when making health care funding decisions is the rule of rescue, which is often applied in situations where a drug fails to meet cost-effectiveness criteria, but is seen as life saving and thus beneficial. It has been argued by McKie and Richardson that if the rule of rescue is an important consideration, then current measuring techniques remain inadequate [155].

Clearly, values play a role in healthcare decision making; often decisions involve tradeoffs between competing values, which further complicates the decision making process. Some of these values have been described above, including equity,
efficiency, health maximization, utility and life saving ability. Saying “no” to drugs that may provide some benefit to some patients is highly contentious and morally controversial. The process of decision making must be fair, transparent, and regulated, and an opportunity to appeal must exist [156]. It is within the context of explicit rationing that it is necessary to establish a climate in which it is acceptable to say “no”. Key elements of such a climate are legitimacy and fairness.

Legitimacy refers to the moral authority of decision makers. Fairness refers to the moral acceptability of decision making, i.e., how decisions are made. Legitimacy and fairness are distinct in that both legitimate and illegitimate decision makers can act fairly or unfairly. They are related in that when legitimate decision makers act fairly, it tends to enhance their legitimacy [16].

Procedural justice (i.e., fairness) is “important to individuals independent of outcomes considerations” [157]. According to Fondacaro et. al., “one of the most intriguing findings in the social justice literature is that people seem to care as much or more about how they are treated in the course of decision-making (procedural justice) as they do about the decision outcome (distributive justice)” [158]. Therefore, for government policy makers who are faced with decisions about whether to reimburse drugs within the confines of limited resources, the goal should be fairness. Furthermore, a study conducted by Murphy-Berman, et. al., found that individuals who felt that they were treated fairly with regards to treatment decisions, had decreased levels of anger and increased levels of pride. Additionally, individuals who felt they were treated fairly, believed that this interaction positively influenced
their relationship with the health care decision maker [157]. The importance of individuals feeling a sense of satisfaction surrounding these decisions lies primarily in the benefit of satisfaction as a predictor of outcomes related to health, including adherence to treatment and health status. The research on patient satisfaction, as it relates to processes and outcomes, has focused mainly on the provider/patient relationship, and more recently, on patient/health plan representative relationship. It is thought that trust and satisfaction in health plans “can help providers who must increasingly make treatment decisions in the context of limited resources” [158].

A component of a legitimate and fair priority setting process is the establishment of an explicit PS process. PS can be done either implicitly, explicitly, or through the combination of both methods. The former type of rationing refers to decisions and rationales concerning the provision of healthcare that are not made known or accessible, while the latter refers to decisions and rationales that are known and accessible [95]. Explicit PS is preferred [159] for a number of reasons. Firstly, it is in accordance with the principles of democracy [160]. Also, implicit rationing does not disclose PS decisions and thus tends to result in decreased public confidence in decisions and decision-makers [161]. Public health policies will improve as decisions will be accountable to the public and inequities will be less likely to occur [160]. Therefore, proponents of explicit rationing claim that it will result in increased equity and fair service, as all of the stakeholders will have an opportunity to participate in the process [96, 162-164].
However, opponents of explicit rationing note two problems that arise from explicit rationing. The first is that it assumes that it is logistically possible and desirable to make all decisions explicit. The second issue is that it may be more optimal to make implicit rationing decisions preventing ‘disutility’ (i.e., something that is inefficient) [94, 95, 97]. Others urge for a mixed method approach [165, 166]. Nonetheless, in recent years, there has been international movement towards explicit rationing [104].

Legitimacy and fairness can be operationalized through a priority setting framework, which is comprehensive and grounded in real life situations - “accountability for reasonableness” (AFR). This conceptual framework was developed by Daniels and Sabin in order to improve priority setting in health care and ensure that “rationales for important limit-setting decisions…be publicly available” [16]. An institution’s priority setting decisions may be considered legitimate and fair if they satisfy four conditions (which operationalize the concept of fairness): publicity, relevance, appeals, and enforcement (Table 1).

Table 1. Conditions of ‘Accountability for Reasonableness’ *adapted from Martin and Singer 2003 [167]

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<tr>
<th>Accountability for Reasonableness (AFR)</th>
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<td>1. Publicity: Limit-setting decisions and their rationales must be publicly accessible, resulting in a transparent process.</td>
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<tr>
<td>2. Relevance: These rationales must rest on evidence, reasons, and principles that stakeholders (managers, clinicians, patients, and consumers in general) can agree are relevant to deciding how to meet the diverse needs of a covered population under necessary resource constraints.</td>
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<tr>
<td>3. Revisions and Appeals: There is a mechanism for challenge and dispute resolution regarding limit-setting decisions, including the opportunity for</td>
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<td><strong>Accountability for Reasonableness (AFR)</strong></td>
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<td>revising decisions in light of further evidence or arguments.</td>
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<td>4. Enforcement: There is either voluntary or public regulation of the process to ensure that the first three conditions are met.</td>
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</table>

This framework has gained international recognition and emerged as the leading conceptual framework for priority setting researchers [59,68,169]. The strength of this framework lies in ethical grounding found in theories of justice and democratic deliberation [117,170,171,172]. Specifically, AFR is rooted in the views of philosopher John Rawls [115, 173], whose concept of justice relied on the central principle of fairness [173]. Further, Rawls particularly notes that publicity is central to justice [173]. Finally, Rawls asserts that “public reason” must constrain the content of public deliberation and decisions about fundamental matters of justice [173].

The AFR framework provides direction for drug recommendation committees to improve their PS processes and operationalize the concepts of fairness and legitimacy in decision-making [174] [168]. Moreover, the importance of values is incorporated in this framework, as is evident through the *relevance* condition. The integration of values in drug reimbursement decisions is critical. Discipline-specific approaches are unable to assess “fairness” in PS.

This framework already has been used in the PS in specific drug contexts [47, 172, 175], as well as international comparison of centralized agencies [17, 26]. It has also been applied to evaluate and improve fairness in PS within a number of different
health systems, such as pharmacy benefit management organizations [47, 48, 175], intensive care units [176], health technology assessment organizations [172, 177], hospitals [178], regional health authorities [179], cancer care organizations [180], and centralized drug review systems [26]. Only one study has looked at the PS of high cost drugs, and did so specifically in the hospital setting [69]. AFR has not been applied to compare and evaluate expensive biopharmaceuticals across different health systems from the perspective of key stakeholders.

One author, Friedman, has criticized AFR. He argues that the four conditions are inadequate for achieving a fair and legitimate priority setting process. Friedman proposes two improvements, the first of which would be to increase public involvement in all stages of deliberation. Second, all types of reasons must be considered in decision making [181]. However, as described above, the stakeholder engagement that Friedman suggests is already a key component in AFR, as evident in the relevance condition, which mandates for the inclusion of all stakeholders, and the consideration of all relevant values and reasons. Another author, Rid, criticized AFR by arguing that it provides little guidance for PS of scarce resources, and does not necessarily result in fair limit-setting decisions. Rid concludes that the conditions must be further clarified in order to result in fair limit-setting decisions [182]. A third author, Daniels, concurs with Rid’s assessment that “much work needs to be done spelling out what a fair deliberative process should look like at different institutional levels…I welcome efforts to extend it” [183].
2.4 Drug Reimbursement Systems

While the focus of this study is six specific drug case studies, it is important to understand the reimbursement systems in which decisions for their reimbursement are being made. Many countries are using drug review agencies as a tool for making drug reimbursement decisions [184-187]. These agencies are responsible for assessing drugs and making reimbursement recommendations for new therapeutics, including expensive biopharmaceuticals [28]. Drug agencies have been studied in relation to their evidence criteria as well as their effect on decision making [188-191]. These studies are mainly focused on the final reimbursement recommendation [192, 193]. This section discusses the eight advisory committees within five health systems which were included in this study. It is divided into five subsections: 1) Canada 2) England and Wales 3) Australia 4) Israel and 5) the United States.

2.4.1 Canada

The Health System

Canada is composed of ten provinces and three territories. The Constitution Act of 1867 (i.e., British North America (BNA) Act) formally established the federal and provincial role within health. Specifically, federal jurisdiction within health was related to navigation, immigration, shipping, trade and commerce, Aboriginal peoples (or Indians in the words of the Act), public works and defense [194, 195]. Provincial jurisdiction was limited to private and local issues [196], including the establishment, maintenance and management of hospitals, asylums, and charities (other than
marine hospitals) [197]. Essentially, provincial and territorial governments are responsible for the provision of numerous health services, including hospitals and physician visits, as well as prescription drug coverage, home care, continuing care and long-term care [119].

The establishment of the public system in Canada, as we know it, can be explained by critical junctures, including Saskatchewan’s instrumental establishment of public Universal Hospital Insurance in 1947. A number of provinces followed suit, resulting in a national initiative, the Hospital Insurance and Diagnostic Services Act of 1957. In 1962, Saskatchewan introduced universal provincial medical insurance. This was followed in 1966 by the national Medical Care Act (MCA), which provided free access to physician services. The MCA was a means of unifying various provincial health funding, and served as a method of government control through funding. The Canada Health Act (CHA) was passed in 1984, and included the principles provided in the federal hospital and medical insurance acts; it added provisions that prohibited extra-billing and user fees for insured services [194, 199, 200]. Pharmaceuticals prescribed outside of hospitals do not fall under the CHA, and consequently, there are thirteen provincial and territorial drug plans [27].

Hospital services according to the Canada Health Act must be publicly administered. Additionally, most hospital services are delivered through not-for-profit (NFP) institutions and are commonly operated by various regional health authorities. Although a large amount of ancillary services are contracted out to private
companies, hospital and physician services are not open to foreign, private investment or delivery by foreign-based companies [119]. Insured hospital service expenditures are eligible for federal funding under the Canada Health Act. Services include medically necessary in- and out- patient care, including drugs administered in the hospital [201]. Many hospitals receive annual adjustments derived from the fiscal considerations of each provincial government [202]. Services that are not insured are supplied through the private sector (e.g., dental care, some chiropractic services, acupuncture, cosmetic or certain elective surgeries) and are paid for by the individual [203]. Prior to placing a drug on a hospital formulary, it must be approved by each hospital’s Pharmacy and Therapeutics (P & T) committee. New drugs are added to the formulary on the basis of safety and efficacy, as well as cost-effectiveness [204].

The Common Drug Review (CDR) was established in 2003 as an attempt to reduce duplication, to increase cost-effectiveness of drugs reimbursed, and to provide timely approval of drugs, as well as to ensure more consistency in formulary practices and policies across Canada [205]. As of April 12, 2007, the CDR will review new indications for previously approved drugs, as well as continue with its original mandate to review new drugs [206].

The CDR process begins when the drug manufacturer, drug plan or the Advisory Committee on Pharmaceuticals submits a drug for review. The CDR then reviews the clinical evidence and critiques the pharmaco-economic data based on the
literature and documentation in the submission. The review is sent back to the manufacturers for comments. The reviewers then respond, and a dossier is presented to the CEDAC; the committee meets to consider the submission. CEDAC’s initial recommendations and rationales are sent, in confidence, to the manufacturers and drug plans. During this time, the drug plans may request clarification and the manufacturer may request that the drug be reconsidered. Only the final recommendations and rationales are publicly available [207]. Manufacturers are now also able to request an expedited review process [208].

In Canada, each provincial and territorial government has a drug benefit plan. Many have programs for specific groups (seniors, social assistance recipients, people with diseases that require high-cost drugs) who need coverage for expensive drugs. The federal government is responsible for drug coverage for the following groups: First Nations and Inuit, members of the military, Veterans, members of the RCMP, and inmates in federal penitentiaries [209].

The Canadian Expert Drug Advisory Committee (CEDAC) is part of the CDR and provides critical appraisals of clinical and pharmaco-economic evidence. CEDAC is an “independent advisory body of health and other professionals with expertise in drug therapy and drug evaluation” [207]. Members are appointed by the Board of Directors for the Canadian Agency for Drugs and Technologies in Health (CADTH). There are currently 12 members, including members of the public, who meet approximately ten times each year. Each provincial and territorial government makes their own formulary listings and drug benefit coverage decisions. However,
provincial decisions take into account CEDAC’s recommendations (with the exception of Quebec) [210]. CEDAC's recommendations to list, list with provisions, or not to list, are evidence-based and reflect current clinical practice [207].

Diagram 1: Canadian Drug Listing Process

Since the 1990's, cancer drug reimbursement decisions have been made by individual provincial cancer agencies. Seven of ten provinces established formally structured provincial cancer agencies, which in general aim to reduce the incidence and mortality of cancer, and improve QOL for persons living with cancer [211]. For example, in 1997, Ontario’s provincial government formally launched and funded Cancer Care Ontario, which is governed by an act of legislation called The Cancer Act [212].

In March 2007, the Joint Oncology Drug Review (JODR) was implemented. This interim process involves the collaboration of all provinces, with the exception of
Quebec, in establishing a consistent national review of cancer drugs in Canada. At present, all active cancer drugs are submitted to Ontario for review [213]. Thus, the CDR will no longer review cancer drugs (with the exception of ambulatory drugs). Cancer Care Ontario is housed within the Ontario Drug Benefit Program’s Committee to Evaluate Drugs (CED) [213].

The CED, formerly the Drug Quality and Therapeutics Committee (DQTC), is an independent advisory committee, which makes drug reimbursement recommendations to the Executive Officer for the Ontario Public Drug Program. Reimbursement decisions are based on clinical evidence, cost-effectiveness, burden of disease and impact on other provincial services. It is made up of 14 members and has two patient representatives. Reviews take approximately three months [214]. Rationales for CED reimbursement recommendations can be found on the CED website [208].
Orphan Drug Access

Currently, there is no national orphan drug policy in Canada, and reimbursement for orphan drugs occurs through each individual, provincial formulary [215]. The Canadian Organization for Rare Disorders, along with other patient groups, is in the midst of working with the government to create an orphan drug policy [216]. Recently, Alberta has established an orphan drug strategy which will begin funding treatments of rare diseases for eligible patients in April 2009 [217].

Infertility Drug Access

Currently, in Canada, infertility treatment is generally privately funded. Prior to 1994, what was then referred to as the Ontario Drug Benefits Program funded all in-
vitro fertilization (IVF) services. Ontario was the only province whose Health Insurance Plan covered all IVF services for qualified patients. However, in 1994, the Ontario Ministry of Health de-insured IVF (except for bilateral fallopian tube occlusion, which represents 1% of infertility problems). This decision was based on questions of medical necessity and clinical effectiveness.

According to Hughes, et. al., these criteria were not defined or applied consistently and the basis of the decision was cost savings [218]. The notion of the lack of medical necessity was echoed in the 1998 Nova Scotia Supreme Court ruling, which ruled that public funding for IVF/ICSI (intracytoplasmic sperm injection) was unjustifiable as the treatment was deemed to be medically unnecessary. In contrast, the Royal Commission on New Reproductive Technologies (1989–1993) has recognized that infertility is a medical and social problem [219].

In November 2007, the Ontario government established an expert panel on infertility and adoption to examine ways to make fertility treatment more accessible [220]. The only other province that currently offers support/subsidy for IVF treatment (including use of Gonal-F) is Quebec, and this is in the form of a tax credit ranging from 30% to 50% [219]. In November 2008, Quebec announced that it will cover up to two IVF treatments for eligible patients [220].

The Canadian system allows for provinces to make decisions that are relevant to their populations. However, this also creates a challenge with regards to drug
reimbursement. Specifically, the decentralized nature of the formulary system gives rise to geographic differences in equity to access of medicines. Additionally, the lack of a national orphan drug policy and infertility policy further aggravates the inequalities in access across the provinces.

2.4.2 England and Wales

The Health System

The National Health Service (NHS) is responsible for the provision of health services to the public in the UK (England, Wales, Scotland and Northern Ireland). The NHS was established in 1948, managed by the Department of Health and funded by taxpayers. Each of the four countries has their own NHS. The United Kingdom is one state composed of four countries with their own health systems.

In Wales, there are 22 Local Health Boards (LHBs) responsible for the commissioning and improvement of health. They receive 75 percent of the overall NHS budget, enabling them to directly commission services other than community services, which remain the responsibility of the NHS Trusts.

In Scotland, Scottish Parliament has legislative authority over healthcare. There are 15 Health Boards, generally containing 1 acute and 1 primary care trust that are responsible for the community.
In **Northern Ireland**, 15 Local Health and Social Care Groups were established in 2002. They are responsible for “planning the delivery of primary and secondary care” [221].

In 2001, **England** established Primary Care Trusts (PCTs), which evolved from the Primary Care Organizations (PCOs) of the 1990s, and are regional organizations that run the local NHS and hold 75 percent of the NHS budget. Currently, patients can choose between four to five providers located within their PCT [222, 221]. There are a total of 152 PCTs [223], all of which receive their budget from the Department of Health. In 2002, PCTs became responsible for the funding and commissioning of local health, while the Health Authorities monitored standards [221,224].

PCTs are generally composed of three groups: the board, the professional executive committee, and the management team. PCTs are supposed to cooperate with surrounding trusts to commission specialized services for costly treatments with low prevalence. Commissions regarding services for 3-6 million people are done regionally, while those for less than 400 people are commissioned nationally by the National Specialist Commissioning Advisory Group [225]. According to the **NHS Act of 1977**, PCTs have a statutory responsibility to remain within the ‘cash limit’ established by the department of health [226].

The National Institute for Health and Clinical Excellence (NICE) was established in 1999 and is an “independent organization responsible for providing national
guidance on promoting good health and preventing and treating ill health” for the NHS in England and Wales [227]. They make evidence-based recommendations, called guidelines, grounded in the evaluation of clinical data, and cost-effectiveness of the intervention (particularly using cost-utility data). As well, they are informed by internal and external expert advice [27, 228]. Towse and Pritchard note that NICE uses an implicit threshold of £20,000–30,000 QALY, above which the likelihood of acceptance decreases [229].

The Technology Appraisals Committee is responsible for creating NICE’s recommendations. It is comprised of health care practitioners, patients, care givers, industry, as well as government. This committee is divided into three groups: A (27 members), B (29 members) and C (29 members) [227]. The final guidance is published by NICE. Initially, the guidance was meant as a recommendation to PCTs; however, as of January 2002, NICE technology appraisal guidance is mandatory and PCTs must fund the drug within three months of the guidance publication [27].

The process works as follows: First the Department of Health and the Welsh Assembly Government request an evaluation of a drug, which may be controversial. Then the NICE and the NHS Health Technology Assessment (HTA) Program identify appropriate independent academic units to conduct the initial assessment. Manufacturers, physician organizations and patient groups may also submit evidence [27]. All of the evidence is considered by the Technology Appraisal Committee.
Orphan Drug Access

Traditionally, the NHS has paid for expensive orphan drugs, because the expenditure for these products was at one time negligible. Now there are increasing numbers of products on the market for such diseases and costs are substantial [225]. In 2004, NICE established an *Orphan Drugs Project*. The objective of this project was to ascertain methods of assessing orphan drugs. Ultimately, no change in methods was deemed necessary for orphan drugs (i.e., drugs used by fewer than 200 000 persons per population). However, when evaluating some ultra orphan drugs (i.e., drugs used by less than 1:50 000, which correlates to less than 1000 people in the UK), NICE recommended to the ministers that an Ultra-Orphan Drugs Evaluation Committee be established [230].
On May 14, 2007, the House of Commons responded to this recommendation by stating that “Ministers have received the National Institute for Health and Clinical Excellence’s report on appraising ultra-orphan drugs and have concluded that it is not appropriate at this time to establish a separate appraisal system for such drugs. This position will be kept under review” [231]. The Secretary of State also stated that “Ultra-orphan drug treatment for a specific set of diseases, Lysosomal Storage Disorders, has been nationally commissioned by the National Specialist Commissioning Advisory Group (NSCAG) since April 2005, for an initial two-year period until March 2007. The 2006-07 budget for this service is £58 million… for 33 very rare conditions on a national basis. Funding arrangements for other ultra-orphan drugs are a matter for individual primary care trusts” [232]. The Department of Health, under the auspices of the NSCAG, nationally funds services for patients with LSD (including the cost of drugs and enzyme replacement therapy (ERT) at six designated centres from April 2005 to March 2007[233].

Infertility Drug Access

In April 2005, the NHS decided to fund one cycle of in vitro fertilization (IVF). The NHS also funds fertility drugs, intrauterine insemination (IUI), intracytoplasmic sperm injection (ICSI) and IVF using donated eggs or sperm, where donors are available [234]. However, there is currently no standard regulation for fertility treatment in the UK. NICE’s final fertility guidelines, entitled “Fertility: Assessment and Treatment for People with Fertility Problems” is scheduled to be published in February 2008. It will cover best treatments, types of treatments and other means of treatment when no problem is found [235]. The Public Health Minister, Caroline Flint MP, has stated
that “We recognise that progress in the provision of fertility services is taking longer in some areas than in others, as it is influenced by local circumstances and the point from which PCTs were starting. However, persistent inequality of provision is hard to bear, and hard to understand, for those affected” [236]. In the meantime, there exist discrepancies across England. Eligibility criteria vary by PCT, and some PCTs refuse to provide fertility treatment. Also, many PCTs are not following NICE’s guidelines [237-241].

Like the Canadian system, this system allows for decisions to be made that are relevant to the specific population. However, this also creates a challenge with regards to drug reimbursement. Specifically, the decentralized nature of the formulary system gives rise to geographic differences in equity to access of medicines. Nonetheless, the establishment of NICE in England and Wales has attempted to address the post-code prescribing within the PCTs of these countries, and minimize health access inequities. Additionally, England and Wales are making strides toward standardization of infertility treatment.

2.4.3 Australia

The Health System

Australia is composed of six states and two territories. It is the responsibility of the state, territory and local governments to deliver and manage public health services [221, 242]. The current public system evolved from a number of critical junctures. The Australian government was involved in the provision of health to portions of the
population since the white settlement. Initially, government involvement in the provision of health was limited to quarantine, but in 1921, with the establishment of the federal health department, the government became responsible for providing public health services together with the states. In the 1940s, the federal government wanted to centralize health care and take responsibility for the provision of all personal health services, which would be universal and free to all citizens. However, this attempt failed [243].

The *Pharmaceutical Benefits Scheme* (PBS) was introduced in 1948 with the intent to provide the population with free “life saving and disease preventative drugs” [23]. The scope of drugs provided for by PBS has since increased. Expenditure on pharmaceuticals grows between 15-20 percent per year. A voluntary health insurance scheme was established in 1953 with the *Medical Benefits Scheme*, which eliminated contract practice in lieu of full fee-for-service. Dissatisfaction with the voluntary scheme spawned a number of bills, most notably the *Health Insurance Bill 1973*, which established *Medibank*. *Medibank*, a national health insurance program, was established in 1975. Its purpose was to provide universal coverage with an equitable distribution of cost, which was easy to manage administratively [243, 244]. Under *Medibank*, patients receive public hospital services at no cost and private hospital services at subsidized costs. Changes were made to *Medibank* as a result of the Fraser government, and *Medibank II* was established in 1976. These changes were rejected under the Hawke Labour government, who returned to the *Medibank* model, which was renamed *Medicare*. Medicare was ultimately
established in 1984 with the passing of the *Health Legislation Amendment Act 1983*,
the amendments to the *Health Insurance Act 1973*, the *National Health Act 1953*
and the *Health Insurance Commission Act 1973* [244].

The Pharmaceutical Benefits Advisory Committee (PBAC) makes recommendations
to the Minister regarding which new drugs to include in the Pharmaceutical Benefits
Scheme (PBS). PBAC is comprised of 18 individuals who represent pharmacists,
physicians, economists, and consumers [245]. PBAC considers the Therapeutic
Goods Administration (TGA) terms of marketing approval of a product [246]. Only
drugs that have been recommended by the committee can be included under the
PBS [23]. PBAC is an independent committee, which was established in 1954 under
section 101 of the *National Health Act 1953*. It is one of the four partners under the
National Medicines Policy (NMP) of 1999. The objective of the NMP is to create a
partnership between the various levels of government, health educators,
practitioners, and suppliers, as well as industry, consumers and the media.

This partnership is essential to order to promote affordable, timely access for
medicines that are needed, and in order to provide standards of appropriate safety,
quality and efficacy, as well as to ensure the quality use of medicines and to
maintain a responsible and feasible pharmaceutical industry [247].

PBAC must consider “the effectiveness and cost of a proposed benefit compared to
alternative therapies” when making recommendations [245]. Additionally, they may
make recommendations on maximum quantities, restrictions and usage. PBAC also
gives advice to the Pharmaceutical Benefits Pricing Authority (PBPA) on cost-
effectiveness [245]. PBAC has two subcommittees, the Economic subcommittee and
the Drug Utilization subcommittee that help them review the relevant evidence [245].
In general, new drugs, which cost more than A$68, 193 per life-year saved are not
listed; drugs which cost less than A$ 36, 450 per life-year saved are listed [23].

Diagram 4

Orphan Drug Access

The Australian Orphan Drug Program was first considered in 1991 and ultimately
established in 1998 [248, 249]. The objective of this program is to give companies
the incentive to research and develop orphan drugs through waiving application
fees, allowing shorter approval times, and providing exclusive approval [250].
Australia worked together with the US FDA Office of Orphan Drug Products in establishing a program modelled on the US program [248]. Two areas in which there is a need for therapeutics are diseases affecting indigenous and paediatric populations. In Australia, orphan diseases are those affecting less than 2000 patients [248].

**Infertility Drug Access**

Most infertility treatments in Australia are covered by Medicare. The “Medicare Plus Safety Net” covers approximately eighty percent of Medicare approved out-of-pocket expenses for services rendered outside of hospitals, excluding oocyte retrieval or Intracytoplasmic Sperm Injection (ICSI). In addition, private insurance may cover some of the expenses [251, 252]. Forty-four percent of the population is covered by private insurance [253]. In order for a treatment centre’s medical activities to be covered, it must meet the standards set by the Reproductive Technology Accreditation Committee (RTAC) of the Fertility Society of Australia (FSA) [254].

The strength of the Australian system lies in its centralized nature. The access inequities found within Canada and UK are not as prevalent in Australia. The Australian system lies in the middle of the spectrum of access to infertility treatment.
2.4.4 Israel

The Health System

Israel is composed of six districts – Jerusalem, Central, Haifa, Northern, Southern and Tel Aviv. Four sick funds (health insurance companies) are responsible for providing medical services to the country [255]. In 1995, Israel established a National Health Insurance law that affirms the state’s responsibility in the provision of health services to its residents. This law requires that every resident must be a member of a sick fund, that the sick fund cannot exclude applicants on any basis (e.g. state of health), and that a standard basket of medical services must be provided by the sick funds.¹ The costs of health services are funded by progressive health insurance premiums paid by each resident, employers’ health tax payments, National Insurance Institute funds, funds from the Ministry of Health budget and consumer participation payments [255]. In 1999, the Minister of Health appointed a public national advisory committee, the “Basket Committee”², to determine which new technologies and therapeutics would be added to the health basket (established in 1994) [256]. The “Basket Committee” is an independent committee made up of representatives from the government, sick funds and the public. It is comprised of 24 members, including government officials, healthcare practitioners, sick fund members, and the public [256]. This committee considers various aspects and uses criteria, including clinical, economic, social, ethical, and legal factors [256].

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¹ Items in the basket include- hospitalization, medical diagnosis and treatment, preventive medicine and health education, surgery and transplants, preventive dental care for children, first aid and transportation to a hospital or clinic, medical services at the workplace, medical treatment for drug abuse and alcoholism, medical equipment and appliances, obstetrics and fertility treatment, treatment of injuries caused by violence, medication, in accordance with an order issued by the Ministry of Health, treatment of chronic diseases, paramedical services (physical therapy, occupational therapy, etc.).
² Participants referred to the committee as the “basket committee”
Orphan Drug Access

At present, Israel is working on an Orphan Drug Policy [e-mail correspondence]. In the interim, the national budget provides funding for Enzyme Replacement Therapy for Gaucher’s Disease (one type of orphan drug) to the sick fund through the health basket for severe treatments [257]. All other orphan drugs are assessed by the Basket Committee.

Infertility Drug Access

Fertility treatments for infertile women are covered according to the 1995 Universal Health Insurance law. Treatments are publicly funded until the conception of two children. In 1999, the following restrictions were established: women over the age of
45 will not receive funding for treatment of their own ova and women over 51 will not be provided with donated ova [258].

Similar to the Australian system in its centralized nature, the Israeli system does not have the access inequities found within Canada and the UK. Additionally, their infertility access is known to be the most generous in the world.

2.4.5 United States

The Health System

The United States is composed of fifty states and one district. The Centers for Medicare/ Medicaid (CMS) are responsible for the provision of health insurance to approximately one in four Americans [259]. Medicare is a federal program responsible for the provision of health insurance for the elderly (65 and older), disabled, and individuals in need of dialysis or kidney transplants for treatment of end-stage kidney disease [260].

Medicaid is a federal program responsible for the provision of health insurance to certain low income individuals and families [261]. Medicaid was established by Congress in 1965 as Title XIX of the Social Security Act [262]. This program is monitored by the federal CMS and is administered by the state. As such, each state establishes its own criteria both for eligibility and services. It is jointly funded by the federal and state governments. All states are required to participate in Medicaid; however, certain programs, such as the outpatient prescription drug benefits
program, are voluntary (nonetheless, all states participate). The outpatient
prescription drug program was added to Medicaid through legislation, i.e., the
Medicare Modernization Act (MMA), in 2003 [263]. Once a state agrees to
participate in the program, they are required to provide all drugs under the federal
formulary listing [259].

In 1990, the Omnibus Budget Reconciliation Act (OBRA) established the Medicaid
Drug Utilization Review (DUR). The DUR is a management tool used to assess
patient safety, provider prescription habits and money saved by avoiding adverse
reactions, drug-disease interactions, therapeutic duplication and over-prescribing
[264]. Some other state legislation related to the provision of prescription drugs
through Medicaid includes preferred drug lists (PDL), or formularies, generic
substitution, cost-sharing or co-payments, multi-state purchasing, pharmacy benefit
managers (PBMs), prior authorization, dispensing fees, ingredient reimbursement
and supplemental rebates from manufacturers [265].
Orphan Drug Access

The United States established the first Orphan Drug Act of any country on January 4, 1983. This act defines orphan diseases based on a prevalence of less than 200,000 individuals. It provides assistance to companies for the development of research protocols and designs. Additionally, it provides tax credits for clinical research conducted in this area, market exclusivity and funding grants. It also enables accelerated approval, a Parallel Track Program and Treatment Investigational New Drugs (INDs) for access to unapproved drugs [266].

Infertility Drug Access

There is no federal legislation governing artificial reproductive technology. Family planning is covered by Medicaid in about half the states, however infertility tests and treatment are usually not defined as part of family planning. Many private insurance policies cover diagnosis of infertility, but not the cost of treatment. Coverage of
treatment by private insurers varies by state and only 10 states require the coverage of treatment for infertility. Most individuals must pay for treatment out of pocket [218, 267].

The Medicaid drug system is centralized in that all states that participate in the program must fund the drugs listed on the federal formulary. The US is the example used when discussing orphan drug policy, as it was the first country to establish such a policy. With regards to infertility access, there is significant inequity in access as funding of such treatments varies by state.

2.4.6 Summary

It is clear that drug reimbursement systems differ vastly in terms of coverage and arrangements. Some are more centralized than others, offering the potential for more equal PS. Others have a very limited scope, offering services and drugs to only a small subset of their population. Countries also differ in terms of their focus on Orphan Drugs. Many countries are thinking about establishing acts to regulate such drugs, but only the US has formally established one. The five countries surveyed also differ in access to fertility treatments: the UK and Israel offer the most coverage in this area.

2.5 Gaps in Knowledge

As shown in this chapter, there are three gaps in knowledge regarding expensive biopharmaceutical reimbursement. This research will attempt to fill these gaps. The following gaps have been identified:
1. There has not been an attempt to describe public reimbursement decisions for expensive biopharmaceuticals using the drug as the case, while considering patient and industry views.

2. There has been no attempt to evaluate the legitimacy and fairness of governmental reimbursement recommendations regarding these biopharmaceuticals.

3. No studies have been conducted that examine the implication of biopharmaceutical reimbursement decisions on the pursuit of biopharmaceutical innovation.
3.0 METHODS

In this chapter I will explain the qualitative research methodology employed to address the gaps in the literature identified in Chapter One. This chapter is divided into eight sections: 1) Design, 2) Setting, 3) Sampling, 4) Data Collection, 5) Data Analysis, 6) Data Evaluation, 7) Conceptual Framework, and 8) Research Ethics.

During this research, I conducted six qualitative case studies of expensive biopharmaceuticals to describe and evaluate priority setting reimbursement decisions within eight committees. These case studies consisted of fifty-six in-depth interviews (see Table 2) with representatives from government advisory committees, academics, industry and patient groups (related to the study drugs), as well as the collection of thirty-two documents (Appendix 2).

3.1 Design

In order to describe and evaluate priority setting decisions surrounding the reimbursement of expensive biopharmaceuticals, qualitative case study methods were used. Qualitative research is

“An inquiry process of understanding based on distinct methodological traditions of inquiry that explore a social or human problem. The researcher builds a complex, holistic picture, analyses words, reports detailed views of informants, and conducts the study in a natural setting” [268].

Case study research is conducted when questions of “how” or “why” are being addressed, when a contemporary phenomenon is being studied, and/or when little
control exists over the events being studied [269]. Case study research allows the researcher to gain an understanding of the issue or issues being studied within a specific real-world context [268]. The case study approach was appropriate for my research because it allowed for an in-depth and rich understanding of the drug reimbursement process for expensive biopharmaceuticals [270].

This study was innovative because I focused on the drug as the case. Previous studies in priority setting have focused on 1) committees, and 2) organizations/institutions. To date, only one study has focused on the drug as the case. Van Rijkom, et al., (1999) focused on three biotechnology drugs: nebacumab, colony stimulating factors, and recombinant human growth hormone [271]. This study looked at the literature surrounding the assessment and diffusion of these biotechnology products as it related to four criteria, 1) safety, 2) efficacy, 3) cost, and 4) ethical, legal and social factors. My study differs from the aforementioned study in a number of ways. First, it spanned five countries, allowing a comparison of values in order to ascertain any differences. Second, the criteria and values I identified were grounded on key stakeholder input, and not just an evaluation of the literature. Third, I evaluated decisions against an ethical framework (Refer to Section 3.7 ‘conceptual framework’). Fourth, I identified areas of improvement through non-compliance with the framework.

In addition, research using the ‘accountability for reasonableness’ framework has never been conducted using the drug as the case. Typically, research related to drugs has focused on the agency responsible for the priority setting decision. Only
one study using this framework has been conducted on expensive drugs [69], and it was based on one hospital committee’s decisions.

Using the drug as the case allowed for a more in-depth study of reimbursement priority setting for a number of reasons. First, it allows for comparative analysis across different health systems and different levels/jurisdictions within these health systems. Second, priority setting studies have focused on theoretical perspectives or on practical experiences of healthcare institutions/organizations. To my knowledge, this is the first study on priority setting that has been conducted which includes the industry perspective. Using the drug as the case not only expands the scope of this study throughout a number of jurisdictions, but also allows for the inclusion of more stakeholders’ perspectives; specifically those of the government, patients, and industry groups. Thus, this method results in data that is better grounded in the real life experiences of the key stakeholder groups.

3.2 Setting

Because the drug was the case, this research was conducted within multiple settings, i.e., both reimbursement recommendation committees and drug manufacturers. The government committees included in this study were as follows: the Canadian Expert Drug Advisory Committee (CEDAC), England’s National Institute for Health and Clinical Excellence (NICE), Australia’s Pharmaceutical Benefits Advisory Committee (PBAC), the Israeli Basket Committee (IBC), and a US State Medicaid P & T Committee (the committee requested to remain anonymous).
These panels were selected because they are bodies which make decisions about public funds, and they provide guidance on drug funding to governments and other funders. In Canada, two additional committees were included: a Toronto Hospital Pharmacy and Therapeutics (P & T) Committee, and Ontario’s Committee to Evaluate Drugs Cancer Care Ontario Subcommittee (CED-CCO). They were included because two of the study drugs – Xigris and Glivec- fell under different jurisdictions. Similarly, in England orphan drug and fertility treatment decisions are under PCT jurisdiction, and therefore the West Midlands Exceptional Drug Review Committee was included for orphan drugs and the West Midlands PCT was included for fertility treatments. Please refer to Table 2 and 3 below for general information about each of the committees. Table 2 includes criteria for decision making, forms of publicity, list of people who have access to the appeals mechanism, committee membership, websites and documents reviewed. Table 3 is a comparison of stakeholders involved in the recommendation process listed by committee. The stakeholders that were most often involved in the decision making process were healthcare professionals, the public and academics. Some other stakeholders included by some committees were ministry representatives (e.g., IBC and CED) and industry representatives (e.g., NICE). For purposes of the table below, the term public was used to refer to lay persons and consumers groups. Please note that during CEDAC’s review of Fabrazyme (in 2004), there were no public members on the committee. The CED had public members on their committee during the review of Glivec (in July 2007).
The companies that manufactured the study drugs were included in this research because the pharmaceutical industry is a stakeholder in reimbursement decisions. They are: Genzyme, Eli Lilly, Novartis, and Serono. A fifth pharmaceutical company, Centocor Pharmaceuticals, declined to participate after numerous e-mails and phone conversations.

Table 2. General Information about Committees

<table>
<thead>
<tr>
<th>Name</th>
<th>Decision Making Criteria</th>
<th>Forms of Publicity</th>
<th>Who Can Access Appeals Mechanism</th>
<th>Committee Members</th>
<th>Websites Reviewed</th>
<th>Documents Reviewed</th>
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<tr>
<td>CEDAC</td>
<td>Safety</td>
<td>Internet</td>
<td>There is 15 days for the following groups to appeal: Manufacturer</td>
<td>Experts (recently added lay member)</td>
<td><a href="http://cadth.ca">http://cadth.ca</a></td>
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<td>PBAC</td>
<td>Effectiveness (compared to alternative therapies)</td>
<td>Internet</td>
<td>Available for manufacturer</td>
<td>Experts</td>
<td>Lay members</td>
<td><a href="http://www.health.gov.au">http://www.health.gov.au</a></td>
</tr>
<tr>
<td></td>
<td>Cost-effectiveness (&quot;value for money&quot;)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Guidelines for the Treatment of Gaucher Disease</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Guidelines for Eligibility to Receive Treatment with Agalsidase through the Lifesaving</td>
</tr>
</tbody>
</table>

(activated) for severe sepsis: technology appraisal 84. 2004

Rheumatoid arthritis – adalimumab, etanercept and infliximab. 2008

Assessment & treatment for people with fertility problems

Understanding NICE guidance – information for people with fertility problems, their partners and the public Feb 2004
<table>
<thead>
<tr>
<th>Name</th>
<th>Decision Making Criteria</th>
<th>Forms of Publicity</th>
<th>Who Can Access Appeals Mechanism</th>
<th>Committee Members</th>
<th>Websites Reviewed</th>
<th>Documents Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>Decision Making Criteria</td>
<td>Forms of Publicity</td>
<td>Who Can Access Appeals Mechanism</td>
<td>Committee Members</td>
<td>Websites Reviewed</td>
<td>Documents Reviewed</td>
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</tr>
<tr>
<td>US State Medicaid P &amp; T</td>
<td></td>
<td></td>
<td>Members of the plan</td>
<td>Physicians</td>
<td><a href="http://www.cms.hhs.gov/">http://www.cms.hhs.gov/</a></td>
<td>Fabrazyme Drug monograph</td>
</tr>
<tr>
<td>Hospital P &amp; T</td>
<td>Clinical efficacy</td>
<td>Internal mailings</td>
<td>Physicians</td>
<td>Experts</td>
<td>N/A</td>
<td>Activated Protein C for Severe Sepsis in Ontario: An Evidence-Based Policy Proposal</td>
</tr>
<tr>
<td></td>
<td>Safety</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hospital P &amp; T Recommend for Xigris</td>
</tr>
<tr>
<td></td>
<td>Cost</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CED-CCO</td>
<td>Clinical value vs. standard of care</td>
<td>Internet</td>
<td>Manufacturer</td>
<td>Experts</td>
<td><a href="http://www.health.gov.on.ca/english/providers/program/drugs">http://www.health.gov.on.ca/english/providers/program/drugs</a></td>
<td>Recommend for Imatinib. 2007</td>
</tr>
<tr>
<td></td>
<td>Interchangeability of generic drug products</td>
<td></td>
<td>Physicians</td>
<td>Lay members</td>
<td><a href="http://www.health.gov.on.ca/english/providers/program/drugs/how_drugs_apprfunding_cco.html">http://www.health.gov.on.ca/english/providers/program/drugs/how_drugs_apprfunding_cco.html</a></td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>Decision Making Criteria</td>
<td>Forms of Publicity</td>
<td>Who Can Access Appeals Mechanism</td>
<td>Committee Members</td>
<td>Websites Reviewed</td>
<td>Documents Reviewed</td>
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<td>----------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>West Midland PCT Exceptional Drug Review</td>
<td>Based on NICE guidance (when available)</td>
<td>Internet</td>
<td>Individual Funding Requests</td>
<td>Experts</td>
<td>Commissioining Policy for Infertility Services within Birmingham For Birmingham Primary Care Trusts. 2006, Birmingham East and North NHS</td>
<td>Policy for Management of Requests to Commission Services &amp; Treatments Outside of the PCT’s Agreed Commissioning Portfolio</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Enzyme replacement therapy: a document prepared for West Midlands PCTs to support the development of a commissioning policy for the treatment of Gaucher's Disease, Fabry's Disease &amp; Mucopolysaccharidosis Type 1</td>
</tr>
</tbody>
</table>
Table 3. Stakeholders Involved in Decision Making

<table>
<thead>
<tr>
<th>Committee Name</th>
<th>Number of Members</th>
<th>Type of Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEDAC</td>
<td>13</td>
<td>• Health professionals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Public (added in April 2006)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Academics</td>
</tr>
<tr>
<td>IBC</td>
<td>24</td>
<td>• Health professionals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Public</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Academics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ministry reps (from health &amp; finance)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hospital managers</td>
</tr>
<tr>
<td>NICE</td>
<td>3 committees</td>
<td>• Members of the NHS (including Health professionals)</td>
</tr>
<tr>
<td></td>
<td>A- 24</td>
<td>• Patient and care organizations</td>
</tr>
<tr>
<td></td>
<td>B- 29</td>
<td>• Academics</td>
</tr>
<tr>
<td></td>
<td>C- 29</td>
<td>• Pharmaceutical and medical devices industries</td>
</tr>
<tr>
<td>PBAC</td>
<td>18</td>
<td>• Health professionals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Public</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Academics</td>
</tr>
<tr>
<td>US State Medicaid Pharmacy Committee</td>
<td>12</td>
<td>• Medicaid staff members</td>
</tr>
<tr>
<td>CED</td>
<td>16</td>
<td>• Ministry of health reps</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Health professionals (Physicians &amp; pharmacists)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Public (added in March 2007)</td>
</tr>
<tr>
<td>Toronto Hospital P &amp; T Committee</td>
<td>No less than 11</td>
<td>• Healthcare staff</td>
</tr>
<tr>
<td>West Midlands Exceptional Drug Panel</td>
<td>3</td>
<td>• Health professionals (Physicians/experts)</td>
</tr>
</tbody>
</table>

3.3 Sampling

3.3.1 The Cases

I selected six drugs that were expensive, genomic drugs. However, I wanted to compare different types of expensive drugs in order to understand if drug type affects reimbursement decisions. Initially, three categories were chosen, based on
the government committees’ recommendation criteria. I selected six drugs, in three categories, as follows;

<table>
<thead>
<tr>
<th>Category # 1 Two Orphan Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs that are used to treat less than 200,000 individuals affected by the disease [272]</td>
</tr>
<tr>
<td>1. Cerezyme (imiglucerase (systemic))</td>
</tr>
<tr>
<td>• Reduces and in some cases reverses Type 1 Gaucher’s disease</td>
</tr>
<tr>
<td>2. Fabrazyme (agalsidase beta)</td>
</tr>
<tr>
<td>• Used in the treatment of Fabry’s disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category # 2 Two life saving drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs that directly save a person from death</td>
</tr>
<tr>
<td>1. Xigris (drotrecogin alfa (activated))</td>
</tr>
<tr>
<td>• Used in the treatment of severe sepsis</td>
</tr>
<tr>
<td>2. Glivec (Imatinib mesylate)</td>
</tr>
<tr>
<td>• Used in the treatment of chronic myeloid leukemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category # 3 Two Quality for Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs that improve life but are not life saving</td>
</tr>
<tr>
<td>1. Remicade (infliximab)</td>
</tr>
<tr>
<td>• Used in the treatment of rheumatoid arthritis</td>
</tr>
<tr>
<td>2. Gonal F (Follitropin alfa)</td>
</tr>
<tr>
<td>• Used in the treatment of infertility</td>
</tr>
</tbody>
</table>

Category 1 Orphan Drugs

Cerezyme (imiglucerase (systemic)), an orphan drug, was developed using recombinant DNA from the enzyme glucosylceramidase. This drug is used to reduce the symptoms of, and, in some cases, reverse the outcomes of Type 1 Gaucher’s disease. Gaucher’s disease is a lipid storage disease which is an
autosomal recessive disorder caused by a deficiency in glucocerebrosidase [273]. This results in the toxic accumulation of glucocerebroside throughout the body and causes skeletal deterioration, blood abnormalities, liver and/or spleen enlargement, and low white cell count [274]. In 1994, the FDA granted the Genzyme Corporation market approval for Cerezyme. Today, Cerezyme is used in more than 70 countries to treat Gaucher’s disease [275]. The cost of this drug has been estimated at $70 000 US to $550 000 US per year per individual (depending on body weight) [276].

In Canada, Cerezyme was marketed prior to CEDAC. Drug funding decisions of Cerezyme (and all drugs not administered in the hospital setting) were and continue to be made provincially. For example, in Ontario, the Ontario Gaucher Review Committee reviews the on-going use of Cerezyme for patients already on Cerezyme and any new patients on Cerezyme living in Ontario. The committee, founded in the early 1990’s, is made up of eight physicians and pharmacists, and meets every six months. It submits its review to the Ministry of Health in Ontario, which then pays for the drug in the approved patients. Initially, Ceredase was available under the Special Access Program (SAP). Ceredase, produced from human placental tissue, was phased out when Cerezyme, produced using recombinant DNA technology (using mammalian cell cultures), was introduced. Currently, Cerezyme is the only drug approved and sold in Canada for this indication [215].

In England, drug funding decisions of Cerezyme were made by each Primary Care Trust (PCT). Cerezyme was used and part of the 33 drugs budgeted for by the
National Specialist Commissioning Advisory Group (NSCAG) from April 2005 – April 2008. However, the commissioning group did not include additional funds for the PCTs for the provision of these drugs [225, 277]. Cerezyme has a prevalence of 270 people with an estimated incremental cost-effectiveness ratio (ICER) of £391,244. A feasibility study for the appraisal of Cerezyme (considered to be an ultra orphan drug) was conducted by a group taken from NICE’s appraisal committee [230]. To date, no recommendation has been made by NICE regarding Cerezyme and funding decisions continue to be made by individual PCTs. For example, in the West Midlands, decisions are made on a case by case basis by the Exceptional Drug Review Committee.

In Australia, drug funding decisions are made nationally through PBAC. Cerezyme was made available through the Life Saving Drug Program [278]. The Therapeutics Goods Administration (TGA) has published “Guideline for the Treatment of Gaucher Disease”[279].

In Israel, Cerezyme was available prior to the establishment of the IBC. Drug funding decisions prior to 1995 were made by the Ministry of Health. Currently, the national budget provides funding for ERT to the sick fund through the health basket for severe treatments [257].

The United States established an Orphan Drug Act on January 4, 1983. This act defines orphan diseases based on a prevalence of less than 200,000 individuals. It
allows for assistance in the development protocol to research design. Additionally, it provides tan credit for clinical research conducted in this area, market exclusivity and funding grant. It also enables accelerated approval and a Parallel Track Program and Treatment INDs for access to unapproved drugs [266]. Within the Medicaid system, drug funding decisions are made federally. However, individual states have the ability to restrict the use of drugs. In one State Medicaid P & T Committee, Cerezyme was funded without restrictions.

**Fabrazyme** (*agalsidase beta*) was developed using recombinant human DNA from the enzyme $\alpha$-galactosidase A [280]. Fabry’s disease is an “X- linked recessive disorder resulting from deficient lysosomal enzyme, $\alpha$-galactosidase” [281], which is used to clear cells known as globotriaosylceramide (GL-3) from the body. This deficiency results in the accumulation of GL-3, which causes cell damage. The cells which are most affected by this accumulation are those located in the kidneys, heart, skin and brain, and therefore eventually results in life-threatening problems. An estimated 1 in 40 000 males has Fabry’s disease [282]. Genzyme Corporation is the producer of Fabrazyme, which was approved in April 2003 in the US. Today, Fabrazyme is approved in the 15 European Union countries as well as Iceland, Norway, New Zealand, Australia, and Israel to treat Fabry’s disease [283]. The cost of this drug has been estimated at $303,147 per patient per year [284].
In Canada, Fabrazyme was reviewed by CEDAC and their recommendation was against the funding of this drug. However, each province must make its own individual formulary decision.

In England, Fabrazyme has a prevalence of 200, with an ICER of £203,009. As of Oct 21, 2003, no general guidance has been provided to the PCTs on the treatment of Fabry’s disease [285]. Therefore, much like Canada, there is variation across regions for access to this drug. Fabrazyme was used and was part of the 33 drugs budgeted for by NSCAG from April 2005 – April 2008. However, the commissioning group did not include additional funds for the provision of these drugs [225, 277]. To date, no recommendation has been made by NICE regarding Fabrazyme and funding decisions continue to be made by individual PCTs. For example, in the West Midlands, decisions are made on a case by case basis by the Exceptional Drug Review Committee.

In Australia, drug funding decisions are made nationally through PBAC. Fabrazyme was available through the Life Saving Drug Program [278]. In Israel, Fabrazyme was recommended by the IBC for the inclusion in the basket and has been part of the basket since 2002. In the United States, within the Medicaid system, drug funding decisions are made federally; however, individual states have the ability to restrict the use of drugs. In one State Medicaid P & T Committee, Fabrazyme was funded with restrictions.
Category 2 Life Saving Drugs

Xigris (drotrecogin alfa (activated)) is an example of a genomic therapeutic life-saving drug. It is a recombinant form of human Activated Protein C, which is used in severe cases of sepsis that would otherwise result in death [286]. Severe sepsis affects approximately 28,000 Canadians, 30-50% of whom will die. When Xigris is used for people affected with high risk sepsis, the number of lives saved is 125 per 1000 [287]. Currently, Xigris is available in the United States, Europe and Canada [288]. This drug, made by Eli Lilly and Company, became available in 2001 [289]. This drug is estimated at $6,800 USD per four day course of treatment [290].

In Canada, Xigris is administered within the hospital setting and, as such, decisions to fund the drug are made by individual hospital formularies. In February 2003, the Council for Academic Hospitals of Ontario’s (CAHO) [formerly the Ontario Council of Teaching Hospitals (OCOTH)] Drugs and Therapeutics Committee published a report on Xigris. This committee develops and implements a common formulary between all hospitals in Ontario [291]. This publication formed the basis of each hospital’s decision regarding Xigris [287].

In England, NICE recommended the use of Xigris in 2004 [292]. In June 2002, Australia’s PBAC made a positive recommendation for the listing of Xigris for treatment of severe sepsis [294]. In 2006, Israel recommended Xigris for inclusion in the health basket. They took into account drug benefits, cost-benefit analysis, safety and efficacy [293]. In Israel the IBC recommended the use of Xigris in 2006.
In the US, Xigris is the only medical product designated as a new technology by the CMS. By receiving new technology status, Xigris qualifies for special payment under a law enacted in 2000. Under the new law, hospitals using the drug for Medicare patients from October 2002 and on are eligible for additional reimbursement, up to a maximum of $3400 [295-297].

**Glivec** (Imatinib mesylate) is a life-saving drug used in the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumour (GIST) [298]. It is the first in a new class of drugs called signal transduction inhibitors, which block signals preventing cell expression in the BRC-ABL protein, thereby reducing the production of white blood cells [299]. Eighty-nine percent of newly diagnosed patients with CML have an estimated survival rate of 5 years when administered Glivec [300]. Glivec costs approximately $3215-4823 US per patient per month [301]. This drug is sold by Novartis and is available in a number of countries, including the US, Korea, the UK and Brazil [302].

In **Canada**, decisions for cancer drugs are currently made by individual provincial cancer agencies. For example, in Ontario, Cancer Care Ontario (CCO), which recently came under the auspices of the Committee to Evaluate Drugs (CED), makes reimbursement recommendations to the Executive Officer in Ontario. Recently they have established the Joint Oncology Drug Review (JODR). In the
case of Glivec, the CED recommended it for listing on the Ontario formulary for the treatment of both CML and GIST [303].

In *England*, NICE made its initial recommendation to fund Glivec in October 2002; it has been reviewed since then, in 2006 [304]. In *Australia*, PBAC recommended the listing of Glivec for treatment of CML and GIST in June 2003, under section 100 authority (i.e., the special authority program) [301]. In *Israel*, the drug was recommended for inclusion in the health basket in 2004 for the treatment of CML and GIST [305]. In the *United States*, the FDA approved Glivec in 2001 [306, 307].

**Category 3 Quality of Life Drugs**

*Remicade* (infliximab) is used for the treatment of rheumatoid arthritis (RA) and was approved by the US Food and Drug Administration in 1999 [308]. It is a biological response modifier, or TNF blocker, which works by turning off parts of the immune system that are believed to be involved in this condition [309]. In the case of RA, it helps stop joint damage which has already begun, as well as prevent joint damage. This drug costs $11 000 US per patient per year and is manufactured by Centocor Pharmaceuticals [310]. Over 1 million patients have been treated with Remicade worldwide for rheumatoid arthritis [311]. It is also used in the treatment of psoriatic arthritis, Crohn’s disease in adults, pediatric Crohn’s disease, ulcerative colitis, plaque psoriasis and ankylosing spondylitis [312].

In *Canada*, funding of Remicade varies by province, and, to date, CEDAC has not reviewed the drug. The CDR has published a review of the drug which indicated a
70% improvement in symptoms; however it did not meet the cost-effectiveness criteria [313].

In England, Remicade was recommended for the treatment of RA in October 2007 [314]. In Australia, in March 2006, PBAC recommended Remicade for the treatment of psoriatic arthritis [315]. In Israel, the IBC recommended Remicade for inclusion in the basket for the treatment of arthritis in 2002 [316].

In the US, Medicare covers Remicade under Part A - i.e., for hospital outpatients, and under Part B - i.e., in doctors offices. However, it does not cover Remicade when provided by home infusion companies or retail pharmacies and Part B. Medicaid covers Remicade, but coverage may require prior authorization or may be limited to certain treatment settings [317]. Medicare, Medicaid and commercial plans have a demonstrated history of covering this drug [318].

**Gonal F** (*Follitropin alfa*) is a genetically engineered follicle stimulating hormone used to treat fertility problems [319], which affect one in six couples [320]. It is a gonadotropin synthetic follicle stimulating hormone (FSH) which helps in the development of eggs in the ovaries. Gonal-F is manufactured by Serono and costs $1062.00 US per 600 iu /ml (1 kit) [321].
Gonal-F is different from the other study drugs in that it was necessary to consider fertility treatment more generally. Gonal-F, when funded, is generally included in the funding of in-vitro fertilization (IVF) treatment.

In Canada, fertility treatment is partially funded in two Canadian provinces (Ontario and Quebec). In England, Gonal-F is funded to varying degrees, depending on the PCT. In Australia, PBAC approved Gonal-F for use in March 2000. In the US, fertility treatments are not publically funded, but Gonal-F was approved in 1997 by the FDA.

**3.3.2 The Participants**

I selected participants based on their experience and knowledge regarding the research questions (i.e., purposeful sampling). This method is appropriate for small studies, as randomized sampling would require a massive number of interviews to adequately represent the groups needed to answer the research questions [322]. Thus, key individuals, based on their anticipated ability to deal with the research questions, were interviewed.

Fifty-six interviews were conducted with members of governmental advisory committees/academics, representatives of drug companies, doctors and patient groups as related to the six specific drugs detailed above (See Table 4 below). Please note that academics were also interviewed (specifically, those academics that studied NICE) as a result of snow ball sampling.
Table 4. Stakeholders as Related to Each Drug Case

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Drug manufacturers</th>
<th>Committees</th>
<th>Patient Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fabrazyme</td>
<td>Genzyme</td>
<td>• CEDAC</td>
<td>• Canadian Fabry Association</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PBAC</td>
<td>• Canadian Organization for Rare Diseases (CORD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• IBC</td>
<td></td>
</tr>
<tr>
<td>Cerezyme</td>
<td>Genzyme</td>
<td>• PBAC</td>
<td>• National Gaucher foundation of Canada</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• CORD</td>
</tr>
<tr>
<td>Xigris</td>
<td>Eli Lilly</td>
<td>• NICE</td>
<td>• ICU doctors *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PBAC</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• US P &amp; T</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hospital formulary</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• IBC</td>
<td></td>
</tr>
<tr>
<td>Glivec</td>
<td>Novartis</td>
<td>• NICE</td>
<td>• Cancer Advocacy Coalition of Canada</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PBAC</td>
<td>• Canadian Cancer Society</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• US P &amp; T</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CED-CCO</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• IBC</td>
<td></td>
</tr>
<tr>
<td>Remicade</td>
<td>Centocor Pharmaceuticals.</td>
<td>• NICE</td>
<td>• Arthritis Society</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PBAC</td>
<td>• Canadian Arthritis Patient Alliance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• US P &amp; T</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• IBC</td>
<td></td>
</tr>
<tr>
<td>Gonal-F</td>
<td>Serono Australia</td>
<td>• PBAC</td>
<td>• Infertility Awareness Association of Canada (IAAC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• IBC</td>
<td>• ACCESS Australia’s National Infertility Network</td>
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<td></td>
<td></td>
<td></td>
<td>• Infertility Network UK</td>
</tr>
</tbody>
</table>

*patient groups do not exist for this drug as it is administered in emergent cases; thus, we interviewed doctors as their proxy.
Initial contact was made with individuals (i.e., advisory board members, patient groups and industry) related to the six study drugs either in-person, by email, or by phone. If a response was not obtained, two more attempts were made (See Appendix 2). Snow ball sampling was also used. Here participants were asked to suggest other potential interviewees. Therefore, in addition to interviewing participants from the aforementioned groups, academics were also interviewed. I continued sampling until the point of saturation, i.e., there was reiteration of the same ideas [323]. As such, there was no formal calculation of sample size.

3.3.3 The Documents

Thirty-two documents related to reimbursement decisions were sampled and analyzed in order to explore issues of fairness related to reimbursement decisions surrounding three drug categories. For the most part, documents were obtained in electric format from government, industry and patient group websites. However, a number of documents were not publicly accessible (particularly in Israel and from the hospital P & T committee) and were obtained through formal letters of request to the agency in question. For a complete list of the documents sampled, please refer to Appendix 3.

3.4 Data Collection

In this research, data were derived from two sources: documents and interviews, compiled from September 2004 – December 2008. I collected thirty-two publicly accessible and secure (i.e., some documents required formal requests) documents regarding the relevant priority setting decisions. This includes documents posted on
government, industry and patient web sites, as well as any press releases.

Rationales that were not available through the web were obtained through direct contact with the agency in question. Some rationales were not available, particularly those from the US P & T committee, as it was prior to their establishment.

I conducted semi-structured interviews with fifty-six key informants. I endeavored to conduct face-to-face interviews, or at least one-on-one telephone interviews whenever possible. Interviews were approximately 30-60 minutes in length. After consent was obtained, I continued with a series of open-ended questions (See Appendix 4). At the end of the interview, participants were asked if they had any questions or comments, and whether they knew other individuals who would be appropriate to interview. All of the interviews were audio taped and transcribed. The data was organized using NVivo, a data management software program.

The initial interview guides were developed based on the literature [59, 66, 174,324,325, 326] the conceptual framework of 'accountability for reasonableness', and the aims of this study (Appendix 4). The questions were designed around priority setting of expensive biopharmaceuticals and issues of fairness and legitimacy. A draft was submitted to my advisory committee for feedback. The revised version was used for the subsequent interviews. Additionally, to facilitate the pursuit of emerging themes, interview guides were revised throughout collection and analysis. For example, questions surrounding priority setting and innovation were refined.
3.5 Data Analysis

3.5.1 Coding

The interviews were analyzed using a modified thematic analysis. First, the data were read to achieve a good working knowledge of the content -- sometimes called ‘immersion’ [327]. Second, portions of data that related to similar concepts or ideas were identified and labeled -- sometimes called open coding [322]. 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 to ensure consistency and comprehensiveness. For example, I compared the information labeled as ‘access’ to ensure that I was coding this idea consistently. Inconsistencies were corrected through either re-coding data portions into more appropriate codes, or they were identified as areas of further analysis. Fourth, concepts that emerged were organized under overarching themes - - sometimes called axial coding. These themes included the four conditions of ‘accountability for reasonableness’ [322]. For example, ideas relating to access of rationales were grouped under the theme of ‘publicity.’ Fifth, primary themes were established and related to the other themes.

During each step, analytic memos were recorded on all observations [268]. For example, I would comment on the location, the manner of the respondent and the way I felt the interview progressed. Memos are an essential part of research and
allow the researchers to reflect on and analyze the research methods and findings [322].

3.5.2 Evaluation

The description was evaluated against the four conditions of 'accountability for reasonableness' (See Box 1 below, in Section 3.7). This involved comparing how reimbursement decisions are actually made against the framework which describes how decisions should be made. All emerging themes were compared with this framework. After evaluating the interviews from key informants (committee members, academics, manufacturers and patient groups), key lessons and areas of improvement emerged from the data [328].

For example, industry often has access to an appeals mechanism. Other stakeholders, namely the public, have no such access. Therefore, according to the framework’s *appeals & revisions* condition, this was identified as an area of improvement.

3.5.3 Validity

The issue of validity was addressed in three ways. First, different data sources were used, including literature, documents and interviews, which allowed for examination of the emerging concepts from different perspectives - sometimes called triangulation [327]. For example, the issue of insufficient data for making a reimbursement decision arose in the interviews. This notion was further supported
in a recent study by Gallego et. al. [69]. Second, codes and themes were developed with other team members as a check on bias. I frequently discussed themes and codes with my supervisor and other Ph.D. students. 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 committee members, research fellows and other Ph.D. students. These meetings provided an opportunity to discuss and explain the rationale behind the codes. While consensus was achieved for most of the codes and themes, some concepts were coded under different themes as a result of the discussions during these sessions.

3.6 Conceptual Framework

My research project employed an explicit conceptual framework -- ‘accountability for reasonableness’ (AFR) [16, 172]. It is an ethical framework used for the evaluation and improvement of priority setting. AFR is based on theories of justice and emphasizes democratic deliberation and provides guidance for priority setting [171, 329]. It was developed by Daniels and Sabin to improve priority setting in health care and ensure that “rationales for important limit-setting decisions…be publicly available”[16]. An institution’s priority setting decisions may be considered legitimate and fair if they satisfy four conditions: relevance, publicity, revisions and enforcement (See Table 1). I used a modified version of AFR based on Reeleder’s research, which suggested the use of leadership instead of enforcement (See Box 1 below) [62]. I identified areas of compliance with these four conditions as lessons of best practice, while areas of non-compliance were identified as opportunities for improvement. This framework has already been used to guide research [17, 26, 62,
69, 75, 175-178, 180, 190, 328, 330-332] and to provide practical guidance to decision-makers on ways to improve the priority setting processes and operationalize the idea of fairness within the priority setting process.

Box 1 Conditions of ‘Accountability for Reasonableness’

<table>
<thead>
<tr>
<th>Accountability for Reasonableness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Relevance: Priority setting decisions must be based on rationales that rest on evidence, reasons, and principles that stakeholders in the context (managers, clinicians, patients, and consumers in general) can agree are relevant to deciding how to meet the diverse needs of a covered population under necessary resource constraints.</td>
</tr>
<tr>
<td>2. Publicity: Limit-setting decisions and their rationales must be publicly accessible.</td>
</tr>
<tr>
<td>3. Revisions and Appeals: There is a mechanism for challenge and dispute resolution regarding limit-setting decisions, including the opportunity for revising decisions in light of further evidence or arguments.</td>
</tr>
<tr>
<td>4. Leadership: Context-specific leaders are responsible for ensuring that the first three conditions are met.</td>
</tr>
</tbody>
</table>

3.7 Research Ethics

This project was approved by the University of Toronto Human Subject Review Committee. The consent form, along with a description of my research, was sent via email to respondent prior to the interview. The consent form was reviewed with each participant at the onset of the interview and all questions and concerns were addressed. During in-person interviews, consent forms were signed and a copy was given to the participant. When interviews were conducted over the phone, the signed consent form was either faxed or sent electronically. All participants agreed to participate, and written informed consent was obtained prior to the interview. All
data is confidential and stored in a secure office. Anonymity of participants was protected.
4.0 RESULTS

This chapter describes findings from my six case studies. My main finding is that while a number of values were considered by committees when making reimbursement decisions, committees tended to focus on values of evidence, effectiveness and efficiency, and not the full range of relevant values. Thus, these contexts did not fully meet the conditions of legitimacy and fairness. This study has demonstrated that in order to create a fair and legitimate drug reimbursement process, we need to ensure the incorporation of a wide range of values, and the involvement of multiple stakeholder groups within the deliberative and appeals/revision processes.

This chapter is divided into seven sections; 1) a description of decisions for each drug by each country, 2) a comparison of: final funding recommendations, evidence used to assess cost-effectiveness and effectiveness, and definitions of values used by committees in their recommendations, 3) a comparison of the values used by each committee based on published rationales, 4) a discussion of the values used by each committee and the participants’ perceptions based on interviews conducted, 5) an evaluation of the decision making process using the framework of AFR, 6) the role of innovation in healthcare sustainability and 7) results section recapitulation. Each case is described using interviews and documents. Verbatim quotes are included to illustrate the specific views of participants. Additionally, there are eight Reflection textboxes highlighted throughout this chapter. They identify some common themes which appear throughout the results, including the rule of rescue,
patient access to the decision-making process, alternative mechanisms for accessing drugs, the impact of meeting cost-effectiveness, notions of medical necessity, the impact of technology and innovation, the impact of insufficient evidence on decision making, and the extent of publicity that is required. The themes in these text boxes will be further explored in Chapter 5, the Discussion.

4.1 Description of decisions for each drug by country

4.1.1 Canada

In Canada drug funding recommendations are made by a number of different bodies including CEDAC, provincial formularies, provincial cancer agencies, and hospital P & T committees. Each of the study drugs will be discussed according to the body that reviewed the particular drug.

Orphan Drugs

_Cerezyme_

In 1992, the drug had not yet received market approval from Health Canada and was accessed through the Special Access Program (SAP). This program provides access to non-marketed drugs for practitioners treating patients with serious or life-threatening conditions when conventional therapies have failed, are unsuitable, or unavailable. Cerezyme was not reviewed by CEDAC in 1992 because the CDR had not been established at that time. Reimbursement decisions for this drug were made by individual provincial formularies and varied by province. Obtaining reimbursement required much negotiation between healthcare professionals, government and public advocate appeals. For example, in Ontario, the Minister of
Health rejected funding of Cerezyme because of the drug’s inability to meet cost-effectiveness criteria. This decision was publicly criticized by the National Gaucher Foundation of Canada in 1993. According to one member of the foundation, the Minister of Health’s decision changed because of the media pressure the National Gaucher Foundation applied:

“I embarrassed the government at that stage. We had 15 minutes on Canada AM, we did 3-4 minutes on the national news. We did a whole newspaper blitz basically embarrassing the government totally. … I was hospitalized because of the disease … all of this came out in the press … we had a meeting in a small meeting room at X Hospital, they wheeled me in with all the tubes and poles and all the stuff and the Deputy Minister, Assistant Deputy Minister was there…, we had another meeting and two weeks later they funded us.”

According to Clarke et. al., the Minister of Health subsequently applied the rule of rescue, a principle which values rescuing an endangered life, and approved a provincial program for the reimbursement of enzyme replacement therapy (ERT) for Gaucher’s disease. In December 2008, Alberta established an orphan drug strategy. Eligible individuals will pay premiums and make co-payments for the drugs.

Reflection 1

<table>
<thead>
<tr>
<th>The Rule of Rescue</th>
</tr>
</thead>
<tbody>
<tr>
<td>How is the rule used? Is there tension between the value of efficiency and the value of saving a life?</td>
</tr>
</tbody>
</table>

**Fabrazyme**

In 2004, CEDAC recommended against the funding of Fabrazyme. The rationale for their negative recommendation was based on 1) insufficient evidence of benefit based on randomized control trials (RCTs) and observational data, 2) inability to meet cost-effectiveness criteria using conventional methods of quality adjusted life years (QALYs), and 3) equity reasons (which typically refers to whether people are
able to access what they need) defined by CEDAC in their review in relation to drugs for other diseases which fail to meet cost-effectiveness criteria that are not recommended for reimbursement (i.e., precedent). A committee member articulated that, in Canada, it was not clear that orphan drugs should be prioritized differently than drugs used for the treatment of common diseases:

“We didn’t have a separate process for reviewing rare drugs and…no one had told us that we needed to prioritize drugs for rare conditions differently.”

Patients argued against CEDAC’s decision and complained because they were not included in the process,

“The Common Drug Review does not allow any public input. Does not allow any public dialogue or communication. So we were very, very frustrated and so we, a group of Fabry’s patients, went to the Common Drug Review’s office and said we’d like to have a meeting with the Chair of the Canadian Expert Drug Advisory Committee …We were not successful in getting a meeting with him but we were successful in getting a meeting with … the head of CCOHTA [Coordinating Office for Health Technology Assessment] at that time which is now called CADTH [Canadian Agency for Drugs and Technologies in Health]...And so how can these groups work in isolation when they’re supposed to be representing patients? And in fact the general public who in fact pay the bills for public health care?”

Reflection 2

<table>
<thead>
<tr>
<th>Access to the Decision-making Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who should have “access” to the decision making process?</td>
</tr>
</tbody>
</table>

Main Finding

Although neither Cerezyme nor Fabrazyme were listed on any provincial formulary, some of the provinces decided to fund both drugs through alternative mechanisms - this differed from province to province. The former drug, Cerezyme, was typically funded through SAPs and, in the case of Ontario, was funded based on the rule of rescue. The latter drug, Fabrazyme, was funded through a post-market study, which
was jointly funded by the federal-provincial-territorial governments and industry (i.e.,
two biopharmaceutical companies including Genzyme). Both invested over $100
million for a three year study on Fabry’s disease treatment. Please refer to Table 4
below for a detailed comparison of provincial reimbursement decisions regarding
both Cerezyme and Fabrazyme.

**Reflection 3**

**Alternative Mechanism for Accessing Drugs**

Should some drugs be accessed through a different mechanism? Does rarity alone
warrant a different mechanism for access to orphan drugs (ODs)? What would be
some key considerations of an alternative mechanism?

Table 5. Reimbursement of Cerezyme and Fabrazyme in Canada

<table>
<thead>
<tr>
<th>Formulary</th>
<th>Cerezyme</th>
<th>Fabrazyme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Listed on Formulary</td>
<td>Other Means of Access</td>
</tr>
<tr>
<td>Alberta Health &amp; Wellness</td>
<td>No</td>
<td>Special authorization process</td>
</tr>
<tr>
<td>BC Pharmacare</td>
<td>No</td>
<td>No exception drug status</td>
</tr>
<tr>
<td>Manitoba Pharmacare</td>
<td>No</td>
<td>Exception Drug Status Benefit</td>
</tr>
<tr>
<td>New Brunswick Prescription Drug Program</td>
<td>No</td>
<td>Special Authorization</td>
</tr>
<tr>
<td>Newfoundland &amp; Labrador Prescription Drug Program</td>
<td>No</td>
<td>Special authorization process may cover it</td>
</tr>
<tr>
<td>North West Territories Health Benefits Program</td>
<td>No</td>
<td>Exception Drug Coverage</td>
</tr>
<tr>
<td>Nova Scotia Pharmacare</td>
<td>No</td>
<td>Exception Drug Status process</td>
</tr>
<tr>
<td>Nunavut</td>
<td>No</td>
<td>Exceptional</td>
</tr>
</tbody>
</table>
Lifesaving Drugs

**Xigris**

In 2003, Xigris was administered within the hospital setting and funding decisions were made by individual hospital Pharmacy and Therapeutics (P & T) committees. In February of that year, the Council for Academic Hospitals of Ontario’s (CAHO) Drugs and Therapeutics Committee recommended that Xigris be funded -- this formed the basis of each Ontario hospital’s decision. CAHO’s recommendation was based on three considerations: *benefit of therapy, harm of therapy, and is it worth it?* (i.e., the term they used in the report which referred to cost-effectiveness). To assess benefit, CAHO used the clinical trial data which demonstrated that treatment with Xigris reduced mortality when compared to placebo. To assess harm, CAHO looked at the incidence of adverse events, most notably haemorrhage (an increase
from 3% to 4.5%, compared to placebo). In their assessment of is it worth it? CAHO looked at cost per life saved.

**Glivec**

Coverage of cancer drugs in Canada depend on the type of cancer drug - i.e., oral or transfused. As Glivec is an oral drug, the provinces and territories typically provide community based coverage of this drug as supplementary benefits through provincial/territorial drug benefit plans. Table 5 below illustrates the different funding mechanisms for this drug. I have focused on Ontario as its rationale for listing Glivec was available. The other provinces generally had clinical guidelines, but no rationales, available.

In 2007, the Ontario Committee to Evaluate Drugs- Cancer Care Ontario Subcommittee (CED-CCO) recommended the reimbursement of Glivec for the treatment of chronic myeloid leukemia (CML). According to the published recommendation, their decision was based on the following: 1) improved survival: more than 90% of patients were still alive after 4.5 years of treatment, 2) cost-effectiveness: based on their assessment of the economic analysis, presented by the manufacturer, the CED-CCO found Glivec provided value-for-money (compared to alternative treatments), and 3) evidence: the CED-CCO found that the evidence, most notably the International Randomized Interferon versus STI571 (IRIS) study, demonstrated treatment of CML with Glivec provided a clinically significant benefit. This study was randomized, controlled and comparative in nature and was
considered by the committee to be of high quality. Glivec was approved and listed by all provincial cancer agencies across Canada for the treatment of CML.

**Main Findings**

Both Xigris and Glivec have demonstrated, through randomized clinical trials, the ability to save lives (e.g. Xigris) or improve survival (e.g. Glivec), and met the cost-effectiveness criteria. They were therefore approved for funding. Table 2 below illustrates the universal coverage of Glivec by all provinces. Typically it is funded through alternative mechanisms, such as Exceptional Drug Access Programs.

**Reflection 4**

<table>
<thead>
<tr>
<th>The Impact of Meeting a Cost Criterion (related to Reflection 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Should drugs that fail to meet strict cost-effectiveness criteria be included in public formularies? What about considerations of the total impact of the drug on the whole system (i.e., keeping people working and contributing taxes)?</td>
</tr>
</tbody>
</table>

Table 6. Cancer Funding Mechanisms for Glivec across Canada

<table>
<thead>
<tr>
<th>Province</th>
<th>Glivec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>Funding Mechanism</td>
</tr>
<tr>
<td>Alberta</td>
<td>Funded by Alberta Cancer Board’s Outpatient Cancer Drug Benefit Program</td>
</tr>
<tr>
<td>British Columbia</td>
<td>Funded by PharmaCare but provided through the BC Cancer Agency</td>
</tr>
<tr>
<td>Manitoba</td>
<td>Funded through exceptional drug status by Pharmacare Manitoba</td>
</tr>
<tr>
<td>New Brunswick</td>
<td>Funded through Special authorization by New Brunswick Prescription Drug Program</td>
</tr>
<tr>
<td>Newfoundland</td>
<td>Funded through Special Authorization by the Newfoundland and Labrador Prescription Drug Program</td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>Funded through Exception Status for Drug Assistance for Cancer Patients by Pharmacare Nova Scotia</td>
</tr>
<tr>
<td>Northwest Territories</td>
<td>Funded by limited use benefit administered by Alberta Blue Cross</td>
</tr>
<tr>
<td>Nunavut</td>
<td>Funded through Non-Insured Health Benefits (NIHB) or Extended Health Benefit program #1</td>
</tr>
<tr>
<td>Ontario</td>
<td>Funded through Ontario Drug Benefit Plan</td>
</tr>
<tr>
<td>Province</td>
<td>Glivec</td>
</tr>
<tr>
<td>--------------------</td>
<td>--------------------------------------------------------------</td>
</tr>
<tr>
<td>Name</td>
<td>Funding Mechanism</td>
</tr>
<tr>
<td>Prince Edward Island</td>
<td>Funded through Exception Drug Status (EDS) by Prince Edward Island Health Program Cancer Assistance Program</td>
</tr>
<tr>
<td>Quebec</td>
<td>Funded through Exceptional drug status by Régie D’assurance Maladie du Québec (RAMQ)</td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>Funded through Exception drug status by Saskatchewan Cancer Agency Alberta - Alberta Cancer Board</td>
</tr>
<tr>
<td>Yukon</td>
<td>Funded through Exception Drug Status by Chronic Disease Program or Pharmacare program</td>
</tr>
</tbody>
</table>

**Quality of Life Drugs**

*Remicade*

Prior to the approval of Remicade by Health Canada, patients accessed the drug through clinical trials or SAPs. Since the approval of the drug in 2001, Remicade is more difficult to access. In 2006, the Canadian Coordinating Office of Health Technology Assessment (CCOHTA) published a review of Remicade, which indicated a 70% improvement in symptoms; however it did not meet the cost-effectiveness criterion. Ontario’s CED has not reviewed Remicade, but Ontarians, through their physicians, may request coverage through the Exceptional Access Program (EAP) and Individual Clinical Review (ICR) on a case-by-case basis (formerly known as section 8). The program requires that the drug be clinically necessary (i.e., there must be a need). Remicade is one of the top 10 drugs requested in Ontario and 79.4% of requests are approved.

*Gonal-F*

Gonal-F was approved by Health Canada in 2007. As with all fertility treatments, Gonal-F is not generally funded in Canada. The exceptions to this are Quebec,
which offers a tax credit for treatment, and Ontario, which funds treatment for bilateral fallopian tube occlusion (which represents 1% of infertility problems). The unilateral decision not to publicly fund Gonal-F, according to Hughes et. al., is based on questions of medical necessity and clinical effectiveness.

Reflection 5

<table>
<thead>
<tr>
<th>Notions of Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Why are some treatments considered medically necessary while others are not?</td>
</tr>
</tbody>
</table>

**Main Findings**

The Government hesitates to fund drugs that are perceived as only improving QOL or medically unnecessary. In the case of Remicade, formulary listings vary by province. However, the provinces that did not list Remicade on their formulary funded the drug through alternative mechanisms – these mechanisms differed from province to province. Generally, a patient’s physician would need to apply for Exceptional Drug Status and decisions to reimburse the drug are made on a case by case basis. The exception to this is Régie de L’assurance Maladie du Québec, which has published a list of Exceptional Medications which are reimbursed, including Remicade (for the treatment of RA).

Table 6 below illustrates that in cases of negative listing decisions, alternative mechanisms, such as Special Authorization, exist. The three provinces that approved Remicade belong to the Atlantic Pharmacare Review Committee (APRC), i.e., New Brunswick, Northwest Territory (NWT), and Nova Scotia. These provinces have posted clinical guidelines, but not rationales for their listing decisions.
In contrast, Gonal-F is only partially funded on one provincial formulary, i.e., Ontario, while Quebec offers tax credits. No alternative funding avenues exist for this drug. Important to the case of Gonal-F, Canadian politicians and many citizens have historically considered fertility treatment to not be medically necessary. Thus, provinces feel no obligation to fund this treatment.

Table 7. Reimbursement of Remicade for RA in Canada

<table>
<thead>
<tr>
<th>Formulary</th>
<th>Remicade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Listed on General Formulary</td>
</tr>
<tr>
<td>Alberta Health &amp; Wellness</td>
<td>No</td>
</tr>
<tr>
<td>BC Pharmacare</td>
<td>No</td>
</tr>
<tr>
<td>Manitoba Pharmacare</td>
<td>No</td>
</tr>
<tr>
<td>New Brunswick Prescription Drug Program</td>
<td>Yes</td>
</tr>
<tr>
<td>Newfoundland &amp; Labrador Prescription Drug Program</td>
<td>No</td>
</tr>
<tr>
<td>North West Territories (NWT) Health Benefits Program (Non-Insured Health Benefits (NIHB) Program)</td>
<td>Yes</td>
</tr>
<tr>
<td>Nova Scotia Pharmacare</td>
<td>Yes</td>
</tr>
<tr>
<td>Nunavut Health Benefit Program</td>
<td>No</td>
</tr>
<tr>
<td>Ontario Drug Benefit Program</td>
<td>No</td>
</tr>
<tr>
<td>PEI Drug Cost Assistance Program</td>
<td>No</td>
</tr>
<tr>
<td>Régie de l'assurance maladie du Québec</td>
<td>No</td>
</tr>
<tr>
<td>Saskatchewan Drug Plan</td>
<td>No</td>
</tr>
<tr>
<td>Yukon Pharmacare (work together with Saskatchewan)</td>
<td>No</td>
</tr>
</tbody>
</table>
4.1.2 England & Wales

Orphan Drugs

*Cerezyme*

Each Primary Care Trust (PCT) was responsible for commissioning orphan drugs. Commissioning involved the assessment of needs, resources, and services, as well as the development of a strategic approach to allocate resources while meeting identified needs. The commissioning process involved determining priorities, purchasing appropriate services, and the subsequent evaluation of the process. Prior to 2004, PCTs automatically funded Cerezyme in England and Wales by convention. In 2004, the West Midlands region (which included 17 PCTs) decided against the funding of Cerezyme for Gaucher’s disease. The West Midlands Specialist Services Agency’s recommendation was based on cost-effectiveness and equity reasons (See Fabrazyme section below for details).

*Fabrazyme*

In 2002, with the arrival of Fabrazyme, the West Midlands region began to re-evaluate their funding of orphan drugs because they were concerned with the subsequent costs they would incur. Thus, the West Midlands Specialist Services Agency, in an attempt to decide whether to fund Fabrazyme, examined ethical, legal, and public perspectives, clinical data and cost-effectiveness data, and policy
considerations regarding the funding of orphan drugs. The West Midlands rejected the funding of Fabrazyme and Cerezyme (for new patients) based on: 1) the drugs’ inability to meet the cost-effectiveness criterion: the ICER score of ERT was too high to make it an efficient use of health services resources, and 2) equity reasons: a greater amount of patients would be deprived of treatments that were equally beneficial. This recommendation was contentious and many stakeholders were concerned, including: 1) patients, concerned with the obvious consequences of not being otherwise able to afford the drug, 2) Genzyme’s lawyers, who were concerned with the “legitimate commercial expectations”, and 3) politicians, who were concerned with variations in drug access across regions.

In 2004, the West Midlands Specialized Services Agency’s published a report on Enzyme Replacement Therapy (ERT). This report reviewed three ERTs, including Cerezyme and Fabrazyme, and considered: 1) Are there other factors besides cost-effectiveness that result in a greater imperative for treatment? 2) Given the limited evidence for these treatments, under what conditions would we fund these treatments? As part of the decision path for a National Policy on ERT, the report urged PCTs to consider a number of variables, including (though not limited to) propensity towards treatments, health inequalities, rule of rescue, significance of cost-effectiveness, and setting boundaries for treatment. When discussing the *rule of rescue*, the report required not only an acknowledgment of whether it should be given significant weight in funding decisions, but also required one to define a point of rescue that is reasonable.
In April 2005, the Department of Health (DH) subsequently decided to move commissioning for lysosomal storage disorders to a national level, i.e., the National Specialist Commissioning Advisory Group (NSCAG). While commissioning became a national responsibility, funding of these treatments remained a responsibility of individual PCTs. Ultimately the PCTs were forced to fund the drugs.

**Main Findings**

Prior to 2004, PCTs funded Cerezyme by convention. The 2002 West Midlands’ decision not to fund Fabrazyme resulted in public outcry and, ultimately, the Department of Health’s decision to move the locus of commissioning to a national level. This ultimately forced the PCTs to fund both Cerezyme and Fabrazyme. The eventual funding of both of these drugs demonstrates the ability of the public, media and industry to change decisions through political pressure, as well as the intrinsic value given to individuals (through the application of the *rule of rescue*), as demonstrated through the DH’s decision to fund treatments that clearly do not meet cost-effectiveness criteria.

**Lifesaving Drugs**

**Xigris**

In 2004, NICE recommended the funding of Xigris for patients with multiple organ failure. Their recommendation was based on: 1) clinical need, there are 21000 cases of severe sepsis per year in England and Wales, and the mortality rate is between 30%-50%, and 2) evidence of both clinical and cost-effectiveness. For the former, they considered evidence from RCTs, i.e., the PROWESS study and the
EVVA study. For the latter reason, they considered published studies, the manufacturer’s assessment, as well as unpublished abstracts. NICE also considered the technology (a condition that NICE assesses as part of their decision-making process). Xigris is a new treatment for severe sepsis using recombinant DNA technology.

**Glivec**

In 2002, NICE recommended the funding of Glivec for the treatment of CML in the chronic phase. Their recommendation was based on: 1) clinical need, as CML is one of the most common types of leukemia found in England and Wales, with approximately 600 new cases each year, and 2) evidence of clinical and cost-effectiveness. In the case of the former, they considered published RCTs (i.e., the IRIS trial) and case series. For the latter, they considered one published study, the manufacturer’s assessment, and the assessment group’s independent model. As one industry representative commented,

“You know Glivec was … considered by NICE as a cost-effective drug, it was something new for NICE because in the first time in their history they considered a drug like Glivec, a biotech… drug that’s cost-effective so it was really important.”

NICE also considered the types of technology. Glivec was the first in a new class of cancer drugs (i.e., signal transduction inhibitors).

**Main Findings**

Both Xigris and Glivec demonstrated, through randomized clinical trials, evidence of clinical and cost-effectiveness. They also met the clinical need component. Additionally, both drugs were considered to be new technologies and NICE discussed this in their guidance.
Reflection 6

<table>
<thead>
<tr>
<th>The Impact of Technology and Innovation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Should public drug funding agencies consider the innovative nature of the drug? If so, how should innovation be defined?</td>
</tr>
</tbody>
</table>

Quality of Life Drugs

Remicade

In October 2007, NICE recommended Remicade for use in patients with rheumatoid arthritis (RA), particularly in those that have a disease activity score (DAS) greater than 5.1, and have undergone trials with two disease-modifying anti-rheumatic drugs (DMARDs). Their recommendation was based on: 1) clinical need as RA affects 400,000 people in England and Wales, and 15% of these have severe RA, and 2) evidence of clinical and cost-effectiveness, including RCTs, published economic evaluations, and submitted economic evaluations (by manufacturer and assessment group). They also discussed the particular technology, i.e., Remicade was a new biologic which controlled pain and inflammation.

Gonal-F

In February 2004, NICE published a clinical guideline entitled “Assessment and treatment for people with fertility problems.” The guideline was designed to address the inequalities in access across the PCTs by setting a national standard of service for fertility treatments (including Gonal-F) across England and Wales. This was followed by the National Health Service’s (NHS) decision, in April 2005, to fund one cycle of in-vitro fertilization (IVF), including the drug Gonal-F. Concurrently, the Welsh Assembly Government announced that one cycle of IVF would be made
available to eligible patients in Wales by April 2005, and eligibility criteria for patients seeking IVF treatment were published in July 2005. In 2007, the Department of Health (DH) began funding a project to improve access to fertility treatment and encourage the implementation of NICE’s guidelines. In July 2007, the Minister of Health wrote a letter which reminded the PCTs of the recommendation to fund three full cycles of IVF, and that the DH would begin to monitor IVF provision and standardization across PCTs. In a survey conducted by the DH, in the autumn of 2007, entitled “PCT survey - provision of IVF in England”, only four PCTs were not funding IVF (due to temporary suspensions of service). This demonstrated progress since a 2006 DH survey recognized that 14 PCTs were not funding IVF.

The West Midlands region’s PCTs funded fertility treatment (including the use of Gonal-F) on a case by case basis, in accordance with the NICE clinical guidance. Some criteria include: maternal age (must be between 23-40), maternal weight (Body Mass Index of 19 – 30), no living children, a demonstration of failure to conceive for a period of 3 years duration, and not having undergone 3 cycles of treatment. Once these criteria are met, a maximum of 3 stimulated cycles of IVF treatment are provided.

**Main Findings**

England and Wales have recognized the importance of improving QOL and the medical necessity of fertility treatment, as illustrated through NICE’s recommendation to fund Remicade and the NHS’ commitment to fund fertility treatment, including Gonal-F.
4.1.3 Australia

Orphan Drugs

*Cerezyme*

In 1998, the PBAC decided that Cerezyme did not meet the cost-effectiveness criterion because of its high cost. However, they considered the drug to be clinically effective, i.e., it produces benefit in a defined population. Therefore, Cerezyme was reimbursed through the Life Saving Drug Program (LSDP). This program falls outside the Pharmaceutical Benefits Scheme (PBS) and is under the auspices of Department of Health and Aging Alternative Arrangement for Medicines. The provision for life saving drugs is part of a special non-statutory arrangement which began in May 1995 and developed from the former Act of Grace payment arrangements (administered by the Department of Finance under section 34A of the Audit Act 1901). The provision for high-cost life-saving drugs demonstrated the government’s recognition of the intrinsic value of the individual.

*Fabrazyme*

Just as in the case of Cerezyme, in 2000, PBAC decided that Fabrazyme failed to meet cost-effectiveness criteria because of its high cost. However, they considered the drug to be clinically effective, i.e., it produces benefit in a defined population. Therefore, Fabrazyme was reimbursed through LSDP.

*Main Findings*

Even though PBAC did not consider Cerezyme or Fabrazyme to be cost-effective, both were reimbursed through an alternative mechanism within the Department of Health and Aging, which was established in 1995. Both drugs’ inclusion in the public
formulary was based on PBAC’s assessment of these drugs as clinically effective; thus, they were recommended for funding through an alternative mechanism – the LSDP.

**Lifesaving Drugs**

*Xigris*

Xigris was reviewed by PBAC in June 2002 and it was recommended for funding in the treatment of severe sepsis. PBAC’s recommendation was based on severity, which is high risk of death defined by acute organ dysfunction of at least two organs or an Apache II score of at least 25.

*Glivec*

Similarly, Glivec was reviewed by PBAC in June 2003 and also recommended for funding in the treatment of CML and GIST. However, in the case of Glivec, the Commonwealth/State Highly Specialised Drugs Working Party (HSDWP) (a non-statutory body established in 1991 by the Australian Health Ministers Advisory Council) recommended to the PBAC the suitability of Glivec under the Highly Specialised Drugs (HSD) Program. This program falls under the National Health Act 1953, Section 100. The HSD Program was established in 1991 as a result of an initiative by the Australian Health Ministers’ Advisory Council. This initiative arose from concerns on the part of the States and Territories regarding the growing use of high cost drugs within the public hospital system. The drugs included in the HSD Program must: 1) be used for the treatment of chronic conditions, 2) require continuous specialized medical supervision, 3) be used for an identifiable patient
group, 4) have obtained market approval from the Therapeutics Goods Administration (TGA) and 5) have a high unit cost. Drug listing revisions are made on an ongoing basis by PBAC. PBAC considers both effectiveness and cost of the treatments proposed for subsidy relative to other therapies. PBAC`s recommendation for the funding of Glivec was based on “an acceptable but high cost-effectiveness ratio”, as well as the HSDWP’s recommendation.

**Main Findings**

Both Xigris and Glivec were approved by PBAC for reimbursement. In both instances the drugs were recommended on the basis of severity of disease, effectiveness, and acceptable cost-effectiveness. However, in the case of Glivec, an additional consideration by PBAC was included in the decision, i.e., the HSDWP’s recommendation for the inclusion of Glivec through the HSD Program.

**Quality of Life Drugs**

*Remicade*

In 2003, Remicade was reviewed by PBAC, which recommended the funding of Remicade in the treatment of RA for patients that have a rheumatoid factor positive status and have failed other treatments. Funding of Remicade, similar to the funding of Glivec, was under Section 100 the HSP Program (see above for details). PBAC`s recommendation was based on HSDWP’s recommendation for the inclusion of Remicade through the HSD Program and cost-minimalization. Cost-minimalization refers to PBAC`s assessment that the least costly alternative therapy after Remicade was demonstrated to be no worse than its main comparator, i.e., Enbrel
(Etanercept) (another drug used in the treatment of RA), in terms of effectiveness and toxicity.

**Gonal-F**

Gonal-F was not reviewed by PBAC, as it is covered by Medicare under the “Medicare Plus Safety Net” (i.e. co-payment system which helps people cope with the costs of out of hospital procedures). One PBAC member commented,

“I know you can get into all sort of arguments with people… but I don’t think the PBAC would regard infertility as an illness.”

Forty-four percent of the population is covered by private insurance and it may cover some of the expenses. In order for a treatment centre’s medical activities to be covered, the centre must meet the standards set by the Reproductive Technology Accreditation Committee (RTAC) of the Fertility Society of Australia (FSA).

**Main Findings**

Interestingly, Remicade was recommended for reimbursement by PBAC through the alternative funding mechanism of section 100, while Gonal-F (which was not reviewed by PBAC) was deemed by some PBAC members as medically unnecessary. Nonetheless, fertility treatment (including Gonal-F) falls under a different section of Medicare and is therefore partially reimbursed.
4.1.4 Israel

Orphan Drugs

*Cerezyme*

In the beginning of 1995, when Cerezyme was first introduced to the Israeli market, it was not reviewed by the Basket Committee (which I refer to as the Israeli Basket Committee –IBC) because the committee had not been established at that time. The Ministry of Health reviewed the drug and decided to reject it for funding (i.e., inclusion in the health basket). This decision was based on the high cost of Cerezyme. Later that year, with the introduction of the New Health Bill, the government passed legislation resulting in health plans receiving separate reimbursement for treatment of patients with five severe chronic conditions, including Gaucher’s disease. These drugs fall outside the health basket but are reimbursed through an alternative mechanism. During this time, Israeli researchers determined that a lowered dose (without negative effects) of Cerezyme would reduce the cost to 25%, compared to the cost of the manufacturer’s recommended dose. It is this lower dose of Cerezyme that is reimbursed.

*Fabrazyme*

Fabrazyme was reviewed by the IBC in 2004 and recommended for funding to the Cabinet. Their decision was based on clinical evidence of effectiveness based on published outcomes, and the positive Israeli experience with the drug.

*Main Findings*

The decision making bodies were different for Cerezyme and Fabrazyme. It is not surprising that there were different criteria used in the decision making process. In
the case of Cerezyme, the Ministry of Health’s main criteria was cost and it was initially rejected for funding. Nonetheless, the Ministry subsequently reimbursed health plans for coverage of Cerezyme, outside the basket of health services, through an alternative mechanism when researchers found a way to reduce its cost. However, when the IBC reviewed Fabrazyme, it was included in the basket of health services (and not through an alternative mechanism) based on clinical evidence and the positive Israeli experience with the drug. Interestingly (as reviewed in section 3.2), the IBC formally considers the clinical and economic evidence, as well as the social, ethical and legal implications of including a particular item in the health basket. They also ranked life saving drugs (which is an application of the *rule of rescue*) higher than non-life saving drugs, which will be discussed further in section 4.3.

**Lifesaving Drugs**

**Xigris**

Xigris was reviewed by the IBC in 2006 and recommended for inclusion in the health basket. Their recommendation was based on: 1) severity, which is high risk of death defined by an Apache II score, observation of a systemic infection, presence of septic shock or failure of two organs, 2) cost-benefit analysis, from published RCTs (most notably the PROWESS and ENHANCE studies) and 3) safety and side effects, as seen in the published RCTs.

**Glivec**

Glivec was reviewed by the IBC in 2004 and recommended for inclusion in the health basket for the treatment of CML and GIST. Their decision was based on evidence of: 1) effectiveness, as demonstrated through clinical research, 2) safety
and side effects, as demonstrated in the published literature and 3) its application as a preventative therapy.

**Main Findings**

The rationale behind the approval of both Xigris and Glivec were different. Nevertheless, both drugs were ultimately approved by the IBC based on their assessment of the drugs’ ability to meet their criteria. Both drugs met the safety and side effect criteria. However, the former was recommended for inclusion in the health basket based on the additional criteria of severity and cost-benefit analysis, while the latter was included based on the additional criteria of effectiveness and use as a preventative therapy. Similar to the orphans above, the IBC formally considers the clinical and economic evidence, as well as the social, ethical and legal implications of including a particular item in the health basket. They also ranked life saving drugs (which is an application of the *rule of rescue*) higher than non-life saving drugs, which will be discussed further in section 4.3.

**Quality of Life Drugs**

**Remicade**

Remicade was reviewed by the IBC in 2002 and recommended for inclusion in the health basket for the treatment of arthritis. Their recommendation was based on evidence of: 1) effectiveness as demonstrated through RCTs, and 2) safety and side effects, described by published literature.

**Gonal-F**
Gonal-F was reviewed by the IBC in 2002 and recommended the inclusion in the health basket. Their recommendation was based on evidence of: 1) effectiveness as demonstrated through the literature, 2) increased safety, comfort and decreased side effects for patients (compared to other treatments), and 3) more efficient mode of treatment as it decreased time spent with nurses. This recommendation is in accordance with the 1995 Universal Health Insurance Law, in which fertility treatments for infertile women in Israel are publically funded for up to two children. In 1999, the following restrictions were established: women over the age of 45 will not receive funding for treatment of their own ova, and women over 51 will not be provided with donated ova.

**Main Findings**

Both Remicade and Gonal-F were approved by the IBC. Effectiveness of the treatment was one of the determining factors in the recommendations of both drugs. The inclusion of Gonal-F in the health basket, as well as its inclusion in the Universal Health Insurance Law, is evidence that the Israeli Government views fertility treatment as medically necessary.

4.1.5 United States

**Orphan Drugs**

* Cerezyme

Recall from section 2.4 that once a state agrees to participate in the Medicaid program, they are required to provide all of the drugs under the federal formulary listing. States only have the authority to restrict the use of the drug. Cerezyme was reviewed by the State (recall that, based on the committee’s request, the name of
State in this study is confidential) Medicaid P & T Committee (date unknown because documents were not available). The State Medicaid P & T Committee recommended the listing of this drug without prior authorization (PA) from the prescribing physician. Listing a drug with PA is one method of restricting a drug’s use. In the case of Cerezyme, their decision to list this drug without PA (i.e., no restriction) was based on the confidence of appropriate prescribing of the drug by the treating physician.

_Fabrazyme_

Fabrazyme was reviewed by the State Medicaid P & T Committee in 2003. The State Medicaid P & T Committee recommended the listing of this drug. However, it requires PA from the prescribing physician. Their decision to list this drug with PA was based on the high cost of Fabrazyme.

_Main Findings_

There exists a discrepancy in the listing of Cerezyme and Fabrazyme. The former is listed without PA while the latter is listed with PA. When members of the committee were asked about this, they were unclear as to why this was the case.

_Lifesaving Drugs_

_Xigris_

Xigris was not reviewed by the State Medicaid P & T Committee. Xigris is used in emergency situations and, as such, is not part of their jurisdiction,

“My scope of responsibility is …outpatient drugs…We don’t have those kinds of controls over what goes on in the emergency department or a hospital… We don’t reach into that.”
Additionally, Xigris is currently the only medical product designated as a new technology by the Centers for Medicare and Medicaid (CMS). By receiving new technology status, Xigris qualified for special payment under the Benefits Improvement and Protection Act enacted in 2000, meaning that hospitals using the drug for Medicaid and Medicare patients from October 2002 are eligible for additional reimbursement of up to a maximum of $3400, i.e., half the cost of treatment. A hospital can only apply for *add-on payments* for technologies that meet strict criteria and if they were approved by CMS, the hospital is only eligible for the *add-on payments* for a minimum of two years, but not longer than three years. Thus, hospitals incur the remainder of the cost for all eligible CMS patients for the first three years. After that time, no additional funds are given to the hospitals and they must rely on the diagnosis-related group (DRG) base payment amounts. In the case of Xigris, it belongs to multiple DRGs, and thus, the full cost of Xigris is not covered and the hospitals must incur the cost.

**Glivec**

Glivec was reviewed by the State Medicaid P & T Committee (date unknown because documents are not available). The State Medicaid P & T Committee listed this drug on the formulary without prior authorization. Their decision was based on the confidence in the appropriate prescribing of the drug by the treating physician.

**Main Findings**

Xigris was not reviewed by the State P & T Committee as it is a hospital drug and beyond the scope of the committee. However, the CMS has demonstrated the value placed on new technology which results in substantial clinical improvement through
its partial and temporary payment of the drug. Alternatively, Glivec was listed without PA due to confidence in the prescribing physician. Also, according to one committee member, cancer drugs tend to be listed without PA because of the nature of the disease, i.e., if patients do not access the drug immediately, they will die. This demonstrates an emphasis placed, by the committee, on the value of saving a life, which is an application of the rule of rescue.

Quality of Life Drugs

Remicade

Remicade was reviewed by the US Medicaid State P & T Committee (date unknown because documents not available). The US Medicaid State P & T Committee recommended prior authorization for the use of Remicade. Their recommendation for prior authorization was based on the high cost of the drug and potential for incorrect prescribing. In general, Medicaid covers Remicade, but coverage in some States may require prior authorization or may be limited to certain treatment settings.

Gonal-F

Gonal-F was not reviewed by the US Medicaid State P & T Committee. Fertility treatments were excluded from Medicaid coverage as a result of the Omnibus Budget Reconciliation Act (OBRA) of 1990, in which Congress permitted states to exclude or limit coverage of fertility treatments from Medicaid coverage as part of the Medicaid Drug Rebate Program in section 1927(d)(2) (4,5). OBRA 1990 reformed the relationship between the pharmaceutical industry and the federal government.
through changing the drug reimbursement programs. Due to state Medicaid pressure, OBRA included ten categories of drugs to be excluded from coverage, including fertility treatments. Additionally, there was no federal legislation governing artificial reproductive technology. Family planning was covered by Medicaid in about half of the states; however, infertility tests and treatment are usually not defined as family planning. Many private insurance policies covered diagnosis of infertility but not the cost of treatment. Coverage of treatment by private insurers varies by state. Only 15 states had laws requiring insurance coverage for infertility treatments (Arkansas, California, Connecticut, Hawaii, Illinois, Louisiana, Maryland, Massachusetts, Montana, New Jersey, New York, Ohio, Rhode Island, Texas, and West Virginia). Most individuals must pay for treatment out of pocket.

Main Findings

Generally, the State Medicaid program restricts the use of a drug when the drug is costly and there is a chance it will be incorrectly prescribed. This has been the case with Remicade. In the case of Gonal-F, the State P & T Committee did not review the drug because fertility treatment was excluded from Medicaid coverage as a result of the OBRA legislation, which considered fertility treatment to be medically unnecessary.

4.2 Comparison of Decisions, Evidence and Values across Countries

4.2.1 Comparison of Decisions by Country

The drugs that were not recommended for reimbursement across the five countries i.e., Cerezyme, Fabrazyme and Remicade through traditional mechanisms (namely formularies) were covered through alternative mechanisms.
In general, governments and committees found alternative avenues to fund the drugs that were considered to be effective but very expensive (refer to Table 8 below), for example, using Special Access Programs. One exception in this study is Gonal-F, because both the USA and Canada do not publicly fund fertility treatments or drugs, and so no decisions were made about this drug in the aforementioned countries and no alternative public funding exists. Additionally, Xigris was not reviewed by the US State P & T Committee because it is a hospital-based drug.

Table 7 below summarizes the recommendations made by each country for each of the six study drugs. It also highlights the alternative mechanisms by which some of the drugs that were given “No” recommendations were subsequently publically funded.

Table 8. Comparison of Drug Listing Decisions across Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Cerezyme</th>
<th>Fabrazyme</th>
<th>Xigris</th>
<th>Glivec</th>
<th>Remicade</th>
<th>Gonal-F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>Initially no, but available though special access</td>
<td>Initially no, but available through post market study</td>
<td>Yes</td>
<td>Yes</td>
<td>Case by case decision</td>
<td>N/A</td>
</tr>
<tr>
<td>England &amp; Wales</td>
<td>Yes</td>
<td>No, but NHS changed decision and now PCTs must fund it</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Australia</td>
<td>Yes under LSDP</td>
<td>Yes under LSDP</td>
<td>Yes</td>
<td>Yes under section</td>
<td>Yes under Medicare</td>
<td></td>
</tr>
</tbody>
</table>
4.2.2 Comparison of Evidence used to Assess Cost-effectiveness and Effectiveness by Country

All countries used both cost-effectiveness and effectiveness as values in their recommendation process. However, the evidence used to assess these values differed, even though the actual terms appeared to be the same. When making comparisons of drug recommendations, it is important to note differences in the common terms used by all committees. This helps to explain differences in recommendation outcomes despite similar values being used. This will be further illustrated in section 4.3. Table 8 below summarizes the types of evidence used to assess both cost-effectiveness and effectiveness by country when making recommendations. For example, effectiveness was assessed using different types of evidence; however, all countries preferred randomized controlled trials (RCTs).

For full comparison of all the common values, refer to Table 8 below.
Please note that the USA was not included in the Table 5 because State formularies only have the authority to restrict the use of drugs. The decision to list a drug on the Medicaid formulary is determined federally. When the State Medicaid P & T committee listed a drug with PA they considered the potential for prescribing errors, and the potential for over-prescribing. If the drug was costly, they were more likely to restrict its usage.

<table>
<thead>
<tr>
<th>Countries</th>
<th>Types of Evidence Used to Determine Cost-effectiveness (i.e., determination of the relationship between monetary inputs and the desired health outcome)</th>
<th>Types of Evidence Used to Determine Effectiveness (i.e., the extent a therapy produces a benefit in a defined population in uncontrolled or routine circumstances)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>Cost per QALY or LYG</td>
<td>RCTs and observational studies</td>
</tr>
<tr>
<td>England &amp; Wales</td>
<td>ICER score &amp; QALY</td>
<td>Based on RCTs and open label extensions. They consider design, duration, # of patients, comparator, and outcomes</td>
</tr>
<tr>
<td>Australia</td>
<td>Cost per QALY preferred</td>
<td>Based on RCTs and compared to other therapies</td>
</tr>
<tr>
<td>Israel</td>
<td>Multiply cost patient Treatment/year, by the number of patients estimated to use it/year to calculate the overall cost of including the drug in the system</td>
<td>Post-market effectiveness data</td>
</tr>
</tbody>
</table>

All committees, with of exception of the State Medicaid P & T committee, considered the cost of a drug when making their recommendations. Typically committees looked at the cost per quality adjusted life year (QALY). A QALY accounts for both quantity and quality of life which results from a given health intervention. It is the product of life expectancy and a measure of the quality of life years remaining. While QALYs
provided a common currency to determine the benefits gained by health interventions (by placing a value on efficiency), many have argued that its application in health care decisions is unethical and discriminates against the elderly because it values life years rather than lives. Nonetheless, QALY’s are being used by many drug reimbursement committees.

The exception in this study is the USA’s Centers for Medicare and Medicaid Services (CMS). Since 1965, the CMS, by law, is required to only consider only whether a drug “is reasonable and necessary” without regard to costs. However, the value of a statistical life which is generally used in the evaluation of safety and health regulations is approximately US$100 000 per QALY.

In England & Wales, NICE considered cost-effectiveness using QALYs. NICE has denied using a strict QALY threshold. However, Rawlins and Culyer’s study in 2004 suggests a threshold of US $50 000 per QALY. Similarly, in Canada and Australia, there is no official threshold but the acceptable cost per QALY in the former is C $50 000 per QALY and in the latter is AU$76 000 per QALY. For a comparison of thresholds in dollar amounts, refer to Table 10 below.

Table 10. Threshold per QALY by Country

<table>
<thead>
<tr>
<th>Country</th>
<th>Dollar Amount per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>US $46,164.26 per QALY</td>
</tr>
<tr>
<td>England &amp; Wales</td>
<td>US $36 000- US $55,000 per QALY</td>
</tr>
<tr>
<td>Australia</td>
<td>US $48 000 per QALY</td>
</tr>
<tr>
<td>Israel</td>
<td>No specific threshold</td>
</tr>
</tbody>
</table>
Country | Dollar Amount per QALY
---|---
USA | US$100 000 per QALY

### 4.2.2.1 Comparison of Values’ Definitions by Country

All countries shared similar values in their recommendation process, with heavy emphasis on cost and effectiveness; however, different committees defined these values differently. Table 10 below summarizes the common values –rule of rescue, equity and benefit – and their definitions, by country, when making recommendations. The *rule of rescue* was considered by all four countries listed in Table 11. For a comparison of all the values used, please refer to tables 12-16.

Each of the countries shared similar definitions related to outcomes - i.e., saving a life, and this demonstrated a belief in the intrinsic value of the individual by these countries. Examples of the way in which countries use the *rule of rescue* will be illustrated in section 4.3. I have included Israel, despite the fact that the term *rule of rescue* was not used. This is because of their formal consideration of a number of other criteria which I believe encompasses this value, including: 1) lifesaving technology with full improvement, 2) potential of technology to prevent mortality/morbidity, and 3) new technology for serious diseases with no alternative treatment.

Equity was considered by all four countries listed in the table, and each had a different definition of this term. Some countries related their definition of equity to the outcome - i.e., some patients would be deprived of treatment (e.g., England & Wales
and Israel), while others related their definition to the process - i.e., assessing drugs using the same criteria (e.g., Canada and Australia). Benefit was defined similarly by three countries who related their definition to outcomes - i.e., significant improvement of illness. The exception was England & Wales, which related their definition to process - i.e., identification and evaluation of benefit. Two countries, Canada and Israel, formally included the importance of improving quality of life (QOL) in their definition of equity. For a complete comparison, please refer to Table 10 below.

Please note that safety and efficacy (i.e., the extent a therapy produces a benefit in a defined population under an ideal setting, in contrast to effectiveness, which produces benefit in a real life setting) were not included in the table because they were assessed prior to coming before the committees. Each of the countries in this study has established a national/federal agency which determines whether a given drug may be marketed in a particular country. These national agencies assess drug products on the basis of safety and efficacy. All drugs that come before any of the committees in this study must be approved by their national agency prior to their reimbursement recommendation. For example, in Canada, the drugs were assessed by Health Canada; in Australia, the drugs were assessed by Australian Drug Evaluation Committee (ADEC); in the US, the drugs were assessed by the Centre for Drug Evaluation and Research (CDER) under the FDA; in England and Wales, the drugs were assessed by the Medicines and Healthcare products Regulatory Agency; and in Israel, the drugs were assessed by the Ministry of Health.
No drug would be assessed for reimbursement if it did not meet the aforementioned criteria. Additionally, the US was not included in the table below for reasons discussed in section 4.2.2 above.

Table 11. Definitions of Common Values used in Recommendations by Country

<table>
<thead>
<tr>
<th>Countries</th>
<th>Values Used</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rule of Rescue</td>
</tr>
<tr>
<td>Canada</td>
<td>Rescuing endangered life</td>
</tr>
<tr>
<td>England &amp; Wales</td>
<td>Accounts for the intrinsic value of the individual when there is opportunity to save a patient from a life threatening disease</td>
</tr>
<tr>
<td>Australia</td>
<td>Must meet these criteria- * no other treatment available * severe disease * few patients * sufficient improvement of disease</td>
</tr>
<tr>
<td>Israel</td>
<td>Considers: * lifesaving technology with full improvement * potential of technology to prevent mortality/morbidity * new technology for serious disease with no alternative treatment</td>
</tr>
</tbody>
</table>
4.3 Comparison of Values Countries’ Used by Drug Type Based on Published Rationales

While countries did share a number of similar values, differences were also evident between countries and even within countries across different drugs. The following section includes five tables, 12 through 16, which illustrate the values used for each drug recommendation by country. N/A denotes values that were not directly mentioned in the rationales of specific decisions. This does not necessarily mean that countries did not deliberate about those values. For example, Australia and Israel did not mention cost-effectiveness in the rationale for some of the drug recommendations; however, it is part of their mandate that all drugs must meet this criterion. In addition to the values listed, England and Wales considered whether a drug was a new technology in the cases of Xigris, Glivec, and Remicade.

No table exists for Gonal-F because, in England and Wales, decisions were made on a case by case basis, and in the USA and Canada, fertility treatments/drugs were not publicly funded. Once again the USA is not included in any of the Tables for reasons mentioned above. Please note the highlighted areas of the tables below indicate values which were not unilateral across drug type within the published rationales of each committee. For example, the rule of rescue was not used by Israel or England & Wales for both Cerezyme and Fabrazyme; equity was not used by Israel for Cerezyme and Fabrazyme; severity was not used by Canada or England & Wales for Xigris; preventative therapy was only used by Israel for Glivec; improved
survival was only used by Canada for Glivec; and cost-minimalization was only used by Australia for Remicade.

Tables 12 and 13 focus on two orphan drugs: Cerezyme and Fabrazyme. The values which appear in these two tables are different from the other three tables, but they are similar to each other. It is evident that when countries are making recommendations about orphan drug reimbursement, they consider other values - namely, the rule of rescue and equity. However, even though these drugs did not meet most of the criteria, they were still ultimately funded through alternative mechanisms across all countries.

Table 14 focuses on Xigris. None of the values listed were used unilaterally across all countries. For example, Australia and Israel considered severity of the disease when making their recommendation for Xigris. Clinical need was only considered by England & Wales. Evidence of cost and clinical effectiveness was considered by all countries except Australia. Nonetheless, Xigris passed all the criteria used by each particular committee and was recommended for funding by all committees.

Table 15 focuses on Glivec. In addition to the common values across drug types, Israel considered the preventative nature of the therapy and Canada considered the improved survival rate. Glivec passed all the criteria used by each particular committee and was recommended for funding by all committees.
Table 16 focuses on Remicade. This table does not include Canada because decisions about Remicade in Ontario were made on a case by case basis. In addition to the common values across drug types, Australia considered cost-minimalization. Remicade passed all the criteria assessed by each particular committee and was recommended for funding by all committees.

The values used and assessed by countries differed slightly by drug type. For example, improved survival was considered in Canada for Glivec but not for any of the other study drugs in Canada. This variation within countries may indicate recognition of the differences in disease types. Moreover, across countries there were differences in the values assessed. For example, clinical need was generally a value assessed in England & Wales, but never in Australia and Israel. Despite the variations in values assessed, the funding outcomes (for countries that looked at the drug in question) were the same across the countries.

Table 12. Values Applied to Cerezyme Recommendations and Countries

<table>
<thead>
<tr>
<th>Subsequent Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Country</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Canada</td>
</tr>
<tr>
<td>England &amp; Wales</td>
</tr>
<tr>
<td>Country</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Australia</td>
</tr>
<tr>
<td>Israel</td>
</tr>
</tbody>
</table>

Table 13. Values Applied to Fabrazyme Recommendations and Countries

Subsequent Assessment

<table>
<thead>
<tr>
<th>Country</th>
<th>Values Used</th>
<th>Funding Outcome</th>
</tr>
</thead>
<tbody>
<tr>
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Table 14. Values Applied to Xigris Recommendations and Countries Subsequent Assessment

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Table 15. Values Applied to Glivec Recommendations and Countries Subsequent Assessment

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Table 16. Values Applied to Spryciz Recommendations and Countries Subsequent Assessment

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Table 16. Values Applied to Remicade Recommendations and Countries

Subsequent Assessment

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4.4 Values Used by Each Committee and Participants’ Perceptions, Based on Interviews

In this section, specific participant’s views of the values which should be used in the drug recommendation process are presented. The first subsection will discuss the values that were actually used by committees (as demonstrated through specific committee published rationales), which have already been discussed in section 4.3 above. The second subsection will discuss other values which were not included in the published rationales, but participants believed were important to the recommendation process, including evidence, cost, lack of alternative treatments, conceptions of medical necessity and quality of life (QOL).

4.4.1 Values Discussed That Directly Correlate to Published Rationales:

Efficiency, Equity of Access, & Rule of Rescue

Efficiency

All committees used the value of efficiency, or cost-effectiveness, when making recommendations. But, the value of cost-effectiveness was problematic for orphan
drugs as they are so costly. Therefore, when drugs that do not meet the cost-effectiveness criterion come before committees, other values were often applied -- for example, the rule of rescue. Additionally, committees differed in the types of evidence they used to assess cost-effectiveness (see section 4.2 and 4.3 above). CEDAC recommended against the funding of Fabrazyme, and part of their rationale was Fabrazyme’s inability to meet their cost-effectiveness criteria. As stated in their rationale,

“Given the drug’s annual cost, and the results of clinical trials to date, agalsidase beta [i.e., Fabrazyme] is unlikely to be cost-effective, using conventional criteria.”

A NICE committee member explained that Glivec actually met their cost-effectiveness criteria,

“You know Glivec was … considered by NICE as a cost-effective drug, it was something new for NICE because in the first time in their history they considered a drug like Glivec, a biotech …drug that’s cost-effective. So it was really important. ”

Alternatively, many others recognized the problem of applying the cost-effectiveness value in the assessment of orphan drugs. As one CED committee member commented,

“It’s very difficult to use cost-effectiveness for these drugs because, you’re talking about treating maybe 10 patients …So these drugs will never look cost-effective because there’s such a small number of patients that are out there, although their budget impact is huge. So, that’s about the only thing we kind of consider in orphan drugs-- is we can’t often times use our classic cost-effectiveness criteria to make a judgment.”

The CED considered the impact on patients for drugs that are not cost-effective, as one member explained, “We make our decisions on clinical information for cost
effectiveness. And we now… have very formally introduced the criteria of patient impact.”

Similarly, another CEDAC committee member noted that the decisions around orphan drugs, like Fabrazyme, are different, “I think you can make the argument that … the decision around … Fabrazyme…is not a cost-effective decision …it’s a different kind of decision.” One NICE committee member commented about the establishment of a different process for such drugs,

“We’re doing some work on whether or not our standard evaluation process actually works for these ultra rare conditions…We’re just coming to the end of that at the moment so it’s possible …Drugs or interventions for very rare conditions like Fabry’s and Gaucher’s …We might set up a different evaluation process with a different decision paradigm associated with it.”

To date, no alternative process has been established by NICE. However, as discussed in section 4.1.2, the DH has established NSCAG, which nationally commissions ERTs.

In Australia, PBAC recognized the inability of both of the study’s orphan drugs to meet their cost-effectiveness criterion. Cerezyme and Fabrazyme were available through the Life Saving Drug Program, which provided financial assistance for drugs PBAC considered to be clinically effective that treat rare, inherited enzyme deficiencies. As one committee 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. So we have what is called a Life Saving Program which those drugs are put into, and the PBAC has to consider those but would simply say to the Minister whether it works or does not. Because even if it gave perfect
Patients recognized the inability of orphan drugs to meet the cost-effectiveness criterion,

“Unfortunately, something like the CDR - we do have one on the most advanced systems around HTA, pharmaco-economics- and for good or bad it’s used a lot more strongly than in almost any other countries… … Rare disorders, they cannot actually meet those kinds of benchmarks. So, in other countries where they don’t apply pharmaco-economics quite as rigorously there is still a lot more sort of qualitative assessment in terms of drugs and there a lot of other factors that are looked at in terms of whether a drug gets funded in a country.”

**Equity of Access**

Equity of access was a value used by some committees and was discussed by a number of patient and industry participants. 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. When access was discussed, it was in relation to the orphan and quality of life drugs in this study. Equity was cited by CEDAC in their rationale for their decision against reimbursement of Fabrazyme. A 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."

Many patients and industry representatives thought that access was an important value to consider when making recommendations. One patient member explained ‘equity of access’ as related to fertility treatments,

“We want equity of access …Something that is reasonable and appropriate and possible within a health care system and within the constraints that governments face.”

One industry respondent, when asked about the federal-provincial-territorial jointly funded initiative for a post market study 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.”

A number of patients linked the concept of access with their personal experiences while advocating for their particular drug. Please refer to text boxes 1 and 2 below, which illustrate some of the patients’ experiences.

Text Box 1. RA Patient Representative Personal Story

I was put on a waiting list. So I started rocking the boat a little bit. And every moment I could [I] advocate[d] to the hospital, to the infusion clinic, to the government, to my member of the Legislative Assembly …to have this drug listed.

I finally received the drug [through]… the Special Access Program. And when the company received their notice of compliance [NOC] I fell into a crack because I
couldn’t receive the drug under the Special Access Program-- it ended at the time they received their notice of compliance. And the drug was not covered by a provincial formulary. And my personal insurance wouldn’t cover it…

So basically what I’ve done is I’ve work two years, advocating hard on the government, on the opposition parties everywhere, in the newspaper and the radio, TV, etc.

Text Box 2. Infertility Patient Representative Personal Story

Well ...what happened is they recognize that when we had several letter-writing campaigns. We put posters up in clinics and when people came into give their blood, we’d have while they were waiting to give blood; we had signs up saying “Okay, this here is a list of politicians. We want you to write to the Health Minister. These are the issues. Like these are the 10 issues. Just write them in your own words, say how it affects you and then put it in an envelope and put it in this box in the clinic. We’ll post them.

Patients also recognized variation in access within and across countries, as illustrated in text Box 3 below.

Text Box 3. RA Patient Representative Personal Story

There’s a remarkable situation in Labrador with a woman who lives in Labrador …And here’s this woman living on the Labrador side whose got very bad Rheumatoid arthritis and the neighbour across the street does too…The neighbour across the street ...[got the drug] and she’s not. So in Labrador they have this cable TV show ... and one night the Premier was on. So this woman gets on the phone and she nailed the Premier…about how come, you know, she gets a life and I don’t?

Similarly, an infertility patient representative commented, “Basically it is incredibly unfair. It’s literally treatment by post code”. Variation in access to drugs across countries was also mentioned by some patients, 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.”
Another finding was that different stakeholders accessed the system differently. For example, in terms of patient involvement in the process, one patient participant said the following,

“I’m not quite sure whether there was something unique in Remicade’s approval process. We don’t invest ourselves heavily in the approval processes for any one drug. We do keep a very active interest in the whole process of listing new arthritis medications and formularies so that people who live with this disease can get access to them in a timely way.”

Another patient representative commented on their access and related it to approval process,

“We know about those things when they’re happening. Because our patient community, our medical advisory processes are engaged all the way along. And frankly most of the pharmaceutical companies establish a relationship long before the approval process with us so that we know way in advance which companies are bringing which drugs to the approval process in Canada.”

**Rule of Rescue**

Life saving treatment was a value considered by all of the committees, some more formally than others, as was evident in the application of the rule of rescue for orphan drugs (see section 4.2 above). 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 committee 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.” While many committees do have specific criteria to review when making recommendations, a number of values, including life-saving ability, were not clearly formulated as part of their 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 ….you’re right, 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.”

PBAC members commented on the use of the rule of rescue when there was no alternative treatment available. For example,

“The rule of rescue is available to PBAC … where there is absolutely no other therapy available…and where death is imminent without therapy…we use it very, very rarely…we invoked what we call a the rule of rescue for CML but…the rule of rescuer does not make a cost …ineffective drug cost-effective.”

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.”

The values discussed by participants that correlated to the committees’ published rationales included efficiency (i.e., cost-effectiveness), equity of access, and saving a life (i.e., the application of the rule of rescue). All committees (with exception of the US case) used cost-effectiveness in their recommendation process. The degree of its weight in the decision making process varied by committee. For example, CEDAC placed a great weight on a drug’s ability to meet the cost-effectiveness criteria, as is evident through their recommendation against Fabrazyme. Israeli, Australian and English systems placed more emphasis on the value of providing life-saving treatments, even if cost-ineffective. However, in each country, this was manifested in different ways. PBAC also acknowledges the inability of some drugs to meet the cost-effectiveness criteria. Therefore, their health system has created an alternative mechanism for drugs that are considered beneficial, yet not cost-effective. Finally, in England, the DH established NSCAG for the national commissioning of such drugs.

4.4.2 Values Discussed That Do Not Directly Correlate to Published Rationales: Evidence, Cost, Lack of Alternative Treatments, Quality of Life, Medical Necessity and Innovation

The values discussed by participants that did not directly correlate to the committees’ published rationales included: evidence, cost, lack of alternative treatments, QOL, medical necessity and innovation. While all committees
considered evidence particularly as it related to cost-effectiveness and effectiveness, they still made decisions in circumstances where there was insufficient evidence, specifically in the cases of Cerezyme ad Fabrazyme. Overall cost of treatment to the system was not considered by committees; rather, cost was measured in QALYs. The value of lack of alternative treatments was used by some committees and many patients and industry representatives believed that this should be a consideration. QOL considerations were not a key consideration for committees; but, similar to the value of lack of alternative treatments, patients and industry representatives believed that it should be a consideration. Considerations of what constituted medically necessary treatment particularly affected public funding of fertility treatment. Finally, innovation was considered to be a value in priority setting.

**Evidence (Decisions in the Absence of Evidence)**

Evidence was believed to be an important value when making decisions, as it was the basis of determining whether other values were met - specifically, cost-effectiveness and effectiveness (recall section 4.2.2 above). However, similar evidence was evaluated differently by different committees. Committees considered certain types of evidence to be of greater quality than other types of evidence. Nonetheless, decisions were often made despite the lack of what committees considered to be sufficient evidence. Participants suggested reliance on international experience with drugs and the use of start/stop mechanisms or conditional listing in light of insufficient evidence.
Evidence was used by all committees to make drug reimbursement recommendations. As one of the Toronto Hospital P & T Committee members pointed out - evidence was a key factor in their decision making, “Obviously most of the decisions are based on evidence, right, and the research is the development of that evidence”. One industry respondent commented on how ‘good’ evidence trumps cost in the case of Xigris,

“No one withholds Xigris from a patient based on cost. When they say they’re giving it to the sickest patients, and it is an expensive drug, the data points to that’s exactly what they should be doing. So that may be different with some other drugs ….with Xigris the data actually shows there isn’t a benefit in extending it to some of the sepsis patients who aren’t as sick. So it’s a little bit different, it’s probably not your textbook case in that regard.”

However, committees differed in their assessment of the evidence. For example, the Israeli Basket Committee recommended Fabrazyme for inclusion in the basket in 2004. Their decision was based on the clinical evidence of the drug efficacy, “the published outcome...indicates that the treatment ....succeeds... and as such slows down the progression of the disease”. Alternatively, CEDAC’s recommendation in 2004 against the funding of Fabrazyme cited the lack of evidence relating to both clinical benefit and cost-effectiveness: “…this trial failed to show a clinical benefit of aglasidase beta on a range of tests”. This may be because the aforementioned committees use different types of evidence to determine cost-effectiveness and effectiveness. Recall section 4.2.2 and Table 9.

Additionally, committees weighted different types of evidence differently --for example, the use of surrogate markers or endpoints to measure effectiveness.
Some members of committees were concerned with the use of surrogate markers, while others did not discuss this issue. As one committee member pointed out,

“All they’re talking about is a reduction in some surrogate marker. Without any evidence whatsoever it’s going to prolong their life, or give them better quality of life - that’s unfair.”

Similarly, committee members believed that the best kind of evidence came from randomized controlled trails (RCTs); as one member explained,

“When we are talking about evidence we talk about quality of evidence. Is it large randomized trials? Is it small randomized trials? Phase III trials? Etc. and so quality of evidence is important.”

Evidence in the form of RCTs is particularly problematic for orphan drugs because their RCTs typically have small sample sizes. As one committee member commented on the small sample size as related to evidence of disease improvement,

“Well, the orphan drug ones are a little more difficult… the information that they actually work to improve quality of life or to improve life expectancy is … not as easy to come by because, there’s not as many patients and the studies are much smaller and shorter.”

Committee members often believed that, in the case of rare disorders, they were making decisions even though there was insufficient evidence. One concern a number of committee members raised, particularly as it related to orphan drugs, was the lack of good clinical evidence regarding, for example, evidence of benefits or harms of the drug. As one member said,

“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.”

Another commented on the lack of evidence surrounding long-term effectiveness,
“We all know that enzyme replacement therapy is effective in reducing the progression of the disease [i.e., Fabry’s or Gaucher Disease]. But how long will it give us? How many extra life years, you know, how many quality of life years will it actually give us?”

Decisions regarding Cerezyme and Fabrazyme were made even though there was insufficient data. Patient and industry representatives recognized this deficit and suggested reliance on international experience with the drugs. One Fabry’s patient explained,

“If you really want to study these disorders you have to work on an international basis and in an international community with registries and international protocols, etc., ...We feel that a solution to this issue ...is to work with the international community, using existing proven models that are already in place, develop an orphan drug policy that not only addresses the issues in other countries but also, addresses the issue on access to these drugs, long term studies, etc., etc. using international accepted standards, criteria and protocol.”

Additionally, start/stop mechanisms, i.e., the ability to start a patient on a drug with the possibility of not continuing the treatment if it is found to be ineffective, were discussed by both committee and patient representatives. One committee member noted the problems committees faced with conditional listing - i.e., placing a drug on the formulary conditionally, in order to monitor the effectiveness of the drug.

“I don’t [think] there’s a simple solution. We’ve ... looked at the option of conditional listing ...but ... politically- it’s actually very difficult. I think for governments to fund something and then stop funding something even when the new drug is ... eventually shown to be harmful- it’s often difficult to stop funding... it’s seen as politically infeasible to stop funding a drug that you’re already paying for.”

However, patients are open to the idea of conditional listing or start/stop mechanisms, as indicated by the following:
“I think, one of the models we certainly do like is the notion of the start/stop rules. That is, if the drug is deemed safe and efficacious, and you find patients ... who would be appropriate then one could then start them on drug. Setting up some clear benchmarks that would need to be met to demonstrate that the drug is in fact effective. Maybe also some benchmarks around safety and adverse events that might occur in that if we do not meet the effectiveness benchmarks...that they would stop... So at least it gives everybody a fair chance to get access to these drugs.”

Reflection 7

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<td>When the evidence of effectiveness is insufficient, what should committees do to improve the reimbursement decision making process?</td>
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Cost

Different respondent groups discussed cost differently. Committees generally focused on the cost-effectiveness criteria, rather then cost. However, patients tended to talk about cost in relation to drug access and believed that cost played too great a role in reimbursement recommendations. Participants offered the use of restrictions as one method to handle expensive drugs.

The value of cost was discussed directly for all drugs except Glivec. For example, one Toronto Hospital P & T committee member commented,

“Obviously a high-ticket item ... you handle a little bit more judiciously and put a lot more thought to why we need it. But basically it is the same sort of procedures, there is nothing different that we do for this drug (i.e., Xigris) ... It all comes down to the cost issue. Who is going to pay for it? “

Additionally, one PBAC member commented on the cost of Remicade,

“We know that if you take the prevalence of Rheumatoid Arthritis in the community and you allowed everyone to have access .... It would have been over a billion dollars in Australia. So we say to the company, you know, this
drug because of its high unit cost and high total cost we’re going to have to come to some consensus about what the restrictions because the government would not be in a position to fund unlimited access to this drug at the price you want.”

A patient explained how it is easy to de-prioritize fertility treatments based on their high cost;

“The fact is that infertility treatment in total is not a huge proportion of any health budget. Yes, it’s an expensive procedure, but in a very particularly managed health care situation, it is very easy to sort of just put it at the bottom of the list or to rule it out altogether.”

Many patient participants focused on the relationship between cost and access to a particular drug. For instance, one patient commented on orphan drugs in Canada (and this comment is applicable to any public paying system),

“Canada fares much worse than other countries, in terms, of the time it takes to get access to treatments. I think it’s because we try to be you know a public system for everybody …I mean it’s the old peanut butter theory-- the wider you spread it the thinner it gets…You only have so much peanut butter… I mean we’re trying to apply it everywhere so therefore you know in many places it’s going to come up very thin …We’ve got a system that is really designed to, I think, ensure that everybody does have access to healthcare …More difficult situations that do not fit the mold --and I think that’s certainly what happens with rare disorders-- is that the system is designed to take care of the norm and to make sure that nobody gets totally left out …on the other hand, that means that everybody at the edges are not going to be taken care of.”

Some patients believed that cost played too great a role in reimbursement decisions.

One member of the Fabry’s group stated, in reference to the drug Fabrazyme in Canada, “The only factor is cost. The drug works, it’s safe, it’s good quality, and it’s not cost-effective - that’s the only problem…” He further noted that one CEDAC member told him “if the drug cost $50 a year versus $300,000 a year,” he said, “the drug [Fabrazyme] would have been approved without question””. Patients also
believed that, when committees calculated costs, they should also look at the
potential for cost savings. As one patient explained,

“Well the problem is that most of the time the decision is made on the cost of
the drug. And they don’t look at the cost savings in other ways - the reduced
number of surgeries, the reduced doctor visits, the reduced physiotherapy,
the fact that people can stay in the workplace much longer. Those things are
not taken into account when they look at just the cost of the drug alone.”

This seems to support what was reported in section 4.2.2’s discussion of QALYs, in
which countries tend to place thresholds on what they are willing to pay for QALY.
Another patient encouraged a greater understanding of patient needs, but also
believed that cost was the main criterion for decision-making in the case of
Remicade:

“I think one of the problems is it’s [Remicade] IV infused. So people have to
go to a medical facility to have an infusion. As opposed to a couple of the
others that are self-injected at home. That’s a huge factor in their decision. I
think that’s probably the major factor because it’s more drain on hospital
resources … the Common Drug Review and the provinces …don’t
understand why patients need more than one option. They just say, okay,
this drug works for this disease and this drug works for this disease -- we only
need to cover one…In the case of Remicade they actually have to go and get
an infusion every six weeks and if there’s gonna be more compliance, more
compliance means a better outcome… They just don’t seem to get that there
needs to be more than one option of a medication…Generally they’ll take the
least expensive drug.”

One patient related cost and precedent setting to the differences in the decisions
regarding Cerezyme and Fabrazyme in Canada,

“To be fair you know Cerezyme [was] before the CDR [Common Drug
Review]. Cerezyme was actually very, very, early. I don’t think that there was
the anticipation with Cerezyme that there would necessarily be a huge host of
other expensive treatments … so it was a bit of a one off in people’s mind.
Here it was a very unique kind of a drug, very unique situation --we can kind
of make a one off decision …with Fabrazyme it became much bigger then
that …we’ve got a whole host of these types of drugs that are going to be coming forth now. And so, the decision I think around Fabrazyme actually was predicated a bit … in terms about what are we going to do if we say yes? What about all the other [s] that are coming up?”

Many participants discussed the use of restrictions as a cost saving method. For example, one committee member said “Certain drugs that have a high cost …they do need some sort of special … [restrictions] because otherwise there will be over use.”

**Lack of Alternative Treatments**

Not all committees used this value in their decision making, but many patient and industry participants believed that the lack of alternative treatments was an important value that committees should consider. Some committees, for example NICE, CED and PBAC, used lack of alternative treatments as a value in decision making. One NICE respondent commented that NICE takes into account the lack of alternative treatments when making recommendations:

“We were talking about the disease where people were in a terrible state with their severe disease and that this was the only drug that was available for people with this disease. So if we had said no to supporting this drug, then we were basically removing any active therapy that would help the patient.”

In the case of Glivec, the CED-CCO recommended it for listing on the Ontario formulary for the treatment of both CML and GIST. In the former, improvement in survival and effectiveness were cited as reasons for approval. In the latter, the fact that there is no other treatment was critical [333]. As one member of the CED explained,
“If there was a drug that was introduced that saved the lives of people with a disease that otherwise had no treatment and no life saving measures, then that would definitely be taken into account as we make our decisions.”

Many industry participants believed that that lack of alternative treatments for orphan diseases should be a consideration,

“From a rare disease perspective…I think that they [orphan drugs] should be evaluated differently because generally these patients don’t have really anything available”.

Patients also noted the lack of alternatives as an important consideration. The following comment was made in relation to orphan drugs,

“These are life saving treatments we’re talking about diseases for no other treatment [are] 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.”

**Quality of Life (QOL)**

QOL was considered formally by some committees and informally by others. Patient and industry participants believed that QOL was not a criterion used by committees to make decisions and that it should be a consideration.

One CEDAC member illustrated the consideration of quality of life by his/her committee,

“Remicade type drugs…you’re right, 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 contrast, the drug Glivec was recommended for inclusion in the health basket by the IBC in 2004 for the treatment of CML and GIST based on, though not exclusively, QOL.
Patient and industry participants believed that the value of QOL was not used by most committees and that it should be a consideration. One patient commented on drugs like Remicade that

“It’s simple mathematics and they don’t get it. It’s more than quality of life. It’s [i.e., Remicade] keeping people working and keeping people contributing and paying taxes and they don’t get it [i.e., the big picture benefits].”

**Medical Necessity**

Related to the notion of QOL is the conception of what is medically necessary. Conceptions of medical necessity are evident in the rationales behind the lack of public funding for fertility treatments. According to one Australian patient participant,

“We are paying our way as citizens who work in our society, and it is reasonable to expect that if [we] need medical treatment for a medical condition, that we will be able to access in the same equitable way that other people in the community can access health care conditions that they also have.”

Another patient participant, from the UK, commented,

“The reason it [fertility treatment] is still not funded so much now is …it is all a matter of priorities. And infertility treatments in many people’s minds is a low priority and PCTs …, are vastly in the red…So they [PCTs] are looking at where they can make savings …you know, this [infertility] doesn’t kill people (although we have had a couple of suicides here)…Also patients find it very hard to stand up and shout…It’s a very private illness. So they [the government] get away with it ….It’s a case of competing demands and infertility treatment has always been…a low priority when it comes to the NHS.”

In the UK and Australia, organized fertility advocacy groups have played a role in creating an environment in which fertility treatment is perceived as a medical necessity. The Australian patient representative explained how advocacy resulted in the government’s recognition of fertility treatment as a medical necessity,
“When we got funding initially…we were fighting for it [and] it took several years… One meeting [with]….people from the Financial Strategies Branch of the Department of Health, …they said “You are not going to get what you want because you are not electorally significant”, ….He told us what we need to do in order to influence government opinion. And he said…….“only … 12,000 women a year [are] going through IVF.” We said “Yeah that may be so, but they have partners and each partner has a family, and all of those people want to see IVF to be made affordable.” And then we instituted a letter-writing campaign to the minister at the end of which he did admit that we were electorally significant.”

Innovation

Innovation was considered to be an important value in priority setting by many participants. A detailed discussion of the value of innovation can be found in Section 4.6, Innovation.

4.5 Evaluation of Decision Making for Each Drug, According to AFR

Conditions

The four conditions of ‘accountability for reasonableness’ can be used to evaluate the legitimacy and fairness of the decision making process regarding reimbursement for each of the study drugs. Elements of the decision making process that comply with the framework can be considered examples of ‘good’ practice, while areas of non-compliance maybe considered opportunities for improvement. The following section is organized according to the four conditions of AFR: relevance, publicity, revisions and appeals, and leadership. Please refer to Text Box 4 below for a summary of key findings.
Text Box 4. Summary of Key Findings

1. Some of the relevant values, as identified by participants, were used in the decision making process.
2. Some of the relevant stakeholders were included in the decision making process most commonly health experts and public members.
3. The degree to which the rationales of decisions were publicized varied by committee. Some committees used numerous methods of publicizing rationales while others had no method of publicity.
4. Israel allows the public to resubmit drugs for review while other national committees have no mechanism for members of the public to appeal decisions.
5. Transparency and the committees’ ability to meet the first three conditions of AFR were directly affected by key people within the committees and policies.

4.5.1 Relevance

Committees used values that all participants agreed were relevant. Participants suggested the inclusion of other values, which were not used, including: evidence, cost, lack of alternative treatments, QOL and medical necessity.

The stakeholders involved in the decision making process varied by committee. Generally, the stakeholders that were most often involved in the decision making process were healthcare professionals, academics and the public. For a complete list of the types of stakeholders involved within each committee, please refer to Table 16 in section 4.2.4. Only NICE had industry representation. PBAC, at one time, had a former industry member. Public members were involved only in the CED, IBC, and PBAC. CEDAC did not have public members on their committee during their review of the study drugs. While NICE did not have public members, they did have patient advocates on their committee. The West Midlands Exceptional Drug Panel did not include industry or public members due to issues of
confidentiality, as decisions were made on a case by case basis. Similarly, the US State Medicaid P & T Committee did not include any public or industry members.

CEDAC partially satisfied the *relevance* condition. CEDAC used some of the relevant values in their recommendation process - i.e., evidence of cost-effectiveness & effectiveness, and equity. However, they did not consider lack of alternative treatments, life saving ability, or QOL, which participants believed were also important considerations. Additionally, CEDAC, at the time of the study, only included health care experts in the recommendation process. Public members were only recently added, and to date, there are no industry members on the committee. In order for CEDAC to fully satisfy this condition, they should include more relevant values and a wider array of stakeholders, including public and industry members. The recent inclusion of public members is a positive move towards greater compliance with the *relevance* condition.

CED partially satisfied the *relevance* condition. CED used some of the relevant values in their recommendation process - i.e., evidence of cost-effectiveness & effectiveness and improved survival. However, they did not formally consider preventative therapy, lack of alternative treatments, or QOL, which participants believed were also important considerations. CED, at the time of the study, only included health care experts and public members in the recommendation process (for Glivec). To date, there are no industry members on the committee. In order for CED to fully satisfy this condition, they should include more relevant values and a
wider array of stakeholders, including industry members. The recent inclusion of public members is a positive move towards compliance with the relevance condition.

The Hospital P & T Committee partially satisfied the relevance condition. They used some of the relevant values in their recommendation process - i.e., evidence of cost-effectiveness and effectiveness. However, they did not formally consider severity, lack of alternative treatments, or QOL, which participants believed were also important considerations. Like CEDAC, at the time of the study, the Hospital P& T committee only included hospital health care experts in the recommendation process (for Xigris). To date, there are no public or industry members on the committee. In order for the Hospital P & T Committee to fully satisfy this condition, they should include more relevant values and a wider array of stakeholders, including patients and industry members.

NICE partially satisfied the relevance condition. NICE used some of the relevant values in their recommendation process - i.e., cost and clinical effectiveness, and clinical need. However, they did not formally consider severity, preventive therapy, or improved survival, which participants believed were also important considerations. Unlike the aforementioned committees, NICE included a robust array of stakeholders, including consumer groups and industry members, as well as experts and government representatives. In order for NICE to fully satisfy this condition, they should include more relevant values.
The West Midlands Exceptional Drug Panel partially satisfied the *relevance* condition. They used some of the relevant values in their recommendation process - i.e., cost-effectiveness and equity. However, they did not formally consider effectiveness or life saving ability, which participants believed were also important considerations. The West Midlands Exceptional Drug Panel was composed of a small group of experts and no public or industry members were included. In order for West Midlands Exceptional Drug Panel to fully satisfy this condition, they should include more relevant values. The addition of more stakeholders would be problematic because of patient confidentiality, as decisions are made on a case by case basis.

PBAC partially satisfied the *relevance* condition. PBAC used some of the relevant values in their recommendation process - i.e., cost-effectiveness, effectiveness, life saving ability, equity, and severity. However, PBAC did not formally consider improved survival, preventative therapy or clinical need, which participants believed were also important considerations. PBAC has public members and experts on the committee. At one time, they had a former industry member, but currently, no industry membership exists. In order for PBAC to fully satisfy this condition, they should include more relevant values and a wider array of stakeholders, including industry members.

The IBC partially satisfied the *relevance* condition. They used many of the relevant values in their recommendation process - i.e., cost-effectiveness, effectiveness,
equity, severity and preventative therapy. They also more generally considered
deesaving technology with full improvement and new technology for serious diseases
with no alternative treatment, as well as QOL issues. The IBC, like NICE, had a
robust array of stakeholders; however, no industry member exists. In order for the
IBC to fully satisfy this condition they should include a wider array of stakeholders,
including industry members.

The US State Medicaid P & T Committee partially satisfied the relevance condition.
While the values used by the committee for restricting drugs were relevant and
appropriate, the CMS (which makes the listing decisions) only considers what "is
reasonable and necessary", without regard to cost-effectiveness. The US State
Medicaid P & T Committee had no public or industry members. In order for the US
State Medicaid P & T Committee to fully satisfy this condition, they should include
more relevant values and a wider array of stakeholders, including industry members.

4.5.2 Publicity

Multiple methods of communication were used by committees, including web
posting, newspaper publications, and radio announcements. Brief rationales for
decisions were available online from CEDAC, CED and PBAC. NICE posted
lengthy rationales for decisions on the internet, both for health professionals and lay
people. The IBC did not post rationales, but they can be requested formally. The US
Medicaid State P & T Committee has begun to post new decisions; however, older
rationales (like that of Cerezyme and Remicade) were not available except through
formal request. In West Midlands, outcomes of individual requests were not publicly available due to confidentiality. The Hospital P & T Committee rationales were not available for the public. However, decisions were often made known to staff throughout the hospital through mailings and word of mouth. Manufacturers are generally the best informed with regards to the process, as related to CEDAC, CED, NICE and PBAC - as they were the initiators of the process - i.e., they submitted the drugs for review. Patient groups, if well organized (according to participants), were able to keep close tabs on the process through informal avenues.

CEDAC and the CED partially satisfied the *publicity* condition. Both committees posted all rationales on their web site; however, rationales are very brief and written in technical language. In order for these committees to fully satisfy this condition, they should have more in-depth rationales and these rationales should be available in non-expert language for people other than health care professionals.

The Hospital P & T Committee did not meet the *publicity* condition because rationales are not available to the public and it is their intention for this not to change; however, hospital staff are informed of the decision, usually through informal avenues.

NICE fully satisfied the *publicity* condition because lengthy rationales are available online for both health professionals and lay people. Additionally, decisions are publicized through radio and newspaper advertisements.
The West Midlands Exceptional Drug Panel did not satisfy the *publicity* condition because decisions are not publicized due to confidentiality.

PBAC partially satisfied the *publicity* condition. While they have posted all rationales on their web site, the rationales are very brief and written in technical language. In order for them to fully satisfy this condition, they should have more in-depth rationales and these rationales should be available in non-expert language for people other than health care professionals.

The IBC did not satisfy the *publicity* condition as no rationales are available online; however, hard copies of rationales can be formally requested. Additionally, final recommendations are publicized through the radio and newspapers.

The US State Medicaid P & T Committee did not meet the *publicity* condition, as no rationales were posted for the study drugs.

**Reflection 8**

<table>
<thead>
<tr>
<th>The Extent of Publicity Required</th>
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<tr>
<td>Is it ever justifiable to not publicize rationales?</td>
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**4.5.3 Revisions and Appeals**

Each committee had an appeals process. However, only some stakeholders had access to an appeals mechanism (See Table 15 below). Manufacturers may appeal decisions made by CEDAC, CED, NICE and PBAC. Patients were not able to
formally appeal the process at CEDAC, CED, NICE, PBAC, and the Hospital P & T Committee. Patients were able to appeal the IBC, West Midlands Exceptional Drug Panel and the US State P & T Committee (if they are members of the plan). Physicians were able to appeal decisions at the West Midlands Exceptional Drug Panel, US State P & T Committee, CED and NICE.

CEDAC partially satisfied the *revisions and appeals* condition because only manufacturers have the ability to appeal decisions. Similarly, the CED and the Toronto Hospital P & T Committee partially satisfied the *revisions and appeals* condition. The former only allows manufacturers and physicians to appeal, while the latter only allows physicians to appeal. In order for CEDAC and CED to fully satisfy this condition, patient access to the appeals mechanism is critical.

NICE partially satisfied the *revisions and appeals* condition. While NICE did allow a number of stakeholders to appeal, the general public did not have the ability to appeal. In order for NICE to fully satisfy this condition, patient access to the appeals mechanism is necessary.

The West Midlands Exceptional Drug Panel partially satisfied the *revisions and appeals* condition because they only allow physicians and patients to appeal, and not industry.
PBAC partially satisfied the *revisions and appeals* condition because patients were not allowed to formally appeal the process. In order for PBAC to fully satisfy this condition, patient access to the appeals mechanism is critical.

The IBC partially satisfied the *revisions and appeals* because manufacturers were unable to appeal the process. Similarly, the US State Medicaid P & T Committee partially satisfied the *revisions and appeals* condition because manufacturers were unable to appeal the process.

Table 17. Stakeholders with Access to the Appeals Mechanism

<table>
<thead>
<tr>
<th>Committee Name</th>
<th>Stakeholders with Access to Appeals Mechanism</th>
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<tbody>
<tr>
<td>CEDAC</td>
<td>• Manufacturers</td>
</tr>
<tr>
<td>IBC</td>
<td>• Citizens</td>
</tr>
<tr>
<td></td>
<td>• Physicians</td>
</tr>
<tr>
<td></td>
<td>• Patient groups</td>
</tr>
<tr>
<td>NICE</td>
<td>• Patient organizations</td>
</tr>
<tr>
<td></td>
<td>• Health professionals</td>
</tr>
<tr>
<td></td>
<td>• Manufacturers</td>
</tr>
<tr>
<td></td>
<td>• Health service providers</td>
</tr>
<tr>
<td></td>
<td>• Statutory organizations</td>
</tr>
<tr>
<td>PBAC</td>
<td>• Manufacturers (can appeal on process error only)</td>
</tr>
<tr>
<td>US State Medicaid P &amp; T Committee</td>
<td>• Members of the plan</td>
</tr>
<tr>
<td></td>
<td>• Physicians</td>
</tr>
<tr>
<td>CED</td>
<td>• Manufacturers</td>
</tr>
<tr>
<td></td>
<td>• Physicians</td>
</tr>
<tr>
<td>Toronto Hospital P &amp; T Committee</td>
<td>• Physicians</td>
</tr>
<tr>
<td>West Midlands Exceptional Drug Panel</td>
<td>• Physicians</td>
</tr>
<tr>
<td></td>
<td>• Patients</td>
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</table>
4.5.4 Leadership

Each committee has key individuals who take on leadership positions. Some individuals were instrumental in making improvements to the process. As a result of key individuals, CEDAC included public members, NICE continues to have industry members, and the US State Medicaid P& T Committee is beginning to publicize rationales. Alternatively, leaders on all committees, with the exception of NICE, have no desire to include industry members on their committees.

CEDAC partially satisfied the leadership condition. This is evident in the recent addition of public members on the committee. The former Chair of CEDAC long advocated for the inclusion of public members on this committee as a means of increasing equitable access. However, there is no indication that current leaders wish include industry members on the committee. In order to fully satisfy this condition, leaders must advocate for the inclusion of more stakeholders, and more in-depth rationales should be made publicly available.

CED partially satisfied the leadership condition. This is illustrated through the enactment of Bill 102, which required an increase in transparency, and thus obligated the committee to post rationales on the internet; however, the extent to which decisions are publicized was not regulated. It should be noted that Bill 102 was not written or passed by leaders of the CED. Nonetheless, the CED leaders enforce this bill. The recent inclusion of public members on the committee also demonstrated the initiative of leaders to improve accountability and inclusiveness in
the decision making process. Nonetheless, like CEDAC, there is no indication on the part of current leaders to include industry members on the committee. In order to fully satisfy this condition, leaders must motivate the inclusion of more stakeholders and more in-depth rationales should be made publicly available.

The Hospital P & T committee did not satisfy the *leadership* condition. This is evident through the lack of desire to include other stakeholders on their committee, as well as the publishing of rationales internally. In order to fully satisfy this condition, leaders must motivate the inclusion of other stakeholders as well as make their rationales available to the general public.

NICE satisfied the *leadership* condition. This is evident through the desire to constantly improve their process and their openness to having their process externally reviewed (as demonstrated through the WHO’s assessment). Additionally, they are the only committee that has posted lengthy rationales for both health professionals and lay people. Moreover, they are the only committee that requires industry representation on the committee.

The West Midlands Exceptional Drug Panel satisfied the *leadership* condition. I believe this despite their limited involvement of different stakeholders and the fact that they do not publish their rationales for decisions. As indicated by their leaders, it is reasonable that when making case by case decisions for a small population that
can be easily identified, the committee must also consider protecting the confidentiality of the patients they serve.

PBAC partially satisfied the leadership condition. Leaders do not have a desire to include industry members on the committee. In order to fully satisfy this condition, more lengthy rationales for both health professionals and lay people must be available. Moreover, the inclusion of industry on the committee is necessary.

IBC partially satisfied the leadership condition. The IBC is required by law to inform the public of all inclusions in the health basket; however, the extent to which decisions are publicized was not regulated. Nonetheless, there does not seem to be the desire (on the part of leaders and committee members) for the future inclusion of industry members on the committee. In order to fully satisfy this condition, lengthy rationales for both health professionals and lay people must be available. Also, the inclusion of industry members in the committee is necessary.

US State Medicaid P & T partially satisfied the leadership condition. This is evident in the recent posting of rationales on the internet in two languages. The Chair of the US State Medicaid P & T Committee advocated and played an integral role in the publicity of rationales. They are in the process of improving their decision making process, but currently, the only stakeholders involved are Medicaid staff. Additionally, there does seem to be the desire (on the part of leaders and committee members) for the future inclusion of public members; however, there is no such
desire for future inclusion of industry members on the committee. In order to fully satisfy this condition, leaders must motivate the inclusion of other stakeholders.

4.6 The Role of Innovation

The six drug case studies explored in the aforementioned sections are all biopharmaceuticals, expensive and innovative drugs. This section emerged from interview questions (see Appendix 4) focused on the impact of health system priority setting on innovation - specifically, drug innovations. The particular interview questions were formulated surrounding: 1) the impact of health system sustainability and the PS formulary recommendation/decision process on innovation, and 2) motivations and impediments to biopharmaceutical innovation. However, participants also discussed the manner in which innovation has impacted on health system sustainability. A discussion of the impact of health system priority setting on biopharmaceutical innovation, and, alternatively, the impact of biopharmaceutical innovation on health system priority setting and ultimate sustainability will be presented.

Based on the participants’ responses, a number of themes emerged about the impact of drug reimbursement recommendations/decisions on innovation. The main themes that emerged included: the need to consider the value of innovation in drug reimbursement recommendations, impact of reimbursement on innovation, the role of investment on stimulating innovation, the impact of innovation on health system
sustainability, and impediments to the uptake of innovations. Please refer to Box 5 below for a summary of key findings.

<table>
<thead>
<tr>
<th>Text Box 5. Summary of Key Findings</th>
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<tbody>
<tr>
<td>1. The value of innovation in PS drug reimbursement recommendations was debated.</td>
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<tr>
<td>2. Participants believed that reimbursement recommendations have impacted on the creation and uptake of innovation.</td>
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<tr>
<td>3. Participants believed that public and private investment in innovation was critical for successful creation and uptake of innovation.</td>
</tr>
<tr>
<td>4. Participants were divided about the impact of innovation on health system sustainability. Some believed that innovation could result in cost increases while others believed that it could result in cost reductions.</td>
</tr>
<tr>
<td>5. Participants believed that price-capping may impede innovation.</td>
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**Value of Innovation**

Innovation was considered to be a value important to priority setting by many participants. Some participants discussed the value of innovation in promoting industry growth. This idea was also reflected in each of the five countries' innovation policies. Recall from the Background and Significance Section that government initiatives, although not specific to health innovation, impact on the health system as some innovations and biotechnologies are applicable to the health sector. For example, the Canadian Ministry of Industry's innovation strategy in 2001 (refer to Section 2.2 page 26) had significant impact.

Recognizing the value of pharmaceutical innovation in reimbursement decisions was considered integral by some patients. According to one Fabry’s patient,

“I know before the Orphan Drug Law came into being there were very few classified orphan conditions that treatments had been developed for...so as far as, ....[there are] incentive[s] for pharmaceutical companies to provide
drugs for these small patient communities. I believe, it’s [i.e., policy] been very essential and extremely positive turn for the patient community in these rare disease groups.”

Similarly, an industry participant noted,

“I think there is a rationing that’s going to take place but I think that innovation needs to be part of their decisions around ration. And I think everybody can probably look into a system and figure that there can be different ways to spend the money. There is just not an infinite amount of money… I think … industry Canada saying [an innovation] strategy, that’s very important.”

Additionally, the involvement in drug reimbursement recommendations by a Government’s Ministry of Industry was also considered integral to fostering innovation. One PBAC committee member identified the role of the Ministry of Industry as critical to the uptake of innovation,

"The Minister for Industry is generally a more powerful figure than the Minister for Health… Industry, because it brings in such a large proportion of the government’s income or the GDP does tend to have a fair amount of power … But I don’t think it’s as powerful as it is in the US. But it’s certainly quite powerful because it brings in dollars."

Recall from Section 2.2 that the Ministry of Industry from each country is generally responsible for implementation of Innovation Strategies. However, in terms of their actual involvement in drug reimbursement recommendations, only Israel formerly included a member of the Ministry of Industry on the IBC (Section 3.2 Table 3).

Alternatively, others believed that priority setting may not be the correct forum for discussions regarding innovation. As one committee member explained,

“The bottom line is that I am not sure whether priority setting is a job to think about innovation, you know, whether it is dampening innovation. I think that
society has to decide what limits are going to be set on the funding but I think the policy makers …are not fully realizing the priority setting decisions they make do have an impact on drugs people do get for therapy.”

Committee members often recognized that companies need to make returns on their investments (i.e., innovation). However, one CEDAC member commented on the need to change the business model and link it closely to the proven clinical outcomes of the innovative drug,

“Companies aren’t going to continue to invest in a product that they’re making absolutely no money from. But I think the business plan needs to change for companies… Maybe their price… could change based on the level of evidence. So their new, innovative drug that is just shown to affect a surrogate end point, maybe they get X price for that. And once they’ve shown that it actually improves clinical outcomes the price goes up… So while companies market these things as innovative and the patient has to use them there’s lots of examples of innovative drugs that a couple of years later have shown to be…. dangerous.”

**Impact of Reimbursement on Innovation**

In this section I will discuss participants’ perceptions of how reimbursement and investment impacted on innovation. My participants stressed that reimbursement decisions have impacted on the creation and uptake of innovation and on a company’s desire to invest in a particular country.

Participants’ ideas varied regarding the impact of reimbursement decisions on innovation. Some believed they had little impact and others believed that the reimbursement decisions had a great impact on its creation and uptake, as well as a company’s willingness to invest in a particular country. Even industry representatives did not agree on reimbursement decisions’ impact on innovation.
One industry interviewee highlighted that reimbursement decisions did impact innovation,

“If you don’t value innovation… then you will start to have less and less money to go to research- certainly from private sector… And that’s not just 100% having positive reimbursement environment, but that’s an element of it. I mean you will look at other things. You will look at a quality of the health care system... You will look at various other things, but reimbursement is definitely a factor in innovation.”

Alternatively, another industry representative said, “I would say the reimbursement perspective is looked at, but it’s not a major driver.” It is likely not a major consideration because of the impact of the US market, which often is the driver for decisions. Yet another industry respondent believed that if obtaining reimbursement in a country is difficult, their company would be less likely to invest in that particular country. S/he explained,

“When we introduce a product in the Canadian market it’s the Canadian market that dictates how the company will invest in the country. Because our global headquarters is strategizing on where they will invest for this drug, where the trials will be conducted and price - will we be flexible or not depending on the country. Canada is being known as one of the toughest countries to obtain reimbursement. So when global headquarters needs to conduct trials they have to look at like is Canada a good place to do business? Do we invest there? Because all the countries want studies in their country because when you submit your file they want to see if there’s Canadian experience.”

Alternatively, some committee members doubted that their formulary recommendations impacted on pharmaceutical companies’ innovations,

“They [i.e., industry] are out to make a buck. That is their priority. And, if innovation is a way to make a buck, they put their money into that. So I do not think...if you do not add it to the formulary, we are not going to be able to put tons of money into research. Yeah, right. What type of research? Hospitals, usually teaching universities settings are doing the basic research. They [pharmaceutical companies] are just manipulating the molecule.”
Similarly, another committee member recognized the need for companies to profit but was unsure if negative recommendations stifled innovation. S/he explained,

“The difficulty from a pharmaceutical point of view is they have invested millions of pounds in years to develop a drug. And, you know, they’ve got an interest in selling it even if it only delivers 4 weeks… extension to life. But I’m sure if we [turned it down]… we’d have much fewer drugs coming to market. But is that a bad thing? And would it really stifle innovation to the amount that they say it would? … I don’t know….It’s an issue but if I start to worry about it, I can’t actually do my job.”

Patients also believed that companies tended to invest in countries that are more likely to reimburse their drugs. Moreover, some believed that governments needed to negotiate with companies to increase economic benefits. As one patient explained,

“I would be saying to companies like Genzyme or Biovail or any of these companies, okay, we’re gonna fund your drugs but we want some of that money back. We want you to set up a research centre …Governments are stupid. The government should be saying to a company like Genzyme, yes, you have a great product. Yes, it works. Yes, it’s approved. We’re gonna fund it…across the country. But you’re going to do business here in Canada. You’re gonna create jobs in Canada and you’re gonna do your R&D in Canada.”

**Role of Investment for Stimulating Innovation**

In this section I will discuss participants’ perceptions of how investment impacted on innovation. Participants discussed the importance of public and private investment in the successful creation and uptake of innovation.

Investment in innovation was considered an extremely important factor that has impacted on the creation and uptake of innovative products, and ultimately on a company’s decision to invest in a particular country. One PBAC member explained
the importance of investment in innovation, while still recognizing the need to be cautious in what innovations are supported and their subsequent cost:

“We’ve gotta invest in the future...However, in any business ... you look at what you’re investing in. So if you look at ...the number of truly innovative drugs in the last two decades [it] has been very small indeed...I can’t think of any other industry in the world where we should pay for things irrespective ...Pharmaceutical manufacturers of the world need to be viable industries to the extent that ... will allow them to reinvest in research and development...If they [industry] want us to take innovation into account then …What does it cost you to manufacture that…? Because this debate it’s proof that they want it both ways. They want us to charge the price that the market will bear which is what … determines the US price … that bears no relationship to the cost of goods.”

Patients also emphasized the importance of governmental investment in innovation. As one respondent noted, governments must be involved in access to drugs in public systems, especially as related to drugs for disease groups which are less profitable,

“The government doesn’t have to reimburse any drug -- that’s for sure… Governments are not worried about these groups, are not really concerned about these groups. How can they expect the pharmaceutical companies … [to] be worried about that?”

However, one Hospital P& T committee member concurred that formularies do not necessarily support innovation,

“I wouldn’t say that the process really supports the research because obviously most of the decisions are based on evidence- right? And the research is the development of that evidence.”

Therefore, participants’ views on the impact of reimbursement were mixed. Some of them cautioned against placing too much value on innovation as a criteria for drug
PS. Still, participants generally seemed to support the notion that government and industry should invest in innovation to stimulate future drug development.

Impact of Innovation on Priority Setting

In this section I will discuss the varying participants’ views about the impact of innovation on priority setting and ultimately on the sustainability of the health system and their views regarding public spending on innovation. Also, I will discuss one suggested solution to potential rising costs: price capping, which is a controversial solution, as it may impede innovation.

Some interviewees believed that innovation did not result in cost increases to the health system. For example, a Hospital P& T committee member stated that “innovation doesn’t necessarily lead to increased cost in the system.” One patient representative also explained how innovation per se is not necessarily increasing the cost of drugs to the health system, but rather, the need for stringent clinical trials for each indication results in increased costs,

“I don’t think research and development became more costly. I think [it] actually [became] less costly...But if you need a new clinical trial every time you have a new ...indication you are going to increase the costs for the company. So you’re not going to be able to promote so many clinical trials to approve each new indication and that’s a problem.”

On the other hand, many others, including patient and committee member participants, believed that innovation resulted in increased costs to the health system. Moreover, they believed the pricing of innovative products were inflated. As one patient respondent commented,
“So I think some of these drugs are priced ridiculously … Some of them have priced certain drugs way beyond any realistic expectation for any public system or private system. In the States it’s the first time I’ve ever seen American cancer patients complaining about costs- they’ve never done that ever before…I don’t know what the solution is for it. But like everything else I think there is a solution and coming together, some compromise on both sides.”

Similarly, a committee member believed that pharmaceutical companies are inflating the price of their drugs because companies realized that public systems will ultimately pay the market price. S/he explained,

“They [the pharmaceutical companies] are overpricing most of their drugs. But you see that’s actually sort of the nature of modern science phenomena. When I first came into public health, I remember we used to get really freaked out by a “Oh my god, 6,000 pounds…for 6 cycles of treatment”….those were really, really high cost. Of course as science has progressed, we’ve now moved into the biologicals….You could argue all about their expensive, I mean the ultra orphans, one of their big things is about the actual production but the problem is they are all long-term treatments…It’s just the nature of where medical science is at. Plus we …are stupid enough to pay those prices. If we are stupid enough to pay those prices in the Western world, they [pharmaceutical companies] will keep upping their costs.”

Some committee members strongly believed that the public system should not bear the cost of innovation. The committee member firmly stated,

“Our health care system should not be paying for innovation. It should be paying for improvement in health outcomes. And so innovative therapies that have not shown themselves to improve health outcomes need to do more research to show that they improve health outcomes before they should be paid for.”

Price capping, where a committee refuses to pay over a certain dollar amount for a drug, was a method recommended to be used to combat the rising cost of innovative biologic drugs. However, price capping does not make allowances for innovations. As one PBAC member explained,
“PBAC in a way is kind of capping the amount that we believe should be subsidized. And it might be that in the process of innovation something becomes more and more and more costly. And we go above that and therefore it'll never be subsidized. And we see that to a lesser extent with biological agents, you know expensive agents now that they take a while to get there. But there are a whole lot of things embedded in that. I mean the notion of innovation which is, you know, there is unquestionably a group of drugs that come to us every year …That are novel innovations with a high likelihood for better outcomes for our community. But the vast majority of drugs that come to us are not like that. They’re either copies or isomers or …not substantially gonna alter the face of the world at all. So I suppose what we haven’t factored into this is we put them all into the same process. And that there isn’t a premium necessarily given to the truly innovative but very expensive intervention and that’s because of a capping phenomenon.”

**Impediments to Innovation**

The following section discusses the following impediments to innovation, as highlighted by participants: 1) lack of a consistent definition of innovation was considered to be problematic; 2) the complex (i.e., multiple jurisdictional filing), lengthy, tough and expensive processes deterred companies from filing their drugs; 3) industry considered price capping as an impediment; and 4) patients believed the reimbursement process was a barrier to innovation.

**Lack of a Consistent Definition of innovation**

One obstacle to discussions surrounding innovation is the lack of a consistent and singular definition between stakeholders. As one PBAC member explained,

“What do you mean by innovation? …Well for some companies’ innovation means new. It should be a new drug. Some people will say innovation … if it’s innovative it provides a health gain, an additional health gain. Some people might say innovation is a new molecular target … but has the potential because it’s a new target to do certain things.”
Complex Process

Many industry representatives discussed companies not filing their drugs in countries which are not industry-friendly - i.e., policies and processes that create an unfavorable environment to invest in. As one respondent explained,

“We know ones [pharmaceutical companies] that have not filed in Canada because it is not worth it for them. They say there … [are] too many barriers; there would be too much human and capital expense to try to change the systems.”

One member of the CED explained that companies are most influenced by the US market:

“In a lot of cases these companies aren’t based here in Canada. We don’t represent a major market share in the world for these drugs so I don’t think it’s impeding innovation. These companies are out there bringing these new innovative products to market in other markets. I mean the United States obviously is the biggest market in the world so they’re developing them in any event because they want to bring them to that [US] market.”

Similarly a CEDAC member stated that,

“Drugs really are developed for the US …they continue to drive innovation but they also are causing a huge problem in that they continue to pay these prices for these medications with very little evidence. And so the rest of us are forced to either do the same or accept the level of information that people in the States are prepared to accept.”

Nonetheless, systems that require multiple drug filings, as is the case in Canada’s provincial formularies, impede access to innovation. As one member of the CED discussed:

“I think …time delays…impede, obviously, patient access in Canada. I don’t think it’s impeding innovation. We don’t represent enough of a market share for it to do that. But it’s certainly obvious any time delay does impede access to the drug for Canadians.”
**Price Capping**

Price capping was discussed above as a method to restrict the cost of innovation - but some participants also discussed price capping as an impediment to innovation.

Price capping is currently practiced in Australia. A PBAC member commented on how, from an industry perspective, price capping is seen as an impediment to innovation,

“So when people in Australia start this debate. And they’ve started it... we get called … the impediments to innovation. I’m sorry, what do you mean? Well the prices you give us don’t allow us to invest... Is price control, as perceived by purchase of health outcomes, that is value for money, is that an impediment to innovation? Well potentially it could be I supposed.”

**Reimbursement Process**

Patients believed that the reimbursement process was an impediment to innovation, particularly for the biologic drugs (a discussion of reimbursement was presented above in greater detail). As one patient explained,

“It [reimbursement process] definitely hinders I think the innovation for new drugs and therapies. I think, that especially biologic drugs, for rare disorders and these kind of things. ...It hinders the actual development of products in Canada. And I think it also hinders to a great degree companies trying to market their product in Canada.”

However, according to one member of the CED:

“I don’t know whether it [the reimbursement process] hampers innovation and why I say that is these companies, that are bringing these new products to market, are doing it in any event and Canada’s process is not gonna hold up these multi-national corporations from doing that development.”

An industry representative further supported the above view,

“I have not witnessed a case where a reimbursement decision has affected what the company has looked at in terms of what to develop. No, I would say that it has not restricted at all but they still look at what molecules they feel would have good promise for patients and that’s how they move forward.”
In summary, while sustainability and cost savings are considered by many committees when making formulary listing recommendations, governments look to innovation as a means to contribute to the economy. Some participants believed that innovation is a value that should be used in formulary recommendations and government policies. Additionally, investment in innovation, both private and public, was seen as a motivator for the successful creation and uptake of innovation. The emergence of pharmacogenomics may impact on the relationship between innovation and sustainability. Pharmacogenomics is leading us towards an era of targeted treatments. While their cost implications remain unclear, it will be necessary to identify core values and norms to be applied in funding decisions. Stakeholder inclusion will become essential to this process.

4.7 Results Section Recapitulation

Eight Reflection textboxes have been highlighted throughout this chapter. These textboxes identified some common themes which appeared throughout this Results Section. Recall the themes were as follows:

1) The Rule of Rescue: How is the rule used? Is there tension between the value of efficiency and the value of saving a life?

2) Access to the Decision-making Process: Who should have “access” to the decision making process?

3) Alternative Mechanism for Accessing Drugs: Should some drugs be accessed through a different mechanism? Does rarity alone warrant a different
mechanism for access to ODs? What would be some key considerations of an alternative mechanism?

4) The Impact of Meeting a Cost Criterion: Should drugs that fail to meet strict cost-effectiveness criteria be included in public formularies? What about considerations of the total impact of the drug on the whole system (i.e., keeping people working and contributing taxes)?

5) Notions of Medical Necessity: Why are some treatments considered medically necessary while others are not?

6) The Impact of Technology and Innovation: Should public drug funding agencies consider the innovative nature of the drug? If so, how should innovation be defined?

7) Insufficient Evidence: When the evidence of effectiveness is insufficient, what should committees do to improve the reimbursement decision making process?

8) The Extent of Publicity Required: Is it ever justifiable to not publicize rationales?

These themes will be explored in Chapter 5.
5.0 DISCUSSION

This Chapter is divided into six sections: 1) Filling the Gaps in Knowledge, which identifies how my research has filled some of the gaps in knowledge described in Chapter 2, and discusses how the findings of my research advance the background literature; 2) Lessons Learned, which elaborates on the Reflections textboxes that appeared throughout the Results Section in chapter 4; 3) Implications for Policy & Practice, which elaborates on the contribution made by this research to policy and practice; 4) Study Limitations, which describes the methodological limitations of this study and discusses some ways in which this project could be improved; 5) Future Research, which identifies areas for future research, and 6) Concluding Remarks, which reflects upon the study and its research findings by my recommendations for improved priority setting in the reimbursement of expensive biopharmaceuticals.

5.1 Filling the Gaps in Knowledge

My research helps to fill some of the gaps in knowledge regarding international expensive drug reimbursement and priority setting. These gaps were initially described in Chapter 2. For a summary of the gaps in knowledge, actions to fill the gaps, and research findings, please refer to Table 19.

Gap #1: There has not been an attempt to describe public reimbursement decisions for expensive biopharmaceuticals using the drug as the case, while considering patient and industry views.

To my knowledge, this is the first study that has used the drug as the case to describe and evaluate drug reimbursement decisions, as well as to describe the views of the patient and industry members regarding this process. This study was innovative because I focused on the drug as the case. Previous studies in priority setting have
focused on 1) committees and 2) organizations/institutions. Van Rijkom et al. (1999) focused on the assessment of three biotechnology drugs. Van Rijkom's study looked at the literature surrounding the assessment and diffusion of these biotechnology products as it related to four criteria: 1) safety, 2) efficacy, 3) cost, and 4) ethical, legal and social factors. My study differs from the aforementioned because 1) it spanned five countries, allowing a comparison of values in order to ascertain if and how they differ, 2) the criteria/values I identified were grounded on key stakeholder input, and not just an evaluation of the literature, and 3) I evaluated decisions against an ethical framework, and I identified areas of improvement through non-compliance with the framework.

My research method allowed for comparative analysis across different health systems and across different levels/jurisdictions within these health systems. This allowed for the identification of potential differences in approaches to the priority setting of expensive drugs. Ultimately, it resulted in the important finding that despite differences in culture and jurisdiction, participants identified similar values that they believed were important to the drug reimbursement process. Using the drug as the case allowed me to tie my analysis closely to PS issues related to biotechnology drugs. The current study also expanded the scope of this research to a number of jurisdictions and allowed for the inclusion of more stakeholder perspectives, such as government, patient and industry groups. Therefore, this method resulted in data that is better grounded in the real life experiences of the key stakeholder groups and closely tied to decisions surrounding biotechnology drugs.
Gap #2: There has not been an attempt to describe and evaluate the legitimacy and fairness of governmental reimbursement recommendations regarding these expensive biopharmaceuticals.

No PS studies have compared and evaluated expensive biopharmaceuticals across different health systems. PS research of drugs has generally been conducted at the macro level, within specific drug contexts [47, 172, 180, 334, 335], or in intensive care units [176, 336]. Limited research has been conducted on expensive or high cost drugs (HCDs) [69, 337, 338]. My research expands on this research by examining the PS of the study drugs across the macro and meso levels. This allows for a greater depth in understanding.

Additionally, the participants in my research, across all jurisdictions, identified three values that were not previously included in priority setting of expensive drugs: lack of alternative treatments – consideration should be made if the drug is the sole treatment available; quality of life – increased QOL should be a consideration; and inclusion of all stakeholders - include all stakeholders in priority setting.

The participants’ views concerning the inclusion of a wider array of values have been identified by other researchers. Martin et. al. noted that drug priority setting is not solely a technical process. At its core is the difficult task of adjudicating between and among a wide range of relevant values [180]. Gallego et. al., indicated that priority setting for high cost drugs is often based on other factors, in addition to effectiveness and cost [69]. My research adds to the literature in that it identifies some values that participants believed were important to the PS of expensive drugs, such as lack of alternative treatments and QOL.
The importance of including all stakeholders in decision making is also supported by the literature. Martin et. al., described elements of fairness in priority setting identified by decision makers for new technology. Decision makers identified including multiple perspectives – representing different stakeholder groups – to be the most important element of fair priority setting \[67\]. My research further adds to the literature in that this promotes the inclusion of industry within the deliberative process and the inclusion of patients in the appeal/revisions mechanism.

My study evaluated the descriptions of drug reimbursement recommendations/decisions across eight committees, using the AFR framework to assess legitimacy and fairness of the process. This research resulted in a number of key findings, all of which advance the literature. First, not all relevant values, as identified by participants, were used in the decision making process. Second, not all relevant stakeholders were included in the decision making process (i.e., industry tended to not be included). Many members of government committees in Canada, Israel and Australia believed that industry representation on the committee presented a conflict of interest. Third, the degree to which committees’ decisions and rationales were publicized varied by committee. Fourth, the public did not generally have the opportunity to appeal decisions on any of the national committees (with the exception of Israel). Finally, key people in leadership positions (within the committees) and policies have impacted on the transparency and the committees’ ability to meet the first three conditions of AFR.

My research demonstrates the importance of including both the values of lack of alternative treatments and QOL in the drug reimbursement process. This aligns with the relevance condition of AFR, which requires making decisions based upon relevant
rationales that all stakeholders have agreed to be relevant [339]. *Inclusion of all stakeholders* is also an element of the relevance condition, as it calls for the inclusion of all relevant stakeholders. When discussing drug reimbursement, a number of key stakeholders come to mind, including the drug manufacturers, the patients/consumers who use the drugs, the public who ultimately pays for the drugs, and the governments that make the final reimbursement decisions.

*Gap #3: No studies have been conducted that examine the implication of biopharmaceutical reimbursement decisions on the pursuit of biopharmaceutical innovation.*

The interviewed participants identified a number of elements that were important to innovation and sustainability, such as the *impact of reimbursement and investment.* Martin and Milway discuss how negative reimbursement decisions impede innovation [340]. It was interesting to note that most industry participants in my study did not believe that negative reimbursement decisions (in small market countries like Canada) impeded their company’s ability to innovate.

All countries in this study heavily invested in innovation to promote economic development, formulated specific innovation policies, and identified obstacles to innovation and its uptake [14,129,132,134,135]. These investment strategies were echoed in the views of the participants interviewed in this study.

My study demonstrated that participants’ views regarding the impact of innovation on priority setting and, ultimately, health system sustainability varied. Ultimately, it is unclear if investment in innovation will result in cost increases, or alternatively, cost reductions, to the health system. Nonetheless, stifling the innovation industry does not
address the cost implications to the health system regarding innovation. The pursuit of better health services, drugs and devices is critical if governments want to provide quality care. I believe there is a need for the creation of a supportive and friendly environment for the pursuit of innovation, including the creation of incentives and policies, which foster biopharmaceutical innovations even if some of these innovations are not publicly funded.

Table 18. Filling the Gaps in Knowledge

<table>
<thead>
<tr>
<th>Gap in Knowledge # 1</th>
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<tbody>
<tr>
<td><strong>Action to Fill Gap</strong></td>
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<tr>
<td>Conducted six qualitative case studies, to describe and evaluate the priority setting activities across five countries using ‘accountability for reasonableness’</td>
</tr>
<tr>
<td>Conducted and analyzed interviews with industry and patient representatives</td>
</tr>
<tr>
<td><strong>Research Findings</strong></td>
</tr>
<tr>
<td>Committees across five different countries shared similar values when making reimbursement decisions</td>
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<tr>
<td>Many study participants supported stakeholder participation in drug priority setting</td>
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<tr>
<td>Patients supported the values used by committees in their recommendation but believed that a greater breadth of values needed to be incorporated</td>
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<tr>
<td>Patient and industry strongly supported stakeholder involvement in priority setting</td>
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<th>Gap in Knowledge # 2</th>
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<tbody>
<tr>
<td><strong>Action to Fill Gap</strong></td>
</tr>
<tr>
<td>Evaluated the data against the framework of AFR and identified areas of improvement</td>
</tr>
<tr>
<td><strong>Research Findings</strong></td>
</tr>
<tr>
<td>No committee fully met all the conditions of the framework</td>
</tr>
<tr>
<td>Based on the lessons learned from the case studies, interviews, and the literature, I created guidance for committees on how to improve the drug reimbursement process (see Table 2)</td>
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<tr>
<th>Gap in Knowledge # 3</th>
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</thead>
<tbody>
<tr>
<td><strong>No studies have been conducted that examine the implication of biopharmaceutical reimbursement decisions on the pursuit of biopharmaceutical innovation.</strong></td>
</tr>
</tbody>
</table>
| Action to Fill Gap | Conducted six qualitative case studies, to describe and evaluate the priority setting activities across five countries  
|                   | Analyzed 56 interviews with committee members, industry and patient representatives |
| Research Findings | There is a need for the creation of a supportive and friendly environment for the pursuit of innovation including the creation of incentives and policies which foster biopharmaceutical innovations |

### 5.2 Lessons Learned

In this research, I described and evaluated the reimbursement decisions surrounding six specific drugs, across eight recommendation committees, using the framework of ‘accountability for reasonableness’. The views of committee members, patients, and industry representatives about the drug reimbursement process were also described through analysis of one-on-one interviews. The following section will begin by elaborating on the eight Reflections textboxes, which appeared throughout Chapter 4 of the Results Section.

**Reflections 1: The Rule of Rescue (ROR)**

<table>
<thead>
<tr>
<th>How is the rule used? Is there tension between the value of efficiency and the value of saving a life?</th>
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*How is the rule used?*

Johnson, in 1986, coined the term ROR, which referred to the moral obligation to save identified individuals who were in immediate peril, regardless of excessive cost [341]. However, the ROR in this study was used particularly for the two orphan drugs. The definition focused on life saving treatments for small populations for whom no alternatives exist.

You can recall from Section 4.2.2 that the ROR was used and applied by Canada, the UK, Australia and Israel. Each of the countries shared a similar definition related to
outcomes (e.g., saving a life), and this demonstrated a belief in the intrinsic value of the individual by these countries. Both the Australian and Israeli committees considered the ROR 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) lifesaving technology with full improvement, 2) potential of technology to prevent mortality/morbidity, and 3) new technology for serious disease with no alternative treatment. The other two countries’ considerations of the ROR will be discussed in the section below.

Is there tension between the value of efficiency and the value of saving a life?

As is widely discussed in the literature, there is often a tension between the cost-effectiveness, which values efficiency, and the ROR, which values saving a life. The ROR is often applied in situations where a drug fails to meet cost-effectiveness criteria, but is seen as life saving. As discussed in the Background Section, McKie and Richardson have argued that “indeed quantitatively significant and if there is a desire to incorporate an individual perspective … then….existing measurement techniques are defective” [155], because they do not incorporate individual perspectives.

My research has supported this finding in the literature. Specifically, the tension between the ROR and cost-effectiveness is best demonstrated through two countries in the study: Canada and UK. In Canada, Ontario’s Ministry of Health applied the ROR,
recognizing that saving a life takes precedence over cost considerations, after Cerezyme failed cost considerations. Alternatively, CEDAC did not consider the ROR 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.

Similar to the case of Cerezyme in Ontario, The West Midlands PCT made a decision against the funding of Cerezyme and Fabrazyme. The West Midlands Specialized Services Agency’s published a report on ERT, which presented key considerations when making funding decisions when treatments were clearly cost-ineffective. The ROR was one such consideration. Shortly thereafter, the DH, in England and Wales, decided to nationally commission for both Cerezyme and Fabrazyme. Recall from section 4.1.2, commissioning is typically done by PCTs and involves the assessment of needs, resources, and services, as well as the development of a strategic approach to allocate resources while meeting identified needs. It is interesting to note that NICE has recently rejected the use of the ROR as a value in their decision making process.

Saving a life is evidently valued across countries and committees; however, it is not the only value in consideration. Often, when making drug reimbursement decisions/recommendations, there is a trade-off between efficiency and saving a life. This study has demonstrated that some stakeholders place a greater value on efficiency - i.e., committee members, while others place a greater emphasis on saving a life - i.e., patients and industry representatives. My findings support the literature, which states that members of the public (for instance, patients) also believed that efficiency should not be the main criteria for reimbursement decisions [342]. This is
further demonstrated through the reaction to the ranking of priorities in the Oregon/Medicaid, specifically the rankings that violated the ROR were criticized and subsequently modified [165]. My findings add to the literature in that they demonstrated committee members’ preference for efficiency over saving a life, particularly when evidence of effectiveness is insufficient. I believe that in order to establish fair and legitimate PS reimbursement decisions, we must incorporate the value of saving a life particularly because a number of stakeholders believe it is valuable.

**Reflections 2: Access to the Decision-making Process**

Who should have “access” to the decision making process?

It has been argued in the literature that transparency would lead to increased confidence in the decision making process, and that it is integral to a fair and legitimate process [14, 16, 343]. Individuals’ (i.e., patients, members of the public, industry representatives, etc.) ability to access the decision making is one component of a transparent system. Moreover, there are different ways in which these individuals access the decision making process - by reading rationales, participating in the deliberation process, revising the process, appealing the decision, taking legal action, letter writing campaigns, demonstrations, and more. According to the AFR framework, stakeholders should be part of the deliberative process, have access to rationales, and the ability to formally appeal decisions.

This study demonstrated that various stakeholders accessed the decision/recommendation system differently. For example, many patients that I interviewed believed they had limited access to the deliberative process. Also, patients
often had no access to the appeal mechanism. Specifically, patients have no formal mechanism to appeal decisions/recommendations made by the following committees: CEDAC, CED, NICE and PBAC. Nonetheless, they did appeal decisions by exercising political pressure, including letter writing campaigns (e.g. Australian fertility patients) and effective use of the media (e.g. Gaucher patients in Ontario). Alternatively, patients could formally appeal decisions/recommendations made by the IBC, the US State Medicaid P & T and the West Midlands Exceptional Drug Review Committee. The US State Medicaid P & T committee allowed its members (i.e., patient beneficiaries) to appeal decisions on a case by case basis. Similarly, the West Midlands Exceptional Drug Review Committee allows appeals by patients on a case by case basis.

Members of committees often believed that a patient’s ability to access rationales on the internet and have public members sit on the committee is sufficient access for patients. Alternatively, patients believed that their testimonials and personal experiences should be considered and they should have access to an appeals mechanism since they are the ones ultimately being denied treatment. I believe that in order for the process to be transparent, it is not enough that there are public members on committees (though it is a positive step towards increased transparency). Patients must also have formal access to an appeals mechanism. This relates to the revisions and appeals condition of AFR and highlights an area of improvement—all patients should have access in order to formally appeal decisions.

Similarly, industry’s ability to participate in the deliberative decision making process varied by country and committee. Unlike patients, manufacturers were often the initiators of the process because they submitted the drugs to be reviewed.
Manufacturers also had access to a formal appeals mechanism. Nevertheless, they were often not included in the decision making process, except for NICE, which included industry members on their Technology Appraisal Committee. When asked about the inclusion of industry, committee members were concerned about the conflict of interest industry represented. Another reason for lack of industry inclusion in the process were proprietary issues - i.e., committee members believed that having an industry member present when discussing innovations made by their competitors was problematic. Industry representatives believed that these issues could be overcome and there was a definite need for involving them further and encouraging more dialogue. This relates to the relevance condition of AFR and highlights an area of improvement—industry should be able to participate in the deliberative process.

Reflections 3: Alternative Mechanism for Accessing Drugs

Should some drugs be accessed through a different mechanism? Does rarity alone warrant a different mechanism for access to ODs? What would be some key considerations of an alternative mechanism?

Should some drugs be accessed through a different mechanism?

In general, most drugs when assessed nationally (i.e., CEDAC, NICE, PBAC and IBC) are evaluated using the same criteria, within the same mechanism. Nonetheless, the mechanism for evaluation differed for the following drugs within this study (see Table 5, 6 and 7): Cerezyme, Glivec, and Remicade in Canada; Cerezyme and Fabrazyme in England & Wales and Australia; and Cerezyme in Israel and the US State Medicaid P & T Committee. Some countries have determined that a one size fits all approach in terms of evaluation mechanisms for drugs may not be appropriate. This is best
illustrated through Australia’s LSDP and Canada’s SAP. Both of these mechanisms allow for the access of drugs outside the usual mechanism.

Additionally, in Canada there were also differences in the way both Glivec and Remicade were accessed across provinces. Glivec is listed on the Ontario formulary, however, a number of other provinces use special access type programs. Remicade is only listed on three provincial formularies for the treatment of RA (New Brunswick, Northwest Territory, and Nova Scotia), while the other provinces use a special access type program.

Many patients and industry participants believed that a different mechanism - i.e., a national process - should be established for orphan drugs in Canada. Decisions about access through SAP type programs are made on a case by case basis, and inevitably lead to inconsistent and unequal decisions. Patients and industry representatives believed that a national approach would eliminate discrepancies in OD access across the country. However, a national approach in Canada may not be feasible because of jurisdictional issues regarding healthcare. Each province is responsible for their local health system decisions, including public funding for drugs. Federal interference in provincial decision making is typically not welcome. For example, the Common Drug Review was set up in order to reduce duplication and provide national guidance on provincial formulary decisions, but CEDAC’s decisions are considered guidance and are not binding, as are the provinces’ decisions. It is the provinces that make the final decision whether or not to list a drug. The CDR would never have received provincial support had CEDAC’s decisions been binding. Thus, a solely national approach is probably not a feasible solution in a federal country like Canada.
Another possibility, suggested by one patient, was to establish an organization similar to Cancer Care Ontario. Specifically, an Orphan Disease Unit could be established to direct and oversee public healthcare dollars for hospitals and other care providers in the delivery of high quality and timely services. This would allow for experts in the particular disease area to make decisions regarding the allocation of funds. However, this approach would be subject to the challenges of any regionalized program. Primarily, issues surrounding equal access across provinces may not necessarily be addressed by this approach.

*Does rarity alone warrant a different mechanism for access of ODs?*

Reimbursement recommendations/decisions for orphan drugs challenged all committees. I believe that this is because they represent a trade-off between the value of efficiency (i.e., cost-effectiveness) and the value of saving a life (i.e., ROR).

Reimbursement recommendations/decisions for the orphan drugs studied were dependant on the rarity and severity of disease and were often the basis of special funding arrangements. For example, Australia’s LSDP considers whether there are alternative treatments available for a small population. The fact that orphan drugs were funded in certain contexts demonstrated that other values, such as severity and rarity, were given precedence over the value of efficiency in these situations.

*What would be some key considerations of an alternative mechanism?*

Before an alternative process is established, a dialogue should occur regarding whether rarity is a sufficient value to warrant a different system of assessment. If it is, then a number of considerations must be explicitly determined. These considerations were succinctly raised by the West Midlands Specialized Services Agency’s report on
ERT in 2004. They included: 1) other factors besides cost-effectiveness that would provide justification for treatment, and 2) under what conditions would we fund these treatments, given the limited evidence of these treatments. The report also considered a number of variables including, though not limited to, health inequalities, rule of rescue, significance of cost-effectiveness, and setting inclusion/exclusion criteria for treatment.

In my research, many participants expressed the view that there should be a different mechanism for ODs, even though the exact implications may be challenging, particularly in a country that is politically organized, such as Canada. What is evident is that there should be further dialogue to determine whether rarity alone is a sufficient justification for the establishment of an alternative mechanism. Additionally, dialogue should focus on alternatives, such as whether the inclusion of other values should be incorporated into the current priority setting reimbursement process (e.g., lack of alternative treatments, and QOL).

Reflections 4: The Impact of Meeting a Cost Criterion

Should drugs that fail to meet strict cost-effectiveness criteria be included in public formularies? What about considerations of the total impact of the drug on the whole system (i.e., keeping people working and contributing taxes)?

Should drugs that fail to meet strict cost-effectiveness criteria be included in public formularies?

All participants agreed that cost and cost-effectiveness should be considered when making drug reimbursement recommendations. Typically, committees looked at cost per quality adjusted life year (QALY). While QALYs provided a common currency to determine the benefits gained by health interventions, some authors have argued that
its application in health care decisions is unethical and discriminatory against the elderly because it values life years rather than lives. Nonetheless, QALY’s were used by all drug reimbursement recommendation/decision making committees in this research.

It is interesting to note that there were discrepancies across committees in their assessment of the evidence pertaining to cost-effectiveness. This was most apparent in the case of Fabrazyme, which according to CEDAC, did not meet cost-effectiveness criteria, while the IBC believed it had met this criterion.

Some drugs may never meet cost-effectiveness criteria. Committee members, patients and industry representatives all provided similar comments on orphan drugs’ inability to meet the cost-effectiveness criteria, citing reasons of small population size and the extremely high cost of these drugs. Nonetheless, NICE has applied cost-effectiveness analysis for 15 orphan drug reviews, including Glivec. McCabe et. al. argued that not only can CEA be performed, but it is reasonable to use the best possible information [344].

*What about considerations of the total impact of the drug on the whole system (i.e., keeping people working and contributing taxes)?*

Patients interviewed in this study believed a more inclusive analysis of costs was necessary. For example, the impact of contributing to society through work output and taxes, as well as the consideration of the impact on families should be considered (e.g., the additional burdens on the family as family members take on additional roles as caregivers).
These two seemingly contradictory views from committee members and patients can be explained. Committee members are focused on cost-effectiveness because it is formally part of their review process. During the 1990s, there was an increase in interest and use of economic assessments of new therapies in decision making [94-97]. This resulted in placing the value of efficiency above other values that are also important in decision making. Committee members are very aware of working within the context of budget constraints and they believed that difficult decisions must be made to control spending. One strategy is to pay exclusively for the drugs that have the greatest efficiency.

My study has illustrated that drugs that fail to meet the cost-effectiveness criteria, but are considered effective, are generally publicly funded through alternative mechanisms. A more inclusive calculation of costs may alleviate the need for alternative mechanism for some of these drugs. Nevertheless, this is unlikely in the case of expensive biopharmaceuticals, particularly the ODs in this study. My study has also shown that while cost considerations are important when making recommendations/decisions regarding drug reimbursement, stakeholders believed that it should not be the sole basis for decisions.

**Reflections 5: Notions of Medical Necessity**

*Why are some treatments considered medically necessary while others are not?*

*Why are some treatments considered medically necessary while others are not?*

The concept of medical necessity is related to PS in that the determination of a treatment as a medical necessity is a value judgment. This concept is most apparent in
discussions surrounding Gonal-F for the treatment of infertility in Canada and the US. In 1994, the Ontario Ministry of Health de-insured IVF because it was deemed to be a procedure that was not medically necessary. This notion was echoed in the 1998 Nova Scotia Supreme Court ruling that public funding for IVF/ICSI (intracytoplasmic sperm injection) was unjustifiable as the treatment was deemed to be not medically necessary. In contrast, the Canadian Royal Commission on New Reproductive Technologies (1989–1993) concluded that infertility was a medical and social problem.

In the US, fertility treatments were excluded from Medicaid coverage as a result of the Omnibus Budget Reconciliation Act (OBRA) of 1990, in which Congress permitted states to exclude or limit coverage of fertility treatments from Medicaid coverage as part of the Medicaid Drug Rebate Program.

Israel is by far the most generous with the funding of fertility treatments, including Gonal-F, while Australia and England & Wales fall somewhere in between. In Australia it is partially funded, while in England & Wales there is still some variation among PCTs, though they are working toward more uniform access.

When participants were asked about international access to Gonal-F, they frequently responded that fertility treatments were not considered life saving and were therefore not considered a priority in terms of reimbursement.

My study has illustrated that the treatments which were considered to be medically necessary by governments tended to be funded. Fertility treatments are particularly challenging for some countries, such as Canada and the US. This is because of their
conception of medical necessity. It is evident in this study that advocacy groups played a crucial role in changing governments’ perceptions of the medical necessity of fertility treatments in both Australia and the UK. I believe that Canada is now at a critical juncture in which we may see a change in the perception of fertility treatments’ status. This is a result of the Ontario government’s creation of an expert panel on infertility and adoption in order to examine ways to make fertility treatment more accessible in 2007, and Quebec’s announcement in 2008 to reimburse up to two IVF treatments for eligible patients [220].

Additionally, when examining the funding of fertility treatments, it is important to note political considerations regarding increasing demographic populations. This has been the case in Israel, and as Birenbaum-Carmeli and Dirnfeld have noted, the generous funding of IVF in Israel is related to the Jewish Israeli tradition of pronatalism [345].

Reflections 6: The Impact of Technology and Innovation

| Should public drug funding agencies consider the innovative nature of the drug? If so, how should innovation be defined? |

Should public drug funding agencies consider the innovative nature of the drug? 

Many industry participants believed that innovation should be a value considered in the drug evaluation process. Nevertheless, some committee members noted the challenge of incorporating the value of innovation and cautioned against placing too much value on innovation as a criterion for drug PS. Promoting innovation was valued across all countries, as demonstrated in their innovation policies/strategies. The literature, as well as some industry participants, noted the need to promote local industry innovations [14, 340]. They believed this would demonstrate a real commitment to the value of
innovation and would encourage further industry investment (through running clinical trials and conducting research) in small market countries like Canada.

Nonetheless, the use of innovation as a value in decision making may create a tension between two conflicting objectives: the creation of strong industry incentives to develop therapies and the ability to afford those therapies while maintaining a sustainable health system [14, 346]. Some have argued that paying high prices now may enable lower prices on the same drugs in the future following patent expiration [140]. Additionally, the lack of public funding for drugs (specifically ODs) would impact their development, or lack thereof [347].

My study has shown that while participants from each group believed that public and private investment was critical for successful creation and uptake of innovation, industry members believed that the lack of public funding for drugs in small market countries did not heavily impact on their company’s decision to pursue a particular research/development. Typically, companies were pursuing drugs for the lucrative US market.

Innovation is clearly valued by governments and the participants in this study. However, it remains unclear to what extent the value of innovation should be used in drug reimbursement decisions. The promotion of innovation is important, but I believe that when making drug reimbursement decisions it may not be a critical value that committees should consider. If committees do consider innovation, a clear definition is necessary. At that point, the value of innovation should be balanced with “no cure no pay” schemes, which will be further explained in Reflection 7 below.
If so, how should innovation be defined?

Currently, the FDA and the EMEA uses therapeutic value as an indicator of innovation. Additionally, the innovative value of a drug is not only based on the actual property of the compound, but also on the specific context in which the drug is introduced, in comparison to treatments for the same indication [348]. The lack of a shared definition can be addressed by opening dialogue between industry and committees to foster the development of a common language about innovation.

Reflections 7: Insufficient Evidence

<table>
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<tr>
<th>Insufficient Evidence</th>
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<tr>
<td>When the evidence of effectiveness is insufficient, what should committees do to improve the reimbursement decision making process?</td>
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When the evidence of cost-effectiveness and effectiveness is insufficient, what can committees do to improve the reimbursement decision making process?

Most participants, from all groups, identified the lack of sufficient evidence for cost-effectiveness and effectiveness on which to make recommendations for orphan drugs. Orphan drugs were unique in this study because they represented such a small population. Given their limited use, country specific clinical studies were impossible. However, reimbursement decisions about orphan drugs were made, despite the insufficient evidence. Some possible solutions to improving decision making, in light 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. One obstacle to
instituting conditional listing seems to be political sensitivity. According to one committee member, politicians are hesitant to de-list drugs because it does not reflect favourably on them. This demonstrated that there should be an increase in the communication that takes place between politicians and the people they serve - i.e., the patients.

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. For example, Xigris was restricted based on the prescriber - i.e., ICU treating physician. Restrictions were also used to combat misuse or abuse of a drug. In general, expensive drugs have restrictions, as was the case with Remicade, in which committees that approved the drug did so with restrictions. Not all drugs are restricted; the US State Medicaid P & T Committee did not restrict the use of Glivec, or cancer drugs in general, because of the urgency associated with these drugs.

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 [349].

**Reflections 8: The Extent of Publicity**

<table>
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<tr>
<th>The Extent of Publicity Required</th>
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<tr>
<td>Is it ever justifiable to not publicize rationales?</td>
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**Is it ever justifiable to not publicize rationales?**

Most committees did publicize their rationales. However, I believe that there are certain circumstances in which the publicity condition should be overridden, primarily when it conflicts with issues of confidentiality.

My study has demonstrated that multiple methods of publicizing rationales were used by committees, including web posting, newspaper publications and radio announcements. Brief rationales for decisions were available online from CEDAC, CED and PBAC. NICE posted lengthy rationales for decisions for both health professionals and lay people. The IBC did not post rationales, but they can be requested formally and are published in local newspapers. The US Medicaid State P & T Committee has begun to post new decisions. However, older rationales (like that of Cerezyme and Remicade) were not available except through formal request. In the West Midlands, outcomes of individual requests were not publicly available due to confidentiality. The Hospital P & T Committee rationales were not available for the public. However, decisions were often made known to staff throughout the hospital via mailings and word of mouth.
The West Midlands’ Exceptional Drug Review Committee raised a particularly interesting point with regards to publicity. That is, they are making decisions regarding a potentially identifiable group. Any publication of rationales regarding case by case decisions may jeopardize the anonymity of the patient. As such, they decided against the publication of rationales. I believe that this decision was appropriate, despite it not being in accordance with the AFR condition of *publicity*.

**Summary**

In summary, my research has supported the literature and also identified a number of findings. These findings include:

1) Committee members showed preference for the value of efficiency over that of saving a life, when evidence of effectiveness was considered insufficient.

2) A legitimate and fair process requires stakeholders to have access to the decision making process, including formal ways to participate in deliberation and mechanisms for revising and appealing decisions/recommendations.

3) A different mechanism for the reimbursement of expensive ODs may be necessary to ensure fair and legitimate decision making. More research is necessary to fully determine whether this is the case.

4) Cost-effectiveness should not be the sole criteria for making drug reimbursement decisions/recommendations, nor should it be valued above all else.

5) The determination of a treatment’s status as medical necessary is socially determined and critical to whether the treatment is ultimately funded.

6) The extent to which innovation should be valued in drug reimbursement decisions/recommendations remains uncertain. More research is needed.
7) When evidence of cost and effectiveness is insufficient, committees should rely on conditional listing, drug restrictions and risk sharing schemes to ensure fair and legitimate decisions.

8) The publicity condition may be overridden to ensure patient confidentiality and the process may still be considered legitimate and fair.

The ensuing section, section 5.3, will relate the above findings to some implications for policy and practice.

5.3 Implications for Policy and Practice

Implications for Policy

This section discusses some policy recommendations for drug reimbursement committees and decision makers for improvement of priority setting of expensive drugs. These recommendations are based on the findings from this study and can be separated into three categories: 1) the role of non-experts in decision making, 2) orphan drug policies, and 3) policy harmonization across governmental departments.

Non-Experts and Decision Making

My research has shown that industry involvement in the actual decision making process remains contentious. Many committee members believed that having industry present during the actual decision making process presented a major conflict of interest. This debate is highlighted by the World Health Organization’s (WHO) assessment of the United Kingdom’s NICE in 2006, which recommended against industry membership in the Guideline Review Panels (GRPs). In general, the WHO’s assessment of NICE was positive regarding their overall methodology and process [350].
The inclusion of lay members in drug reimbursement committees has acquired far greater acceptance. Most national committees have non-expert members in the form of public/consumer or patient representatives, including the IBC, PBAC, and NICE. In 2007, CEDAC included a position for a public member. In 2006, Ontario enacted Bill 102, the Transparent Drug System for Patients Act, which mandated the establishment of a Citizens’ Council to advise the Ministry of Health and Long Term Care (MoHLTC) on the social aspects of drug policies and priorities [351].

Nonetheless, the Hospital P &T Committee saw no reason to involve non-experts in their formulary decisions. The PCT Exceptional Drug Review Committee, for reasons of confidentiality, also had no future plans for the inclusions of non-experts in their decisions. Finally, the US State Medicaid P & T Committee currently has no non-expert involvement. However, the US State Medicaid P & T Committee is beginning to change their process and other State Medicaid Committees have included non-experts in their process.

My research demonstrates that based on AFR and participants’ views, involvement of non-experts in decision making is important, particularly in the deliberation process and the revisions/appeals process. Moreover, the inclusion of stakeholders is a necessary condition of AFR and would ensure a legitimate and fair process.

**Orphan Drug Policies**

Many patients, representing those affected by rare disorders, identified the need to establish policies that create an environment that is friendly toward orphan diseases. The value of rarity is often reinforced by governmental policies and industry incentives concerning innovation for orphan drugs [14]. Some governments, such as the US and
the EU, have recognized the obstacles in the development of ODs. The US’ and Japan’s orphan drug policies provide incentives to pharmaceutical companies for research and development of orphan drugs [352]. The US Orphan Drug Act was the first major initiative to provide incentive for pharmaceutical development to aid those with rare disorders [346]. Canada and Israel have no orphan drug policies to date. Australia’s orphan drug policy was established in 1997. The policy is aimed to improve availability of drugs through 1) the use of information from the US Food and Drug Administration to hasten the evaluation process; 2) no annual registration fees or application and evaluation fees; and 3) five year exclusivity [352]. Additionally, the government conducts post market surveillance to ensure that the cost-effectiveness of the drugs was in keeping with their predictions [23].

My research has shown that both patients and industry representatives support the development of an OD policy or an alternative mechanism for access to ODs in Canada. More research is necessary to determine what type of mechanism should be established.

**Policy Harmonization**

Harmonization of policies requires that all levels of government, i.e. the federal, provincial/territorial and municipal levels, and branches within these levels, e.g. Ministry of Health and Industry, communicate with one another. This will ensure consistent policies across all branches of government, thereby avoiding the possibility of one branch refusing to reimburse the very innovations the other branches are promoting [14]. The expansion of scope to include representatives from all levels of government may result in conflict between departments and jurisdictions, but this is necessary in order to establish consistency.
Implications for Practice

This section discusses some recommendations for drug reimbursement committees and decision makers to improve the priority setting of expensive drugs. These recommendations are based on the findings from this study and can be separated into three categories: 1) incorporating values, 2) communication, and 3) stakeholder involvement, including non-experts, i.e. industry, patient and public representation.

The Incorporation of Values

Drug funding decisions have traditionally been made by civil servants and experts and are based on the paradigm of evidence-based medicine and economic evaluation [14]. Economic evaluation is currently used in a number of European, American and Asian countries [353]. However, there are problems associated with economic evaluation. For example, in the 326 pharmacoeconomic analyses submitted to PBAC, there were 249 methodological problems present. Similarly, in Ontario’s former DQTC (now replaced by the CED), clinical factors outweighed economic analysis [354, 355].

Decisions concerning drug funding involve value choices about which there is no consensus [14, 15]. Stakeholders can identify core values and norms that are relevant to funding decisions. In addition to providing a critical perspective on values and priorities, their input will result in better quality assessments and increased acceptance of decisions [353, 356]. This study has identified some values that require further exploration, including the explicit use of the ROR, calculations of what is considered a cost, notions of medical necessity, and the value of innovation.

Participants in this research study discussed how values were used, both formally and informally, in relation to drug reimbursement decisions. Patients and industry
representatives often believed that committees tended to focus on economic evaluations and that the inclusion of other values was crucial, especially when related to discussions surrounding orphan drugs. Committees generally did not consider these other values (e.g., it was the only treatment for a particular disease) formally. Therefore, establishing a multi-stakeholder panel, including experts, patients, public and industry members to help determine which criteria are valuable when making drug reimbursement decisions would greatly assist and improve the decision making process.

The Importance of Communication

Both committee members and patients identified communication as an area for improvement. Committee members identified the quality of information. Conversely, patients noted the amount of information they could or could not access and the areas in which they were able to participate and communicate their perspectives. Specifically, patients were able to access the rationales posted on websites, but were unable to access minutes from meetings. Moreover, while most committees had public representation, patients are often not able to appeal decisions. It is crucial that the process, committees’ decisions, and rationales are transparent because transparency, along with inclusiveness and responsiveness, characterize a legitimate and fair process [14]. Rationales should be accessible and understandable to lay individuals. Committees should publish different versions of their rationales to enable knowledge transfer. Therefore, as was recently recommended for wait-list management organizations, a communication panel should be created, including expert patient, public and industry members, to develop a communication strategy [356].
The Importance of Stakeholder Involvement

The inclusion of stakeholders, i.e. manufacturers, professional organizations, health authorities, academic groups, patient organizations and public representatives, is important for a number of reasons, one of which was discussed above - i.e., identifying core values and norms. Some additional reasons to include stakeholders are 1) stakeholders fund as well as use the health system therefore they have the right to be involved, 2) the inclusion of stakeholders improves trust and confidence in the system, 3) stakeholder inclusion can enhance legitimacy and fairness of priority setting [16, 356, 357].

Based on the research conducted, it is apparent that patients and industry are often not fully involved in the decision making process. In order to facilitate shared decision making, committees should establish positions for patients and industry members on expert panels. In order to mitigate issues surrounding conflict of interest, all members would be required to fully disclose their conflicts of interest and members would be asked to excuse themselves from certain discussions where a conflict of interest was obvious.

Table 19. Recommendations for Drug Recommendation Committees

<table>
<thead>
<tr>
<th>Incorporation of Key Values</th>
<th>Foci</th>
<th>Implementation</th>
</tr>
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<tbody>
<tr>
<td><strong>Inclusion of Values Strategy</strong></td>
<td>1 ) Establish a multi-stakeholder panel, including experts, patient, public and industry members, to determine which criteria are valuable when making drug reimbursement decisions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• strategy should be aimed at all stakeholders, especially the public, patient groups and industry</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• disseminate the rationales (how? and why?) used</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2) Conduct focus groups with the key stakeholder groups regarding the appropriateness of the criteria chosen</td>
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### Communication

<table>
<thead>
<tr>
<th>Foci</th>
<th>Implementation</th>
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</table>
| Communication Strategy      | 1) Create a communication panel, including expert patient, public and industry members, to develop a communication strategy  
- strategy should be aimed at all stakeholders  
- disseminate the rationales used  
- Different versions of the rationales should be made available (lay person, health professional etc.)  
- Dissemination of rationales should be done through a number of venues not exclusively on-line  
2) Conduct focus groups with patients and public regarding the usability of the website and the accessibility to the information posted. Specifically, to identify  
- what information is desired  
- how information can be presented so it is easily understood by the reader, and provide feedback on the usability of the website |

#### Stakeholder Involvement

<table>
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<th>Foci</th>
<th>Implementation</th>
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<tbody>
<tr>
<td>Shared Decision Making</td>
<td>1) Establish positions for patient and industry members on expert panels</td>
</tr>
<tr>
<td>Ongoing Advice</td>
<td>1) Construct a Citizens’ Council, consisting of the assembled public from the expert panels, to provide ongoing advice on priority setting</td>
</tr>
</tbody>
</table>
| Feedback and Appeals Mechanism | 1) Establish a formal feedback/appeals mechanism for all stakeholders, including the patients, public and industry, to comment on drug reimbursement recommendations  
2) Synthesize and analyze the feedback |

### 5.4 Study Limitations

There are a number of limitations to this study. Below I will discuss some limitations related to the methodology used, case selection and social bias. This section concludes with areas of improvement.

#### 5.4.1 Methodology

Case study methods have a number of limitations. The main criticism of case study research is that the results are not “generalizable in the conventional sense” [270]. Nonetheless, while results cannot be generalized in the statistical sense, i.e. as in a
large N study, well-structured and researched case studies can inform us beyond the actual cases studied. For example, theories developed based on the cases studied can be applied to other cases. Also, findings may be evident in other settings. Finally, results can provide provisional truths. I believe that case study research was appropriate and that steps were taken to ensure the appropriate structure of the cases.

Another criticism of case study methods is that results can be easily dismissed by individuals who do not agree with the outcome [270]. However, the results of my study have been triangulated with documents and literature that supports the findings and thus cannot be easily dismissed.

5.4.2 Case Selection

The exploration surrounding innovation is limited because innovation issues were examined in countries that conducted very little innovation in comparison to the US in which the vast majority of innovation occurs. An analysis of an innovative drug within its country of origin would expand on our knowledge of the relationship between drug priority setting and innovation.

5.4.3 Social Bias

The participants’ views may reflect what they believed the researcher wanted to hear. To some extent this limitation is unavoidable. However, I tried to verify interview data with data derived from documents.
5.4.4 Areas of Improvements

In retrospect, there are a number of changes I would implement to improve this study’s design and execution. The design of this study relied on case studies of particularly expensive drugs. It would have been better to compare drugs under the same jurisdiction, i.e. on a national, provincial/state, or hospital level. Drugs were selected on the basis of their cost, innovation, and whether most of the proposed committees reviewed the drug. Nonetheless, this allowed for an understanding of the different systems countries have in place for the public reimbursement of drugs and the various methods patients access the system.

Another challenge I faced was gaining access to industry. Industry representatives were very hesitant to be interviewed. One company, Schering Plough, refused to take part in the study. In the end, a total of eight industry representatives were interviewed. If time permitted, I would have attempted to access industry through surveys. Since a great concern was that I would try to illicit proprietary information from them, surveys may have allowed participants to feel more in control of the information being provided.

Finally, there have been a number of criticisms of the evaluation framework, ‘accountability for reasonableness’, which was the framework used in this study. Gibson et. al. have argued for a fifth condition of “empowerment” to be included. This condition aims to minimize the power differences in priority setting decision making [358]. Moreover, Reeleder et. al. noted that leadership is an “enabler of the enforcement condition in healthcare settings”, but it is dependant on attention to ethical components of priority setting and leadership approaches, which align with
‘accountability for reasonableness’ [359]. In my study, I have incorporated this change to the ‘accountability for reasonableness’ framework by renaming the enforcement condition to leadership. Most recently, Friedman has argued that the framework is insufficient in ensuring that decisions will be fair, reasonable and legitimate. Friedman suggests increased public involvement at all stages of deliberation and the inclusion of all types of reasons should be considered and evaluated on the basis of “consistency, plausibility and explanatory power, without any regard for their alleged sources of authority” [181]. Friedman’s suggestions support the findings of this study. Increased stakeholder involvement was one recommendation of this study resulting from the relevance condition of ‘accountability for reasonableness’. Another recommendation was the increased inclusion of a greater breadth of values in decision making.

5.5 Future Research

The study has raised a number of areas for future research.

The study results suggest support for wider stakeholder involvement. More research is required to determine the specific impact of stakeholder involvement in drug priority setting.

My research has also suggested the need for an alternative funding mechanism for drugs that do not meet the efficiency criteria. Further investigation is required to determine the exact implication of such a mechanism, particularly for different arrangements health systems.
Innovation was identified as a value important to the consideration of expensive drugs, yet the extent to which innovation should be valued in drug reimbursement decisions remains inconclusive.

This study primarily focused on the similarities in values used in the drug priority setting process and the outcomes of those decisions. I focused on similarities because there were many, despite differences in countries, value culture, decision structure, and jurisdiction. Another research agenda could examine the variation which exists regarding the values used by different recommendation committees.

Many of the drugs in this study had similar final outcomes - i.e., the drugs were ultimately funded, sometimes by alternative mechanisms when they were initially rejected by the original committee. The outcomes of the recommendations were not taken into consideration when choosing the drug cases in my study. Further research could examine the same drug across different countries with different funding outcomes.

My study focused on expensive drugs partly because committees are often challenged when making funding recommendations regarding beneficial high cost drugs, and because these decisions often elicit much public and media interest. Given that governments and drug fundors are trying to decrease drug expenditures, priority setting for all drugs is becoming more critical. Further research could elucidate drug priority setting using more mainstream drugs as the cases.
The study drugs were examined across five countries. These countries 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 as the cases (as these countries would not be able to afford the drugs included in this study).

Finally, future research should be conducted on how to evaluate drug recommendation agencies. One agency, NICE, has attracted attention and criticism internationally for its guidance [24, 185, 188, 229]. According to a report by the Foundation for Genomics and Population Health, NICE is the ‘gold standard’ of health assessments because of its rigorous procedures [360]. However, my research has indicated that NICE, according to the AFR framework, has only fully met the publicity condition. Areas of improvement would be to include a greater array of values in decision making, and to establish a formal mechanism for the general public to appeal decisions. Moreover, others have criticized NICE for the drug selection process (drugs are only reviewed on referral by the Department of Health), its focus on centralized decision making (values may differ across regions), and its receptor capacity (extent to which guidance is mandatory) [27].

Fair and legitimate processes have been characterized by inclusiveness, transparency, and responsiveness [14]. If I were to create an evaluation tool to assess drug recommendation agencies, I would begin with a systematic literature review of the
conceptual frameworks and policies related to agency evaluation. Additionally, I would identify different tools currently used to assess agencies. My methods would have five stages: 1) Create a framework based on the synthesis of existing frameworks of agency evaluation. 2) Derive usable criteria for the selection of goals and values from focus groups conducted with agency members that would be mapped onto the goals of fair and legitimate priority setting. 3) Submit the tool to a select group of interdisciplinary researchers in the field for comments and feedback. 4) Revise the tool based on the feedback received. 5) Further revise tool based on original subjects’ opinions.

5.6 Concluding Remarks

Drug funding decisions which provide some benefit to only some patients is highly contentious and morally controversial. It is clear that PS decisions will need to be made about which biopharmaceuticals to reimburse, how to regulate them, and who will have access to them. In the absence of consensus about how to set drug priorities it is necessary to establish a climate in which it is acceptable to make decisions against the funding of some drugs. Key elements of such a climate are legitimacy and fairness. A central component of a legitimate and fair priority setting process is to make priority setting explicit and to involve pertinent values and stakeholders in decision making [16]. This study has demonstrated that in order to create a fair and legitimate drug reimbursement process, we need to ensure the incorporation of a wide range of values and the involvement of multiple stakeholder groups within the deliberative and appeal/revisions processes.
### APPENDICIES

**Appendix 1. Comparison of International Spending on Drugs**

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<tbody>
<tr>
<td>Australia</td>
<td>20,329,000</td>
<td>In 2004, $3120 per capita was spent on health care totaling $62,687,040,000</td>
<td>In 2002, spending on pharmaceuticals accounted for 14.2% of total health spending in Australia, up from 12.6% in 1999 and 11.0% in 1994[361]</td>
</tr>
<tr>
<td>Canada</td>
<td>32,271,000</td>
<td>In 2004, $3,165 per capita was spent on health care</td>
<td>In 2004, spending on pharmaceuticals accounted for 17.7% of total health spending in Canada, up from 15.5% in 1999 and 13.1% in 19.][361]</td>
</tr>
<tr>
<td>Israel</td>
<td>6,990,700</td>
<td>In 2005, $1669 per capita was spent on health care totaling $11,669,480,431 (USD)</td>
<td>In 2002, total expenditure on drugs was 4846 million New Israeli Shekels which was 738 per capita.[362]</td>
</tr>
<tr>
<td>UK</td>
<td>59,989,000</td>
<td>In 2005, $2508 per capita was spent on health care totaling $150,063,672,000</td>
<td>In 1997 total expenditure was 238 million ppp. [362]</td>
</tr>
<tr>
<td>US</td>
<td>296,410,000</td>
<td>In 2004, $6,102 per capita was spent on health care totaling $1,791,895,014,000</td>
<td>Over the past decade, the share of health expenditure spent on pharmaceuticals in the United States increased from 8.5% of total health spending in 1994 to 12.3% in 2004.[361]</td>
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# Appendix 2. Sampling Table

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<td>TEC</td>
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<tr>
<td>US P &amp; T</td>
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<td>Hospital P &amp; T</td>
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<td>Patient groups associated with Fabry</td>
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<td>Patient groups associated with Gaucher</td>
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<td>ICU doctors</td>
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<td>Patient groups associated with infertility</td>
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<td>Patient groups associated with cancer</td>
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<td><strong>7</strong></td>
<td><strong>23</strong></td>
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</table>

* Four academics were interviewed related to NICE

** Inappropriate board contacted 21 people regarding the correct committee (1 NORD, 2 patient groups, 2 FDA, 11 MEDCAC, 1 CMS and Coverage and analysis group, 1 academic, 2 people from CMS conference, 1 State P & T advisory committee member)

*** The person interviewed from Serono Previously worked for Genzyme and commented on it

**** While 58 people were interviewed only 56 related directly to the study committees
### Appendix 3 Documents Collected

<table>
<thead>
<tr>
<th>Document Name</th>
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<tbody>
<tr>
<td>1. IBC recommendation regarding Glivec</td>
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<td>2. IBC recommendation regarding Remicade</td>
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<td>3. IBC recommendation regarding Gonal F</td>
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<tr>
<td>4. IBC recommendation regarding Fabrazyme</td>
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<tr>
<td>5. IBC recommendation regarding Xigris</td>
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<td>6. CEDAC’s recommendation regarding Glivec</td>
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<td>7. CEDAC’s recommendation regarding Remicade</td>
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<td>8. CEDAC’s recommendation regarding Fabrazyme</td>
</tr>
<tr>
<td>9. CED-CCO Recommendation for Imatinib. 2007</td>
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<td>10. Toronto Hospital P &amp; T Committees recommendation regarding Xigris</td>
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<td>11. PBAC’s recommendation regarding Glivec</td>
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<td>12. PBAC’s recommendation regarding Remicade</td>
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<td>14. PBAC’s recommendation regarding Fabrazyme</td>
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<tr>
<td>15. PBAC’s recommendation regarding Xigris</td>
</tr>
<tr>
<td>16. PBAC’s recommendation regarding Gonal – F</td>
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<td>17. NICE’s recommendation regarding Glivec</td>
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<tr>
<td>18. NICE’s recommendation regarding Remicade</td>
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<tr>
<td>19. UK treatment guidelines for Cerezyme</td>
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<tr>
<td>20. UK treatment guidelines for Fabrazyme</td>
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<tr>
<td>21. NICE’s recommendation regarding Xigris</td>
</tr>
<tr>
<td>22. NICE’s recommendation regarding Gonal F</td>
</tr>
<tr>
<td>23. Assessment and treatment for people with fertility problems Understanding NICE guidance – information for people with fertility problems, their partners and the public</td>
</tr>
<tr>
<td>24. US State Monograph for Fabrazyme</td>
</tr>
<tr>
<td>25. Commissioning Policy for Infertility Services within Birmingham for Birmingham Primary Care Trusts. 2006, Birmingham East and North NHS</td>
</tr>
<tr>
<td>26. Policy for Management of Requests to Commission Services and Treatments Outside of the PCT’s Agreed Commissioning Portfolio</td>
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<tr>
<td>27. Enzyme replacement therapy: a document prepared for West Midlands PCTs to support the development of a commissioning policy for the treatment of Gaucher's Disease, Fabry's Disease and Mucopolysaccharidosis Type 1</td>
</tr>
<tr>
<td>29. IAAC position paper</td>
</tr>
<tr>
<td>30. CACC’s report card</td>
</tr>
<tr>
<td>31. CORD’s position paper</td>
</tr>
<tr>
<td>32. CAPA position paper</td>
</tr>
</tbody>
</table>
# Appendix 4: Interview Guide

## Interview Guide

### Recommendation Committees:

1. How are decisions made regarding funding for expensive biotech 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 are involved?
4. What considerations do you feel are important in making the decision?
5. How are decisions 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. Do you think the process hinders innovation?
10. Do you think the reimbursement process affects a company’s decisions to pursue innovation in the area of biotechnology? How?
11. Do you think health care sustainability affects a company’s ability to pursue innovation in the area of biotech? How?
12. Is there someone else you think I should speak to?

### Drug Manufacturer:

1. Do you think that priority-setting decisions regarding biotech drugs should differ from other types of drugs?
2. Do you think the process hinders innovation?
3. Do you think the reimbursement process affects a company’s decisions to pursue innovation in the area of biotechnology? How?
4. Do you think health care sustainability affects a company’s ability to pursue innovation in the area of biotech? How?
5. How did the decision making process of _____affect the drug commercialization process?
6. Has governmental decisions affected your R &D process?
7. Please tell me what factors you think are important in how the decision regarding _______ was made.
8. How was the decision communicated/disseminated?
9. What was the extent of your involvement if any in the decision-making process?
10. Can you tell me about any important opposition to this decision?
11. How was that taken into consideration?
12. Do you think it is a fair process? How do you define fair?
13. What do you think could be done to improve this process?
14. Is there someone else you think I should speak to?

### Patients Groups:

1. Do you think that priority-setting decisions regarding _____should differ from other types of drugs? And why?
2. Do you think the process hinders innovation?
3. Do you think the reimbursement process affects a company’s decisions to pursue innovation in the area of biotechnology? How?
4. Please tell me what factors you think are important in how the decision regarding _______ was made.
5. How was the decision communicated/disseminated?
6. What was the extent of your involvement if any in the decision-making process?
7. Can you tell me about any important opposition to this decision?
8. How was that taken into consideration?
<table>
<thead>
<tr>
<th>Question</th>
</tr>
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<tbody>
<tr>
<td>9. Do you think it is a fair process? How do you define fair?</td>
</tr>
<tr>
<td>10. What do you think could be done to improve this process?</td>
</tr>
<tr>
<td>11. Is there someone else you think I should speak to?</td>
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</table>
Healthcare sustainability and the challenges of innovation to biopharmaceuticals in Canada

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b McLaughlin-Rotman Centre for Global Health at University Health Network/University of Toronto
and McLaughlin Centre for Molecular Medicine, University of Toronto, Canada
c McLaughlin-Rotman Centre for Global Health at University Health Network and Department of Medicine at the University of Toronto, Canada
d Department of Health Policy, Management and Evaluation and the Joint Centre for Bioethics, University of Toronto, 88 College Street, Toronto, Ontario, Canada M5G 1L4
Abstract

Governments around the world have focused on issues of sustainability, innovations and priority setting within their health systems. Tension exists between governments’ desire to increase biotechnology innovation and the need to address health system sustainability. This commentary will: 1) review government initiatives in biotechnology in health innovation, 2) discuss how innovation, specifically biopharmaceuticals, challenges health system sustainability, and 3) explore how the tension between innovation and sustainability can be addressed using fairness and legitimacy. It is evident that a uni-jurisdictional approach may not be optimal in promoting innovation while ensuring a sustainable health system. Harmonization of biotechnology policies across the federal, provincial, and territorial governments will ensure consistent policies across all branches in order to circumvent the possibility of one governmental branch refusing to reimburse the very innovations other branches are promoting.

Key words: Priority setting; Resource allocation; Fairness; Biotechnology.

Introduction

Isaac McFayden is a 2 year-old Ontario boy suffering from Maroteaux-Lamy disease (MPS VI). MPS VI is a rare type of mucopolysaccharide disease characterized by an enzyme deficiency that affects many cells and organs. Recently a portion of Isaac’s skull and vertebrae in his neck were removed because they were compressing his spinal cord. Until July 2005 the treatment for this disease, the drug Naglazyme (galsulfase) whose cost was approximately $500,000/year was not covered by the provincial government in Ontario. Naglazyme, an enzyme-replacement therapy, is not
a cure but it is the only treatment available, and it can improve an affected individual’s ability to walk and climb up stairs. (2-5) Naglazyme is an orphan drug and is example of an expensive innovative biotechnology pharmaceutical, or biopharmaceutical. Over 6000 rare/orphan diseases exist, and definitions vary. Canada has yet to define ‘rare’ diseases. (6, 7) Generally, rare diseases are defined as affecting less than 1 person per population of 2 000. (7) Biotechnology is “the application of science and technology to living organisms, as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services.” (8) Biotechnology motivates change in innovation processes in many sectors including the pharmaceutical sector. (9) Biopharmaceuticals, are often very expensive. The high cost of such drugs can be associated with research and development (R&D), which “confronts levels of risk and uncertainty well beyond what is entailed as “normal” R&D.” (10) As well, the cost of such R&D is very high (estimated between 400 - 25 000 million for a new molecular entity using biotechnology). This coupled with low success rates of taking a drug to market accounts for the likely high cost of such drugs. (10)

Introducing expensive biopharmaceuticals that benefit patients while simultaneously ensuring a sustainable healthcare system is complex and difficult. According to the Organization for Economic Cooperation and Development (OECD), increases in health care expenditures can be attributed to a number of factors including technology/medical treatments. And while new drugs can be cost saving (11), their “impact on expenditure will depend on the price elasticity of the demand for health care.” (12) Moreover, even when new technologies are not expensive in unit costs, they may amplify demand through increasing the selection and quality of medical products on the market.
Ultimately, health system funders may be forced to refuse reimbursement of beneficial but expensive treatments. Their refusal to reimburse beneficial innovative therapeutics may in turn have an impact on their industrial pursuits and therefore the promotion of innovation. These issues are amplified when discussing orphan drugs because the market is small leading, to their subsequent high cost (no economies of scale exist). Additionally, these decisions become complicated when treatments have a potential for great benefit coupled with a great cost. (13)

We argue that decisions to refuse the reimbursement of beneficial treatments are necessary to ensure the sustainability of health systems, but these decisions must be made in a fair and legitimate manner. Moreover, there is an urgent need for policy alignment between the federal and provincial government departments in order to ensure that one governmental branch does not refuse to fund the very innovations another branch is promoting. Canada is an instructive example of a country that must resolve these tensions: Lessons from a Canadian analysis can be helpful for other similarly challenged countries. In this commentary we will 1. Review some actions taken by the Canadian Ministry of Industry and Health towards biotechnology in health innovation, 2. Discuss how innovation challenges health system sustainability, and 3. Explore how the tension between innovation and sustainability can be addressed.

1. Government Initiatives Fostering Innovation & Biotechnology

“The biggest risk to public medicare in Canada is, in fact, the risk of failing to innovate.”(14)
- - David McKinnon, former president of the Ontario Hospital Association
The Canadian government is pursuing a number of different strategies to promote innovation and biotechnology. Innovation is any advancement that results in the creation of a new product, reduces the production cost of a current product or improves a current product’s therapeutic value. (15)

Innovation is key to the successful growth of the health sector (i.e., all industry related to the production and service of health) which is one of the largest growing economies. The ‘consumption’ of health care is a contributor to the growth of the economy. (14, 16) Innovation has been recognized as crucial by the OECD countries. This is evident from the OECD January 2004 meeting which “reaffirmed that knowledge creation and diffusion are increasingly important drivers of innovation, sustainable economic growth and social well-being.” (17) Health system sustainability is linked to the promotion of innovation and biotechnology in that health care funders consider applications of innovative biotechnology for reimbursement.

A number of factors are attributed to influencing the innovation process of science- and technology- based innovations in the health sector. They include the extent of scientific progress, governmental policies, funding, type of intellectual property rights, role of universities, clustering of firms, demands from the health system on innovation etc. (18) Several governments are beginning to recognize some of these factors in promoting innovation in biotechnology and are taking steps towards enhancing this industry. These initiatives are not necessarily specific to health; however some of these resulting innovations and biotechnologies are applicable to the health sector.

Primarily governments have focused on increasing government investment in innovation and establishing policies which motivate innovation. However, no studies have been conducted on the effectiveness of these innovation strategies. Such an
evaluation would be complex as the study intersects multiple sectors and governmental departments. Innovation strategies, in Canada, must be understood within the context of federalism which creates jurisdictional boundaries for the federal and provincial governments. As such, these strategies are located within multiple governmental departments, and implemented under different jurisdictions with little or no cross-communication despite their subsequent effect on each other. This presents a challenge to successful uptake of these strategies.

Specifically, Canadian initiatives including policies, budgets, and strategies for innovation and biotechnology are established federally, implemented provincially, and coordinated by the National Research Council (NRC). Its objective is to increase awareness of Canada within science and technology fields globally, making Canada one of the top five R&D countries by 2010. (19) The Canadian Institute for Health Research (CIHR) is the Canadian government’s main health research funding agency. CIHR’s budget in 2005-2006 was $699 million. (20)

The federal Ministry of Industry (Industry Canada) is promoting the growth of biotechnology and innovation through policy and funding. In 2001 Industry Canada published an innovation strategy entitled “Achieving Excellence: Investing in People, Knowledge and Opportunity Canada’s Innovation Strategy”, which identified three areas which challenge innovation: knowledge performance, skills, and innovation environment. (21) Moreover, Industry Canada established the Public-Private Partnership (P3) Office which provides information on issues related to P3s. Technology Partnerships Canada (TPC) also financially supports R&D and projects that result in social, economic, and environmental benefits. (19)

The federal Ministry of Health (Health Canada) is promoting innovation through four policy areas: reform of the health system, regulatory reform of therapeutic
evaluations, community development as well as science and research. Moreover, federal, provincial and territorial health ministries are beginning to cooperate to improve post-market therapeutic effectiveness of drugs, and to promote cost-effective therapies. (22) Clearly, the Canadian government believes innovation is important. Over the past five years Canada has taken action, through increased spending and policies, towards improving growth in biotechnology innovation and has responded to the policy recommendations made by Industry Canada. This has resulted in a 183% growth of the biotechnology sector. (23)

The Canadian government also supports the biotechnology industry through funding. In 2003 $1.7 billion in new funds was budgeted for R & D and innovation. (24) Additionally, Canada established policies which aid in creating and sustaining innovative biotechnological firms. Canada has generous R&D tax incentives placing it ahead of the United States (19) and Canada is creating collaborative institutional structures to help with technology transfer of innovations. For example, the establishment of the National Biotechnology Strategy (NBS) in 1983 (25) and seven Centres of Excellence created in 1986. (26)

In 1997 Industry Canada put forth Canada’s Biotechnology Strategy (CBS). CBS plans for and supports the emerging area of biotechnology while complimenting “the regulatory and research activities of various federal departments and agencies.” (27) The federal government is trying to “coordinate 'horizontal' decision-making across the Canadian Biotechnology Strategy departments and agencies” (27) within the federal domain through the establishment of the Canadian Biotechnology Secretariat. The federal departments involved are Industry, Agriculture and Agri-food, Health, Environment, Fisheries and Oceans, Natural Resources and International Trade. (28) In 2000, the Canadian Regulatory System for Biotechnology (CRSB -a collaboration
between five departments, Environment Canada, Department of Fisheries and Oceans, Health Canada, Industry Canada, Department of Natural Resources Canada and one agency, the Canadian Food Inspection Agency) received $90 million over three years (2000–03) and $34.6 million per year in subsequent years to support and facilitate the regulation of biotechnology. (29)

Canada’s actions towards the pursuit and uptake of innovation and biotechnology are similar to those undertaken internationally for example, the development of a National Biotechnology Strategy in 2000 by the Australian government (30) and recognition of the innovation challenges in the United Kingdom. (31)

Despite Canada’s strategy to improve innovation particularly, in the biopharmaceutical area, no leading companies have emerged, salaries are lower than in comparable US clusters, patent output is lower, and finally per capita R&D is lower than in other developed countries. (32) According to Martin and Milway, one of the main factors which negatively affects the biopharmaceutical cluster is “the industry in Ontario suffers from unsophisticated demand conditions.” (32) The federal and provincial governments are the main purchasers of biopharmaceuticals in Canada. Their fixation on cost containment rather than on value and innovation “reduces opportunities for innovation… and indirectly prevents the development of a healthy supplier infrastructure that can provide specialized support”. (32) Additionally, they limit the reimbursement and delay the introduction of new products. In order to be successful in the area of innovation and biotechnology a national approach needs to be taken thereby surmounting the federal-provincial jurisdictional issues.

The Canadian government’s investment of billions of dollars in the promotion of innovation and biotechnology may negatively impact on the sustainability of the health
system by creating biopharmaceuticals that the health system cannot afford. Thus a uni-jurisdictional approach to promoting innovation may backfire by creating the environment within which the successful uptake of biopharmaceuticals will be impossible. Successful uptake of biopharmaceuticals requires that appropriate receptors be established within the health system.

2. Health System Sustainability and the Challenge of Biopharmaceuticals

Sustainability of the health system “means ensuring that sufficient resources are available over the long term to provide timely access to quality services that address Canadians’ evolving health needs.” (33) In contrast, public spending on health presents considerable economic pressure in most OECD countries. (12) For example in 2006, Canada spent $148 billion on health care services; per capita spending reached $4,548. (34) Specifically, the bulk of healthcare spending is devoted to pharmaceuticals. Sales of drugs (both prescribed and non-prescribed) were estimated at $25 billion in 2006 making it the second largest category of drug expenditure and “one of the fastest-growing components of total health expenditure. (11)

Biopharmaceuticals are an instructive example of the tension which exists between innovation and sustainability. On the one hand, biopharmaceuticals are innovative in that they are produced in a novel manner and may address new disease groups. On the other hand, biopharmaceuticals contribute to the rising cost to the health system because they are often very expensive. (10)

While statistics about government spending on biopharmaceuticals does not exist, total drug expenditure is “forecasted at $23.7 billion in 2005 and $25.2 billion in 2006, representing annual increases of 8.7% and 6.0%, respectively”. (11)
Biopharmaceutical sales have increased from 2001 to 2005 in the US (127%), Canada (213%), France (227%), Germany (235%), Italy (189%), Spain (190%), UK (158%), Australia (230%), Japan (82%), and Mexico (82%). (35) As governments are one of the main purchasers of drugs these statistics indicate that governments are spending more on biopharmaceuticals.

Currently, the coverage of new expensive drugs in health systems is not balanced by cost reductions elsewhere within the health system. (36) As more new expensive beneficial drugs become available governments will not be able to incur all the costs and difficult choices must be made regarding which drugs to fund in order to ensure sustainability. (14, 37)

Alternatively, some industry perspectives focus on cost reduction but rather on the cost of disease. (38) Focus on disease state approaches, i.e., approaches that assess the “full cost of preventing and treating the disease through its life”, (32) could encourage competition and thus innovation. Through investment in innovative approaches to healthcare the cost of disease can be lowered. (38) Additionally, some pharmaceuticals may decrease costs of nursing time and hospital stays. Some research suggests that this cost reduction may off set the cost of such pharmaceuticals. (39)

There are a number of expensive beneficial biopharmaceuticals that have been assessed by a number of countries. In Canada, the Common Drug Review (CDR) established in 2003 attempts to reduce duplication, increase cost-effectiveness and provide timely approval of drugs, as well as ensure more consistency in formulary practices and policies for participating provincial health ministries. (39) The Canadian Drug Advisory Committee (CEDAC), which is part of the CDR, provides critical appraisals of clinical and pharmaco-economic evidence to the provinces with exception
of Quebec (Please refer to the Drug Approval Process in Canada Chart). (40) In 2004 CEDAC rejected Fabrazyme (agalsidase beta) which is used to treat Fabry’s disease and costs $303, 147 US per patient per year. The basis for their final recommendation was its inability to meet cost-effective criteria. (41) Ed Koning, president of the Canadian Fabry’s Association stated that the “CDR [is] not [the] correct body to determine funding of life saving orphan drugs”. (42)

Interestingly, Naglazyme, the drug mentioned in at the onset of this paper, did not go through the normal drug approval process. It was not reviewed by the CDR nor did it receive a notice of compliance (NOC) from Health Canada. Isaac received his drug through the Special Access Programme (SAP) which permits a physician to request access to drugs which would otherwise be unavailable for sale in Canada. The SAP can only be used for “life-threatening conditions on a compassionate or emergency basis when conventional therapies have failed…” (43) To date, the company which manufactures Naglazyme, Biomarin, (3) has not submitted to Health Canada. (44)

Drug Access in Canada
Scholars, researchers and policy makers continue to debate future costs of biopharmaceuticals innovations and potential cost saving to health system as well as improvement of national economy but this debate has yet to be resolved. To reconcile growth in innovative biopharmaceuticals and the maintenance of a sustainable health system, reimbursement choices are being presented to government formulary committees. Reimbursement decisions ultimately depend on the review process established making the process imperative.

3. Negotiating Between the Tensions
Governments planning innovation strategies think about the long-term creation of jobs and increases to the economy. However, innovation involves research whose outcomes are unpredictable. There is no simple mechanism for linking government investment in innovation to the eventual adoption of these innovative products within only one sector, i.e., health. Moreover, there are different types of returns, including jobs created, that cannot be easily quantified.

The OECD recognizes the tension between the goals of encouraging innovation, affordability, priority setting, and sustainability and suggests the tension can be alleviated through policy. According to the OECD, governments must
“develop … policy tools to ensure that the benefits of research and development can be appropriately used to improve the health of citizens and to ensure that the innovation coming through biotechnology is not blocked by a system that does not have frameworks in place to cope with such challenges.” (45)

The OECD NEHRT (New and Emerging Health Related Technologies) project concluded that more work must be done in order to “align health system objectives with policy decisions in new technology sectors.” (45) The OECD report *Innovation in Pharmaceutical Biotechnology: Comparing International Systems at the Sectoral Level* identified systematic failures in national biopharmaceutical innovation systems. A number of policy recommendations emerged. They stress the importance of governments’ ability to coordinate with and between multiple departments, located within different jurisdictions that are responsible for innovation. (9) A recent report from the Canadian Biotechnology Advisory Committee entitled, *Toward a Canadian Action Agenda for Biotechnology*, notes

“Much work remains in this emerging area of biotechnology and includes efforts to connect research to policy development, develop new frameworks or modify existing ones to ensure that methodologies incorporate social and ethical considerations systematically.” (46)

Currently, it is unclear how policy makers will decide whether to fund expensive effective biopharmaceuticals. During the 1990’s there was an increased use of economic assessments of new therapies and a greater emphasis on explicit rationing -- for example, in the UK’s National Institute for Health and Clinical Evidence (NICE) and the Oregon Health Services Commission. (47) Although economic analysis was explicitly emphasized in many drug priority setting contexts (e.g. the Drug Quality and Therapeutics Committee of Ontario), an examination of their decision making revealed that it contributed very little to the actual policy decisions. (48)
Another approach to decision making is Deber’s approach, discussed by Clarke et al., who classifies technologies according to “adoption zones” based on the relation between costs and benefits as compared to alternative therapies. She notes that this approach “highlights the fact that a cost-effectiveness analysis can be used to identify the adoption zone for a particular technology, but it cannot help in determining whether the added benefits are worth the additional costs”. (49) Ultimately these decisions “reflect the values of the decision makers.” (13)

A number of barriers exist when attempting to translate assessment results into policy concerning the adoption and use (regulation) of new technologies. Conflicting interests and organizational features can impede optimal policies (i.e., rational choices based on evidence which try to maximize goals). The perspectives of policy makers is an integral part of the decision making process,

“…for what policy-makers define as problems, and how they define them, depends to a large extent on who participates in decision-making and what values they bring into it. The outcome of policy debates will therefore largely be determined by the manner and extent to which various interests participate in the process that leads to policy development, as well as the weight ascribed to their concerns.” (50)

Traditionally, drug funding decisions are made by bureaucrats and experts, using evidence-based medicine and cost-effectiveness analysis, and an opaque reasoning process. Innovation industries do not know how and why these decisions will be made in the future. Moreover, patients, for whom the system exists, and members of the public, who fund the system through their taxes or insurance premiums, do not know how these decisions will be made. But, as Wiktorowicz and Deber note decisions about drug funding involve value choices about which there is no consensus. (50) For example, when should we refuse to fund drugs that are beneficial but very expensive?
Saying “no” to drugs that may provide some benefit to some patients is highly contentious and morally controversial - - different people will hold different views. Therefore it is necessary to establish a climate in which it is acceptable to say “no”. Key elements of such a climate are legitimacy and fairness. Legitimacy and fairness can improve the manner in which decisions are made. As well, both impact on the way in which decisions are perceived and whether or not decisions are accepted by the public.

Legitimacy refers to who makes decisions as well as who has the moral authority to make decisions. Fairness refers to the process of decision making i.e., how decisions are made. Legitimacy and fairness are related in that both legitimate and illegitimate decision makers can act fairly or unfairly. Moreover, when legitimate decision makers act fairly it tends to enhance their legitimacy. (51)

Procedural justice (i.e., fairness) is “important to individuals independent of outcomes considerations.” (52) According to Fondacaro et. al., “one of the most intriguing findings in the social justice literature is that people seem to care as much or more about how they are treated in the course of decision-making (procedural justice) as they do about the decision outcome (distributive justice).” (53) Therefore, for government policy makers who are faced with decisions about whether to reimburse drugs within the confines of limited resources a goal should be fairness. Furthermore, a study conducted by Murphy-Berman et. al., found that individuals who felt that they were treated fairly, with regards to treatment decisions, had decreased levels of anger, and increased levels of pride. Additionally, they felt it would positively influence their relationship with the health care decision maker. (52) It is important that individuals feel a sense of satisfaction around these decisions as it is a predictor of outcomes related
to health including adherence to treatment and health status. The research on patient satisfaction, as it relates to processes and outcomes, has mainly focused on the provider/patient relationship and recently on patient/health plan representative relationship. It is thought that trust and satisfaction in health plans “can help providers who must increasingly make treatment decisions in the context of limited resources.” (53)

A legitimate and fair process is characterized by inclusiveness, transparency, and responsiveness. A fair process would include stakeholders in the deliberative process i.e., patients, public, and industry. (51) Forging partnerships between industry and health sectors is imperative when attempting to create a legitimate and fair process. Currently, industry involvement is limited to product submission. Industry has no direct involvement in the reimbursement decision making process within Canada. For instance, the Committee to Evaluate Drugs (CED) (54) and the CEDAC (40) have no industry representation. The inclusions of industry within the decision making process is contentious. This debate is highlighted by the World Health Organization’s (WHO) assessment of the United Kingdom’s National Institute of Health and Clinical Evidence (NICE) in 2006 which recommends against industry membership on the Guideline Review Panels (GRPs). (55) Despite this recommendation NICE continues to have industry representation because “The function of GRPs is to ensure that the stakeholder process has been conducted fairly and that the stakeholders’ comments have been responded to appropriately. We believe our current configuration is fit for purpose. We do not believe that configuration as recommended would offer any improvements over the current arrangements”. (56)

Moreover, industry inclusion in the decision making process may deter lobbying and litigation by pharmaceutical companies as all government reimbursement
decisions, even those perceived as unfavourable, would be, and would be seen to be, more legitimate and fair.

Transparency has been recognized by a number of authors and stakeholders as fundamental to fair processes. Transparency requires that the public have access not only to the decisions but also to the rationale behind the decisions. All of the CEDAC’s recommendations and rationales for decisions can be found on the Canadian Agency for Drugs and Technologies in Health (CADTH) website.

Responsiveness is the ability of the organization to revise decisions based on new evidence, or appeals. In Canada, CEDAC does not have a formal process for the public to appeal enabling responsiveness. However, manufacturers have 10 business days to request reconsideration and clarification of the recommendation. If new clinical evidence or cost-effectiveness information exists the manufacturer must resubmit.

Recommendations
The McFayden family’s struggle and eventual success in gaining access to one drug, Naglazyme, demonstrates the complexities governments must address when making decisions surrounding the reimbursement of expensive therapeutics. New drugs are constantly being introduced at higher cost and many governments are moving towards a model of explicitly rationing funds. Consequently, the legitimacy and fairness of these complex policy decisions are more crucial than ever. How should the Canadian government negotiate the tension between the goals of encouraging pharmaceutical innovations such as Naglazyme and health system sustainability in a fair manner?

The application of a legitimate and fair process to policies regarding innovative biopharmaceuticals will help maintain a sustainable system. It will also ensure that the
priority setting system is in compatible with innovation system, thus preventing the creation of policies which could block innovation. Healthcare priority setting needs to work hand-in-hand with industry in an environment of fairness. A partnership must be established between the Ministries of Health and Industry Canada that promotes communication between these governmental departments at both the federal and provincial levels. This equal partnership would foster an environment in which both Ministries value each other’s input thereby promoting decisions which are well informed by stakeholders. Stakeholder involvement increases legitimacy and is crucial to fair decision making.

The primary recommendation which follows from our analysis which addresses the tension between the goals of encouraging innovation and health system sustainability in a fair manner is the Biotechnology Secretariat, responsible for harmonizing biotechnology policies across the federal government, should expand its scope to include all levels of government (the provincial and territorial governments) -- beginning with the provincial and territorial Ministries of Industry and Health. Harmonization of policies requires that all levels of government communicate with one another. This will ensure consistent policies across all branches of government thereby avoiding the possibility of one branch refusing to reimburse the very innovations other branches are promoting. The expansion of scope to include representatives from all levels of government may result in conflict between departments and jurisdictions however it is necessary in order to establish consistency.

Secondary recommendations include: First, when making reimbursement decisions governments should use a disease state approach rather than using the current narrowly defined cost-effectiveness criteria in assessing value for money. A disease state approach will motivate innovations and enable a more comprehensive
approach towards incorporating value for money which is based on all costs and
success outcomes. Second, in order to legitimate and ensure fair reimbursement
decisions collaboration with all the pertinent stakeholders including industry must occur.
Third, all decisions and related rationales should be transparent and accessible to the
stakeholders and the general public. This includes hard copies, electronic versions, and
media releases articulated in accessible language. Finally, a formal dispute mechanism
should be established whereby stakeholders and the general public are able to voice
their objections of recommendation as well as provide further information/evidence to
decision makers. A mechanism is already in place for manufacturers to dispute
decisions. Expanding the scope of this mechanism to include all stakeholders is also
possible and is a key element of a legitimate and fair process.

Acknowledgments:
The authors would like to thank Halla Thorsendottir assistant professor at the School of
Public Health Sciences University of Toronto for her advice.

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from: http://www.theglobeandmail.com/servlet/Article-
News/freeheadlines/LAC/20060715/BOY15/health/ Health.
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of rare diseases to death? A call for a national orphan drug review policy. CMAJ 2006;
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orphan cancers. CMAJ 2007;176(3).


[45] Biotechnology, Innovation, and Health [cited December 5, 2005]; available from: http://www.oecd.org/document/10/0,2340,en 2649 201185 33790794 1 1 1 1,00.html.


Appendix 6: Forthcoming Article in CPHS Working Paper Series

Valuing Rarity: A Case Study of Orphan Drug Priority Setting

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Abstract

Objectives: In order to identify best practices we will 1) describe the process of priority setting for two orphan drugs – Cerezyme and Fabrazyme.

Methods: We conducted a qualitative case study in three independent drug advisory committees. PS was evaluated against a leading conceptual framework for legitimate & fair PS. Interviews were conducted with 23 informants (i.e. committee members, patient groups and industry).

Results: 1) Description: OD reimbursement recommendations by expert panels were based on clinical evidence, cost and cost-effectiveness analysis. 2) Evaluation: Committee members expressed preference for the current process, but were concerned with the fairness of the process for ODs. Other informants suggested the inclusion of other relevant values (e.g., drug’s life-saving ability) in order to improve the PS process.

Conclusions: PS for drugs is not solely a technical process (involving cost-effective analysis, evidence-based medicine etc.). PS of expensive orphan drugs illustrates how consideration of a wider range of relevant values in drug reimbursement will enhance the fairness of the PS process.
Introduction

“Who lives, who dies? The astronomical cost of treatment for rare diseases means some people are left to fend for themselves while others with more common ailments need not always worry about funding. Is it fair? Not on your life.” (Ubelacker 2005) Drug expenditures are rapidly increasing in every health system and account for a large proportion of health spending, and many orphan drugs -- i.e., drugs used to treat an illness affecting 0.65-1 per population of 1000 (Lavandeira 2002) -- are extremely expensive. Currently over 6000 orphan/rare disorders have been identified. (Clarke 2006)

Priority setting regarding orphan drugs involves complex value-laden choices that are often ethically controversial because they directly affect the interests of not only the stakeholders, such as government officials, pharmaceutical companies and patients, but also the public who are ultimately paying for the drugs. Expensive orphan drugs present a challenge to many drug recommendation committees because these drugs seldom meet the cost-effectiveness and clinical evidence criteria commonly used to evaluate drugs under review for reimbursement. In particular, orphan drugs are not subject to large clinical trials due to the small number of patients affected by the disease.

This problem has a potentially enormous scope because, as the science of genomics advances, medical treatments are becoming personalized thereby gaining quasi-orphan status. Today’s policy making for a few orphan drugs may become the precedent for future thousands of products.
Cerezyme and Fabrazyme are two examples of expensive orphan drugs. Cerezyme (*imiglucerase* (systemic)), 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. Today, Cerezyme is used in more than 70 countries to treat Gaucher’s disease. The cost of this drug has been estimated at $350,000 US per year per individual. (Clarke, Amato et al. 2001) Fabrazyme (*agalsidase beta*,) was developed using recombinant human DNA from the enzyme $\alpha$-galactosidase A to treat Fabry disease. Fabry disease is a potentially fatal lysosomal storage disorder (Mignani and Cagnoli 2004) which affects an estimated 1 in 40,000 males. Today, Fabrazyme is approved for use in a number of countries for example, the 15 European Union countries as well as Iceland, Norway, New Zealand, Australia, and Israel to treat Fabry’s disease. The cost of this drug has been estimated at $200,000 USD per patient per year. (Bengtsson, Johansson et al. 2003)

The purpose of this study was to identify the values used by three drug reimbursement recommendation committees regarding Cerezyme and Fabrazyme. To date, no study has described priority setting in the context of orphan drug reimbursement decisions. Describing and identifying the values involved in the process of drug reimbursement decisions within an international context is an essential initial step towards understanding and improving the process.

**Methods**

**Design**

We conducted a qualitative study of priority setting in three drug priority setting committees regarding two drugs, Cerezyme and Fabrazyme. Please refer to Table 1
and 2 below for summary information about the aforementioned drugs. This study involved semi-structured interviews with 23 committee members, patients and manufacturers.

**Table 1. Cerezyme (imiglucerase (systemic))**

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Genzyme, approved by FDA in 1994</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use</td>
<td>Reduces and in some cases reverse the chronic and debilitating symptoms of Type 1 Gaucher disease</td>
</tr>
<tr>
<td>Cost</td>
<td>$350,000 US per patient per year</td>
</tr>
<tr>
<td>Reimbursement Recommendation</td>
<td>Prior to establishment of CEDAC and IBC; PBAC recommended funding through the Life Saving Drug Program (LSDP)</td>
</tr>
</tbody>
</table>

**Table 2. Fabrazyme (agalsidase beta,)**

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Genzyme, approved by FDA in April 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use</td>
<td>Treats Fabry disease, a potentially fatal lysosomal storage disorder</td>
</tr>
<tr>
<td>Cost</td>
<td>$300,000 USD per patient per year</td>
</tr>
<tr>
<td>Reimbursement Recommendation</td>
<td>CEDAC recommended against funding; IBC recommended funding; &amp; PBAC recommended funding through the LSDP</td>
</tr>
</tbody>
</table>

Setting

The committees included in this study, which made funding recommendations to fundors about Cerezyme and Fabrazyme, were: the Canadian Expert Drug Advisory Committee (CEDAC); Australia’s Pharmaceutical Benefits Advisory Committee (PBAC); and the Israeli Basket Committee (IBC). These panels were chosen because: they make recommendations about public funds, they provide guidance on drug funding to governments, and these particular committees have made recommendations regarding
either one or both of the study drugs. For general information about each of these committees please refer to Tables 3, 4, and 5 below.

**Table 3. General Information about PBAC**

<table>
<thead>
<tr>
<th>Decision Making Criteria</th>
<th>Forms of Publicity</th>
<th>Appeals Process</th>
<th>Committee Composition</th>
<th>Websites reviewed</th>
<th>Documents Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>(compared to alternative therapies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Guidelines for Eligibility to Receive Treatment with Agalsidase through the Lifesaving Drugs Program</td>
</tr>
</tbody>
</table>
### Table 4. General Information about CEDAC

<table>
<thead>
<tr>
<th>Decision Making Criteria</th>
<th>Forms of Publicity</th>
<th>Appeals Process</th>
<th>Committee Composition</th>
<th>Websites reviewed</th>
<th>Documents Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>Internet</td>
<td>Available for manufacturers</td>
<td>Experts, Lay members</td>
<td><a href="http://cadth.ca">http://cadth.ca</a></td>
<td>Recommend a-tion for agalsidase beta. 2005</td>
</tr>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutic advantage (relative to current treatments)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost-effectiveness (related to other treatments)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 5. General Information about IBC

<table>
<thead>
<tr>
<th>Decision Making Criteria</th>
<th>Forms of Publicity</th>
<th>Appeals Process</th>
<th>Committee Composition</th>
<th>Websites reviewed</th>
<th>Documents Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical evidence</td>
<td>Internet, Radio, Newspaper</td>
<td>Re-submit in the new year</td>
<td>Experts, lay people, members of the ministry of finance, members of the health insurance</td>
<td><a href="http://www.health.gov.il/english/Pages_E/default.asp?maincat=1">http://www.health.gov.il/english/Pages_E/default.asp?maincat=1</a></td>
<td>Fabrazyme recommendation Guidelines for the submission of a request to include a pharmaceutica l product in the national list of health services</td>
</tr>
</tbody>
</table>
Sampling

Participants were key informants who were selected based on their experience with the drug decisions in question. This method is appropriate for small studies, as randomized sampling would require a massive number of interviews to adequately represent the groups needed to answer the research questions. (Maxwell 1996)

Twenty-three interviews were conducted with members of advisory committees, representatives of drug companies, and patient groups. Initial contact was made with individuals (i.e., advisory board members, patient groups and industry) either in-person, email, or phone. If a response was not obtained two more attempts were made. Snowball sampling was also used -- participants were asked to suggest other potential interviewees. I continued sampling until the analysis reached saturation i.e., there was reiteration of the same ideas. (Strauss and Corbin 1998) There was no formal calculation of sample size.

Five documents and three websites related to orphan drug reimbursement decisions were sampled and analyzed in order to explore issues of fairness related to reimbursement decisions. Mainly documents were obtained in electric 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 in question.

Data Collection

Interviews explored decision making in drug reimbursement of the study drugs [See Interview Guide Box 1 below]. We conducted face-to-face interviews or one-on-one telephone interviews. Interviews were between 30-60 minutes in length. All interviews were audio taped and transcribed.
### Box 1. Interview Guide

#### Sample Questions

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

#### Data Analysis

The interviews were analyzed using a modified thematic analysis. First, the data were read to achieve a good working knowledge of the content -- sometimes called ‘immersion.’ (Denzin and Lincoln 2005) Second, portions of data that related to similar concepts or ideas were identified and labeled -- sometimes called open coding. (Maxwell 1996) For example, the ideas that related to accessibility, such as the ability of public to review recommendations, were labeled as ‘access.’ Third, concepts were compared between and within transcripts to ensure consistency and comprehensiveness. Inconsistencies were corrected through either re-coding data portions into more appropriate codes or they were identified as areas of further analysis. Fourth, concepts that emerged were organized under overarching themes --
sometimes called axial coding. Fifth, primary themes were established and related to the other themes.

During each step analytic memos were written on observations. (Creswell 1998) For example, I would comment on the location, the manner of the respondent and the way I felt the interview progressed. Memos are an important part of research and allow the researchers to reflect on and analyze the research methods and findings. (Maxwell 1996)

We addressed the issue of validity in three ways. First, different data sources were used, including literature, documents and interviews, which allowed examination of the emerging concepts from different perspectives - - sometimes called triangulation. (Denzin and Lincoln 2005) For example, the issue of insufficient data for making a reimbursement decisions arose in the interviews. This notion was further supported in a recent study by Gallego et al., (Gallego, Taylor et al. 2007 ) Second, codes and themes were developed with other team members as a check on bias. We frequently discussed themes and codes with the research team. 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.
Research Ethics

This project was approved by the University of Toronto Human Subject Review Committee. The consent form along with a description of the research was sent via email to respondent prior to the interview. The consent form was reviewed with each participant at the onset of the interview and all questions and concerns were addressed. During in-person interviews consent forms were signed and a copy was given to the participant. When interviews were conducted over the phone the signed consent form was either faxed or sent electronically. All respondents agreed to participate and written informed consent was obtained prior to the interview. All data is confidential and anonymity of participants was protected. Additionally, all raw data were protected and available only to the research team.

Results

Our main finding was that participants from three reimbursement committees, across three different health systems, reported using essentially the same values when making reimbursement recommendations for the orphan drugs Cerezyme and Fabrazyme -- those values were: evidence (as assessed through cost-effectiveness and effectiveness), life-saving ability (i.e., application of the 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 the committee names of CEDAC and IBC are missing. This is because Cerezyme was created before the establishment of both committees. In Canada, reimbursement decisions for this drug were made by individual provincial formularies and varied by province. Obtaining reimbursement required much negotiation between healthcare professionals, government and public advocate appeals. For example, in Ontario, the Minister of Health rejected funding of Cerezyme because of the drug's
inability to meet cost-effectiveness criteria. This decision was publicly criticized by the National Gaucher Foundation of Canada in 1993. According to Clarke et al., 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. (Clarke, Amato et al. 2001) In Israel, the Ministry of Health rejected funding Cerezyme on the basis of its high cost. In 1995 the Ministry included Cerezyme externally from the basket in a New Health Bill which gave special funding to chronic diseases including Gauchers. This decision to fund Cerezyme 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% compared to the cost of the manufacturer’s recommended dose. (Gross 2002) Despite, the drugs ability to meet the values listed below all three countries have funded the drugs through alternative mechanisms.

**Table 6. Values Used in Cerezyme Recommendations**

<table>
<thead>
<tr>
<th>Values Used</th>
<th>Canada’s Ontario Ministry of Health</th>
<th>Israel’s Federal Ministry of Health</th>
<th>PBAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Cost-effectiveness</td>
<td>Failed</td>
<td>Initially failed Passed</td>
<td>Failed Passed</td>
</tr>
<tr>
<td>- Effectiveness</td>
<td>N/A</td>
<td>Passed</td>
<td></td>
</tr>
<tr>
<td>Rule of Rescue</td>
<td>Passed</td>
<td>Passed</td>
<td>Passed</td>
</tr>
<tr>
<td>Equity</td>
<td>N/A</td>
<td>N/A</td>
<td>Passed</td>
</tr>
<tr>
<td>Final Funding Outcome</td>
<td>Funded</td>
<td>Funded</td>
<td>Funded</td>
</tr>
</tbody>
</table>

**Table 7. Values Used in Fabrazyme Recommendations**

<table>
<thead>
<tr>
<th>Values Used</th>
<th>CEDAC</th>
<th>IBC</th>
<th>PBAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Values Used</td>
<td>CEDAC</td>
<td>IBC</td>
<td>PBAC</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------</td>
<td>-------</td>
<td>--------</td>
</tr>
<tr>
<td>Evidence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Cost-effectiveness</td>
<td>Failed</td>
<td>Passed</td>
<td>Failed</td>
</tr>
<tr>
<td>▪ Effectiveness</td>
<td>Failed</td>
<td>Passed</td>
<td>Passed</td>
</tr>
<tr>
<td>Rule of Rescue</td>
<td>N/A</td>
<td>Passed</td>
<td>Passed</td>
</tr>
<tr>
<td>Equity</td>
<td>Failed</td>
<td>N/A</td>
<td>Passed</td>
</tr>
<tr>
<td>Final Funding Outcome</td>
<td>Post market study</td>
<td>Funded</td>
<td>Funded</td>
</tr>
</tbody>
</table>

**Evidence**

**Cost-effectiveness**

All 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...”

Another committee member noted,

“Well, the orphan drug ones are a little more difficult. As you know, the information that they actually work to improve quality of life or to improve life expectancy is … not as easy to come by because, there’s not as many patients and the studies are much smaller and shorter. ”

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 aglasidase beta on a range of tests…” (CEDAC 2005) One 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 …”

Similarly, Israel’s Ministry of Health initially rejected Cerezyme for funding because of the high cost associated with the high prevalence of the disease in Israel. The government was willing to provide the treatment if costs could be reduced. Ultimately, Cerezyme was funded in 1995 because Israeli researchers determined lower doses without negative effects (< one quarter of the manufacturers recommended dose) would reduce the cost significantly, saving $80,000,000.(Gross 2002)

Evidence of cost-effectiveness was used by all three committees. However, many committee members’ recognized the problem of applying this value in the assessment of orphan drugs,

“it’s very difficult to use cost-effectiveness for these drugs because, you’re talking about treating maybe 10 patients …So these drugs will never look cost effective because there’s such a small number of patients that are out there -- although, their budget impact is huge.”

One committee member noted that the decisions around orphan drugs like Fabrazyme are different,

“I think you can make the argument that which I think the Fabry’s people have made that you know the decision around Fabry’s, Fabrazyme, and Reprigal is not a cost-effective decision it’s a it’s a different kind of decision.”

Nonetheless another committee member articulated that it was not clear that orphan drugs should be prioritized differently,

“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.”

Moreover, one patient with Fabry’s Disease suggested,

“So, if you really want to study these disorders you have to work on an international basis and in an international community with registries and international protocols, etc., ... So, we feel that a solution to this issue in Canada, is to work with the international community, using existing proven models that are already in place, develop an orphan drug policy that not only addresses the issues in other countries but also, addresses the issue on access to these drugs, long term studies, etc., etc. using international accepted standards, criteria and protocol.”

Industry also 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.”

Effectiveness

A drug’s ability to provide therapeutic benefit was considered by many respondents to be an important decision making value. But, from one patient’s perspective, increased recognition of Fabrazyme as a preventative therapy would aid in the decision-making process. As one patient stated,

“What is really frustrating for Fabry’s patients...is that the world basically is now administering enzyme replacement therapy for Fabry’s disease as a preventative therapy prior to organ failure... But yet, in Canada the protocol that we have to deal with is the most stringent in the world. For example, you have to have 10% kidney function loss before you can have enzyme replacement therapy. I’m sorry, that’s just not acceptable.”
Another patient explained that the cost is negligible when compared with the benefit of the treatment,

“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.”

**Rule of Rescue**

Life saving treatment was a value considered by both the IBC and PBAC. 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 Basket Committee 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 ... you’re right, 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’ 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.”

**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 CEDAC in their rationale for their decision against reimbursement of Fabrazyme,
“Using conventional criteria, aglasidase beta has not been shown to be cost-effective, though this by itself, is not one of the factors that may be used in making a decision about funding...It has been argued that the costs of drugs to treat rare disease are often high because of the relatively small number of patient ...On the other hand, reimbursement ...would raise questions about equity, since drugs that have not been shown to be cost-effective for other diseases are not generally reimbursed.” (CEDAC 2005)

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.”

Variation in access of drugs across countries was also mentioned by some patients 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.”

**Synthesis**

There are a number of common values which emerged from the discussions with stakeholders most notably evidence, rule of rescue and equity. However, the three committees differed in their final recommendations (please refer to Table 7). The inability of orphan drugs to meet the cost-effectiveness criterion was problematic for both the Canadian and Australian systems who clearly weight this criterion heavily.
Canada’s drug priority setting system is biased 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 benefit more heavily, and they occasionally make positive funding recommendations for drugs with an undesirable cost-effectiveness ratio.

**Discussion**

In this paper we have described the values used by drug reimbursement recommendation committees in three countries in regard 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 Cerezyme and Fabrazyme -- those values were: evidence of cost-effectiveness & effectiveness, rule of rescue, and equity. This provides powerful evidence about the global dominance of this approach to drug priority setting, despite its obvious and contentious limitations.

During the 1990’s there was an increasing interest and use of economic assessments of new therapies and explicit rationing in decision making. (Dean 1991; Klein 1993; Coast 1997; Sabin 1998) Even though countries continue to use economic assessments, problems remain. 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 (EBM) is another popularly used tool which is used to understand effectiveness. However, it does not weigh effectiveness against other values (i.e., benefits, costs etc.). Limitations of the economic approach include it can not place a numeric value on a health outcome, as well benefits and
costs are subjective and therefore dependant on the person conducting the evaluation. Limitations of EBM include the frequent lack of sufficient evidence to make decisions. (Martin and Peter 2000)

Drug priority setting is not solely a technical process. At its core it involves adjudicating between and among a wide range of relevant values. (Martin, Pater et al. 2001) As Gallego et. al., recently indicated, priority setting for high cost drugs are often based on other factors in addition to effectiveness and cost. (Gallego, Taylor et al. 2007)

The participants' views regarding values were supported by the committees' assessment mandates. That is, all three values identified- evidence, rule of rescue 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 criteria. Additionally, the IBC listed a number of decision making criteria which were not discussed by many respondents particularly, legal considerations.

Do priority setting committees value rarity? The criterion of ‘rarity’ was not explicitly believed to be a relevant decision making value by committee respondents. However, in both the cases of Cerezyme and Fabrazyme, the committees did emphasize their core values differently because the disease was rare. For example, cost and therapeutic benefit seemed to be weighted differently in light of the diseases’ rarity. Patients and industry representatives argued that rarity is something to be valued.

The value of rarity is often reinforced by governmental policies and industry incentives concerning innovation for orphan drugs (Rosenberg-Yunger, Daar et al.
For example, the Unites States’ and Japan’s orphan drug policies which provide incentives to pharmaceutical companies for research and development of orphan drugs. (CORD 2005)

However, many priority setting committee members noted that rarity alone should not be the sole criteria of reimbursement decisions. Moreover, despite orphan drugs inability to meet the cost-effectiveness criteria a number of countries are publically funding these drugs through special drug access programs or by considering a fuller range of values (e.g. social and ethical impacts etc.).

Priority setting for orphan drugs involves deliberation about values, many of which conflict, and many of which are not quantifiable. Priority setting committees are very proficient at identifying quantifiable criteria, but struggle with other unquantifiable values -- such as the ‘rule of rescue’. Israel has tried to develop a more inclusive strategy for making decisions. In addition to cost they consider life saving ability and prevention of mortality (for a more detailed account see Shani et. al.) (Segev, Siebzhner et al. 2000)

Related to the issue of drug access is the role of orphan drug policy in patient drug access. Canada and Israel have no orphan drug policies to date. Currently, Cerezyme is the only drug approved and sold in Canada for the treatment of Gaucher disease. Australia’s Orphan drug policy was established in 1997. The policy is aimed to improve availability of drugs through 1) use of information from the US Food and Drug Administration to hasten the evaluation process; 2) no annual registration fees or application and evaluation fees; and 3) five year exclusivity. (CORD 2005)

**Conclusion**

Priority setting for expensive orphan drugs is a challenge for many health systems. Our paper reports decision making in three countries (Canada, Australia, and
Concerning two orphan drugs (Fabrazyme and Cerezyme). Describing and evaluating decision making in specific contexts is the first step toward improving drug priority setting.

### Table 6. Availability of Cerezyme & Fabrazyme in Canada

<table>
<thead>
<tr>
<th>Formulary</th>
<th>Cerezyme</th>
<th>Fabrazyme</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Listed on Formulary</td>
<td>Listed on Formulary</td>
</tr>
<tr>
<td></td>
<td>Other Means of Access</td>
<td>Other Means of Access</td>
</tr>
<tr>
<td>Alberta Health &amp; Wellness</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>special authorization</td>
<td>Post market study</td>
</tr>
<tr>
<td></td>
<td>process</td>
<td></td>
</tr>
<tr>
<td>BC Pharmacare</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>No exception drug status</td>
<td>Under review</td>
</tr>
<tr>
<td>Manitoba Pharmacare</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Exception Drug Status</td>
<td>Post market Study</td>
</tr>
<tr>
<td></td>
<td>Benefit</td>
<td></td>
</tr>
<tr>
<td>New Brunswick Prescription Drug</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Program</td>
<td>Special Authorization</td>
<td>Post Market Study</td>
</tr>
<tr>
<td></td>
<td>process may</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cover it</td>
<td></td>
</tr>
<tr>
<td>Newfoundland &amp; Labrador Prescription Drug Program</td>
<td>No</td>
<td>No exceptions yet</td>
</tr>
<tr>
<td></td>
<td>Exception Drug Coverage</td>
<td>Post Market Study</td>
</tr>
<tr>
<td>North West Territories Health</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Benefits Program</td>
<td>Exception Drug Status</td>
<td>Post market study</td>
</tr>
<tr>
<td></td>
<td>process</td>
<td></td>
</tr>
<tr>
<td>Nova Scotia Pharmacare</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Exception Drug Status</td>
<td>Exception Drug Status</td>
</tr>
<tr>
<td></td>
<td>process</td>
<td>process</td>
</tr>
<tr>
<td>Nunavet Health Benefit Program</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Exceptional Circumstances</td>
<td>Exceptional Circumstances</td>
</tr>
<tr>
<td>Ontario Drug Benefit Program</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Special Drug Program</td>
<td>Post market study</td>
</tr>
<tr>
<td>PEI Drug Cost Assistance Program</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>High Cost Drug Program</td>
<td>High Cost Drug Program</td>
</tr>
<tr>
<td>Régie de l'assurance maladie du Québec</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Can appeal with process</td>
<td>Can appeal with process</td>
</tr>
<tr>
<td></td>
<td>lead by referring physician</td>
<td>lead by referring physician</td>
</tr>
<tr>
<td>Saskatchewan Drug Plan</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Not even by exception</td>
<td>Not even by exception</td>
</tr>
<tr>
<td>Yukon</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Will only be</td>
<td>Reviewed on</td>
</tr>
<tr>
<td>Country</td>
<td>Cerezyme</td>
<td>Fabrazyme</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------------------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>Australia</td>
<td>Life Saving Drug Program</td>
<td>Life Saving Drug Program</td>
</tr>
<tr>
<td>Canada</td>
<td>Varies by province (see table 1)</td>
<td>Post market study</td>
</tr>
<tr>
<td>Israel</td>
<td>Available since 1995 through New Health Bill for funding of chronic diseases</td>
<td>Included in the health basket since 2004</td>
</tr>
</tbody>
</table>

Table 7. Availability of Drug by Country

Acknowledgments

Thank you to all the participants.

References

Appendix 7: Draft Article on Stakeholder Involvement

Stakeholder Involvement across Five Countries: A Case Study of Drug Reimbursement Priority Setting

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**Introduction**

Government reports, scholars and patient groups have believed that stakeholders should have greater involvement in health care priority setting despite the limited evidence on the impact of stakeholder involvement on decision-making. (1) The following paper reviews the extent to which stakeholders, including drug reimbursement committee members, patient groups and industry representatives are involved in the priority setting and appeals processes across five drug reimbursement recommendation committees.

It has been argued in the literature that transparency would lead to increased confidence in the decision making process and that it is integral to a fair and legitimate process. (2-4) Individuals’ (i.e., patients, members of the public, industry representatives etc.) ability to access the decision making is one component of a transparent system. Moreover, there are different ways in which these individuals access the decision making process by reading rationales, participating in the deliberation process, revising the process, appealing the decision, taking legal action, letter writing campaigns, and demonstrations etc. According to the AFR framework, stakeholders should be part of the deliberative process, have access to rationales, and the ability to formally appeal decisions.

**Methods**

*Design*

We conducted a qualitative study of priority setting in five drug reimbursement recommendation committees (located in Canada, England and Wales, Australia, Israel and the US) regarding six drugs: Cerezyme, Fabrazyme, Xigris, Glivec, Remicade and Gonal F. The study involved semi-structured interviews with 45 committee members, patients and manufacturers.
Setting

The committees included in this study made funding recommendations to fundors about drugs -- they included: the Canadian Expert Drug Advisory Committee (CEDAC); National institute for Health & Clinical Excellence (NICE); Australia’s Pharmaceutical Benefits Advisory Committee (PBAC); the Israeli Basket Committee (IBC); and the US State Medicaid Pharmacy Policy Committee. These panels were chosen because they make recommendations about public funds.

In general, the stakeholders that were most often involved in the decision making process were healthcare professionals, the public and academics. Some other stakeholders included by committees were ministry representatives (e.g., IBC) and industry representatives (e.g., NICE). For a complete list of the type of stakeholders involved within each committee please refer to Table 1 Committee Composition below.

Please note, during CEDAC’s review of Fabrazyme (in 2004) there were no public members on the committee.

Table 1. Committee Composition

<table>
<thead>
<tr>
<th>Committee Name</th>
<th>Number of Members</th>
<th>Type of Member</th>
</tr>
</thead>
<tbody>
<tr>
<td>Israeli Basket Committee</td>
<td>24</td>
<td>Healthcare professionals, ministry of health, ministry of finance, economists, hospital managers, public representatives, ethicist, and lawyer.</td>
</tr>
<tr>
<td>NICE, Technology Appraisal Committee</td>
<td>3 committees:</td>
<td>members of the NHS, patient and care organizations, academics, pharmaceutical and medical devices industries</td>
</tr>
<tr>
<td></td>
<td>A - 24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B - 29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C - 29</td>
<td></td>
</tr>
<tr>
<td>Organization</td>
<td>Sample Size</td>
<td>Participants Description</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-------------</td>
<td>------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>PBAC</td>
<td>18</td>
<td>Health professionals, academics, consumer representatives</td>
</tr>
<tr>
<td>CEDAC</td>
<td>13</td>
<td>Health professionals, public</td>
</tr>
<tr>
<td>US State Medicaid Pharmacy Policy Committee</td>
<td>12</td>
<td>In-house Medicaid staff and members of the DUR e.g., pharmacists, physicians</td>
</tr>
</tbody>
</table>

**Sampling**

Participants were key informants who were selected based on their experience with the drug decisions in question. This method is appropriate for small studies, as randomized sampling would require a massive number of interviews to adequately represent the groups needed to answer the research questions. (5)  

Forty-five interviews were conducted with members of advisory committees, representatives of drug companies, and patient groups. Initial contact was made with individuals (i.e., committee members, patient groups and industry) either in-person, email, or phone. If a response was not obtained two more attempts were made. Snowball sampling was also used -- participants were asked to suggest other potential interviewees. I continued sampling until the analysis reached saturation i.e., there was reiteration of the same ideas. (6) There was no formal calculation of sample size.

Twenty-eight documents related to reimbursement decisions of the six study drugs were sampled and analyzed in order to explore issues of fairness related to reimbursement decisions. Mainly documents were obtained in electric 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 in question.

**Data Collection**
Interviews explored decision making in drug reimbursement of the study drugs [See Question Box Below]. We conducted face-to-face interviews or one-on-one telephone interviews. Interviews were between 30-60 minutes in length. All interviews were audio taped and transcribed.

<table>
<thead>
<tr>
<th>Interview Guide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation Committees:</td>
</tr>
<tr>
<td>10. How are recommendations made regarding funding of expensive orphan drugs?</td>
</tr>
<tr>
<td>11. Is there a distinction made between drugs which are life saving, orphan, and/or QOL?</td>
</tr>
<tr>
<td>12. Who was involved in the decision-making process and what was the extent of their involvement? Specifically which stakeholders were involved?</td>
</tr>
<tr>
<td>13. What considerations do you feel are important in making the reimbursement recommendations for orphan drugs?</td>
</tr>
<tr>
<td>14. How were recommendations communicated / disseminated?</td>
</tr>
<tr>
<td>15. What happens if someone disagrees with a decision? Is there a formal process that people including the general public can challenge the decision?</td>
</tr>
<tr>
<td>16. Do you think it is a fair process?</td>
</tr>
<tr>
<td>17. What do you think could be done to improve this process?</td>
</tr>
<tr>
<td>18. How do you think the process affects innovation in the area of biotechnology?</td>
</tr>
<tr>
<td>19. Do you think priority setting affects innovation in the area of biotechnology-how?</td>
</tr>
</tbody>
</table>

**Data Analysis**

The interviews were analyzed using a modified thematic analysis. First, the data were read to achieve a good working knowledge of the content -- sometimes called ‘immersion’. (7) Second, portions of data that related to similar concepts or ideas were identified and labeled -- sometimes called open coding.(5) For example, the ideas that related to accessibility, such as the ability of public to review recommendations, were labeled as ‘access.’ Third, concepts were compared between and within transcripts to ensure consistency and comprehensiveness. Inconsistencies were corrected through
either re-coding data portions into more appropriate codes or they were identified as areas of further analysis. Fourth, concepts that emerged were organized under overarching themes -- sometimes called axial coding. Fifth, primary themes were established and related to the other themes.

During each step analytic memos were written on observations. (8) For example, the interviewer would comment on the location, the manner of the respondent and the way interviewer felt the interview progressed. Memos are an important part of research and allow the researchers to reflect on and analyze the research methods and findings. (5)

We addressed the issue of validity in three ways. First, different data sources were used, including literature, documents and interviews, which allowed examination of the emerging concepts from different perspectives - - sometimes called triangulation. (7) For example, the issue of insufficient data for making a reimbursement decisions arose in the interviews. This notion was further supported in a recent study by Gallego et. al., (9) Second, codes and themes were developed with other team members as a check on bias. We frequently discussed themes and codes with the research team. 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.
Research Ethics

This project was approved by the University of Toronto Human Subject Review Committee. The consent form along with a description of the research was sent via email to respondent prior to the interview. The consent form was reviewed with each participant at the onset of the interview and all questions and concerns were addressed. During in-person interviews consent forms were signed and a copy was given to the participant. When interviews were conducted over the phone the signed consent form was either faxed or sent electronically. All respondents agreed to participate and written informed consent was obtained prior to the interview. All data is confidential and anonymity of participants was protected. Additionally, all raw data were protected and available only to the research team.

Results

Our main findings from the data collected on the six drugs from five committees, across five different health systems, were that different stakeholders were allowed, in varying degrees, to participate in formal mechanisms of revisions and appeals of decisions. Additionally, respondents identified a number of stakeholder groups which were included as well as stakeholders whom they believed should be included in the decision-making process.

Revision and Appeals

Each committee had an appeals process. However, only some stakeholders could appeal decisions through a formal mechanism (See Table 2 below) for example, manufacturers could appeal decisions made by CEDAC, NICE and PBAC. However, patients were not able to formally appeal the process at the aforementioned committees. Nonetheless, patients were able to appeal the IBC and the US State P & T
Committee (if they were members of the plan). Additionally, physicians were able to appeal decisions at the US State P & T Committee, and NICE. The following section is organized according to the different stakeholder groups which were identified by participants including: The Public and Patient Groups, Industry, and Others.

Table 2. Stakeholders with Access to the Appeals Mechanism

<table>
<thead>
<tr>
<th>Committee Name</th>
<th>Stakeholders Able to Appeal Decisions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEDAC</td>
<td>• Manufacturers</td>
</tr>
<tr>
<td>IBC</td>
<td>• Citizens, Physicians, Patient groups. The above groups must re-submit</td>
</tr>
<tr>
<td>NICE</td>
<td>• Patient organizations, Health professionals, Manufacturers, Health service providers, Statutory organizations</td>
</tr>
<tr>
<td>PBAC</td>
<td>Manufacturers (appeals can only be made based on process errors)</td>
</tr>
<tr>
<td>US State Medicaid P &amp; T Committee</td>
<td>• Members of the plan, Physicians</td>
</tr>
</tbody>
</table>

**The Public and Patient Groups**

Public members were involved only in the IBC and PBAC. CEDAC did not have public members on their committee until 2007. While NICE did not have public members they did have patient advocates on their committee. The US State Medicaid P & T Committee did not include public.

Patient groups who had no means to appeal decisions formally often used informal means to appeal decisions. One member of the IBC explained that the public do use informal means to appeal decisions however; professional opinions have greater impact on changing an outcome than public opinions;

“There isn’t an official way but it is done … all the time. Because they know that the public is discussing these technologies. So the committee gets all sorts of
letters from people. There are also demonstrations outside ... but all these are not the real things ... which can change the committees mind...Before things are closed, when they are brought to them through the medical profession and through the members of the committee who had reconsideration and they say ok this is the new information that we didn’t have before and so on so discussion is somewhat ongoing until the recommendations are brought to the companies”

However, Israel was unique in that they allow citizens to submit technology coverage requests to the committee. As one member explained,

“Everybody who is an Israeli citizen can ask for a technology to be added to the list. I mean medical doctors, I mean laymen, I mean anyone…”

Additionally, decisions made by the IBC can be appealed, as one person noted

“they can contest it in the courts and they can decide to [re]-apply .... They don’t have a process during the Committee [the only] recourse is to ask for it for the next year.”

In addition to writing letters and participating in public demonstrations patient groups, who are unable to formally participate in the process, use the media to publicize their concerns or try to get political support for a particular issue. For example, one Canadian Gaucher patient relayed the following incident when s/he was denied treatment,

“I embarrassed the government at that stage. We had 15 minutes on Canada AM, we did 3-4 minutes on the national news. We did a whole newspaper blitz basically embarrassing the government totally. .. I was hospitalized because of the disease ... all of this came out in the press ... We had a meeting in a small meeting room at X Hospital. They wheeled me in with all the tubes and poles ... and the ...Assistant Deputy Minister was there...We had another meeting and two weeks later they funded us.”

The use of media by the public and patient groups is common as one IBC member explained how patient group use the media for their plight and how it resulted in one particular case in an increased health budget,
“The public and mostly patient groups, various kind of diseases, they come and try to press the committee by the newspaper, by the radio, by T.V., by politicians to adapt pharmaceuticals to the health services basket. And this year…it was the most aggressive year ….because there was a shortage of the budget and there was a big strike. All the politicians said they were going to give a hundred of millions of shackles to the basket and so on. After the committee finished their work after the election, and a few drug against colon cancer remain outside the basket, a few people go to the strike …. After three weeks, there was a big headline in the newspaper, by T.V. and so on and finally the Prime Minister, knowing his position, he gave up and gave the committee another 400 million.

In Canada too the public and patient groups cannot appeal formally as one CEDAC member notes,

“Members of the public can write in. There’s a form on the website for providing feedback. And I probably once a week get letters from members of the public asking why this wasn’t funded or … you know, a little bit upset and we respond to those but that doesn’t initiate another look back at that medication per se. If members of the public were really upset then we do get requests for advice back from each of the provincial drug plans. If they’re concerned about a particular decision but no, there’s not a … the public can’t sort of initiate a re-look at a medication.”

An Australian respondent also noted while there is no official system for the patient or clinical group to appeal,

“…Often they'll write to us about a change in a listing. Would we consider changing the listing or removing that or doing such and such? Then the answer is yes. We do that, and that can be done by any individual clinical group or patient group.”

Committee members recognize the imbalance and see increased public involvement as an area that needs improvement,

“I think from a public sort of consumer involvement there’s a bit of imbalance because there isn’t the same sort of formal avenues displayed by which consumers or consumer groups can have input as well so that’s what they’re working on now”

Similarly, patient groups are aware of the lack of inclusion,

“The Common Drug Review does not allow any public input. Does not allow any public dialogue or communication. So we were very, very frustrated and so we, a
group of Fabry’s patients, went to the Common Drug Review’s office and said we’d like to have a meeting with the Chair of the Canadian Expert Drug Advisory Committee …We were not successful in getting a meeting with him but we were successful in getting a meeting with … the head of COHTA at that time which is now called CADTH …And so how can these groups work in isolation when they’re supposed to be representing patients? And in fact the general public who in fact pay the bills for public health care? ”

Industry

Only NICE had industry representation. PBAC at one time had a former industry member. Committees that did not have industry representation on their committee had no desire to include industry on their committees in the future. In general, industry is the best informed of the process as they are the initiators of the process in the England, Canada and Australia. As one industry representative explains,

“… well actually the company is usually working directly with the agency … The other way primarily sort of the major link between all of this, and even on the private payer said, is sometimes the link is the physician, the treating physician. So sometimes they’ll only have a dialogue with the treating physician and then the treating physician will let the company know what the outcome is and where things are sometimes. So it’s a little of each sometimes they will talk directly to the company and sometimes we have to go through the treating physicians.”

Industry in Canada are permitted to submit a ‘Request for Reconsideration’ to the committee prior to the final recommendation. A request can only be presented if 1) CEDAC has not acted according to its review guidelines or has acted in an unfair manner or 2) their recommendation is note based on the submitted evidence. In 2007 CADTH was externally evaluated by EKOS Research Associates. According to this review CADTH is meeting their objectives of timely decisions, meeting needs of and supporting stakeholders, equity, responsiveness to change, and cost-effectiveness. Additionally, the House of Commons Standing Committee on Health conducted a study
which examined the status of and progress accomplished under the (CDR). However, according to the chair of Best Medicines Coalition Louise Binder

“We are disappointed that the Common Drug Review has been given more power when in fact it has proven to be a largely ineffectual body. It has not been successful in meeting some of its main targets, including creating a level playing field for treatment in this country, conducting timely reviews and cutting bureaucratic duplication”.

Moreover the decision made prior to the completion of the Standing Committee's review.

Likewise, there is a formal appeals process at NICE. They accept appeals from the manufacturer within 15 working days of the final recommendation. Alternatively, manufacturers may pursue a judicial review of a recommendation. In 2003 the WHO conducted a review of the TAC. Overall they were impressed by its rigorous processes and methods. There were a number of recommendations including (but not limited to): reconciliation between transparency and confidential materials, reduction of duplication during the assessment phase, collection of information form all stakeholders early in the assessment, membership on committee should be based on skill (i.e., industry should be involved in the consultation phase but not be part of the committee).

In Australia manufacturer are permitted to resubmit an application, or pursue a judicial review based on procedural grounds. As explained by one individual

“The only appeals mechanism available to a sponsor is what we call on process and over the last 10 years there have been three occasions where the PBAC has been taken to court, to the federal court in this country, on the basis of what was deemed to be a breach of process. So there is no appeal on the decision of PBAC. …there is now an established review process … which means if a sponsor disagrees with a decision of PBAC and normally that would be only if we rejected the application they can seek an independent review. Now the government’s set up an independent review mechanism, they have established a convener …the convener will appoint independent reviewer or reviewers depending on what the company is complaining about…There’s no hearing before the reviewer. The reviewer will consider all the data and all the
correspondence between the sponsor, will consider all the minutes of the PBAC and sub-committees and then the person will report to the convener who reports to the PBAC. The PBAC then considers the reviewer’s report taking into account the issues that were raised by the sponsor and the reviewer and will then reconsider if it wishes to change its original decision...So the final decision-maker is the PBAC.”

Additionally there is a possibility for informal meetings between the Chair of the Committee and manufacturer to negotiate as one participant noted

“particularly with the more high profile deliberations … there would be a stakeholder meeting prior and also after particularly if it’s a negative decision where both the sponsor, the drug company, the professional/medical group that’s involved and the consumer group would be brought together to discuss the notion. The problem is the system is set up whereby the sponsor has the power in terms of challenging decisions in submission.”

While industry actively participated in the appeals process they do not participate in the decision making process specifically, no committee except NICE has industry representation on their committee. For example, one CEDAC member said the following regarding industry and conflict of interest,

“…there’s huge issues around conflict of interest…We all give a statement of our conflict of interest as do the public members … Sometimes our own members are excluded from consideration … But you can only imagine if we actually had an industry representative. I mean they’ve got a clear, blatant conflict of interest both directions. If we’re looking at a drug that’s, made by their company or, if we’re looking at a drug that’s not made by their company.”

Similarly in Israel one committee member noted, “No, they [industry] are not allowed - it’s a conflict of interest.” Another CEDAC member explained that their presence on the committee is unnecessary because,

“..from the point of view of the pharmaceutical industry-- it’s extremely fair ....In this process it seems like the industry will just continue to appeal until they’re worn down or something happens. So I think it’s from an industry point of view it’s sort of fair...”
In Australia the PBAC is not required to have industry representation however one member commented that,

“…there was a lot of discussion some years back about industry representatives. And in fact it caused an enormous amount of disquiet …and there was an industry representative appointed for a number of years …At the moment there’s no industry representative on the Committee. And that member was ex-industry rather, than current industry.”

Others

An interesting stakeholder which was identified by Israeli respondents was the inclusion of the ministry of finance on the committee. In Israel it is crucial to have communication between the committee and the finance department as they are making decisions within the confines of a finite budget i.e., the basket committee is given a budget and they must decide along with the budget and other criteria which drugs they are going to list. One member explains the presence of the ministry of finance on the board as follows,

“…They want to be involved in the decision making because …they consider different elements. For example,…what they propose[d] last year in the discussions, was that if there is a drug that is a primary one [brand name] and they are allocating a certain money to the drug for the first year, if in two years the drug will be generic, they should made another because the cost will be less. So this year or the 1st two years they will get to this money (the health funds) and then they will get less because there is a generic! In these things they are interfering! …They think it’s not interfering that it is the correct thing to do! ”

Physicians were also identified as a key stakeholder. One member of the basket committee explains the value of physician’s opinions regarding the technologies they are reviewing,

“You can’t fight the physicians. You can argue with them; I don’t want to say they work like a guild….Many are too strong…when the professional committee are very convinced that one technology isn’t important, it’s very difficult not to go with them.”
Physicians are also recognized by the industry and patients as the one that begins the process. As one industry representative explained,

“… Sometimes the person who has to begin all this is the treating physician but the treating physician … The physician has identified a patient that they want to treat. And sometimes the treating physician is the one who has to initiate saying: “I’d like to get this drug for my patient”.

In Australia a group of physicians can request coverage, as one PBAC member states,

“…While 99% of the submissions we get are from drug companies every now and again, we get a submission from a group of clinicians asking for answers to certain things. Normally however, if it requires an economic analysis … they would have to provide us with an economic analysis and we would treat it in no different way.”

Discussion

The importance of including a robust array of stakeholders in decision making is supported by the literature. Martin et al. described elements of fairness in priority setting identified by decision makers for new technology. Decision makers identified including multiple perspectives – representing different stakeholder groups – to be the most important element of fair priority setting. (10) This study further adds to this literature in that it promotes the inclusion of industry within the deliberative process and the inclusion of patients in the appeal/revisions mechanism.

This study demonstrated that various stakeholders accessed the decision/recommendation system differently. For example, many patients that were interviewed believed they had limited access to the deliberative process. Also, patients often had no opportunity to use the appeal mechanism. Specifically, patients have no formal mechanism to appeal decisions/recommendations made by the following committees: CEDAC, CED, NICE and PBAC. Nonetheless, they did appeal decisions through informal means for example, by exercising political pressure, including letter
writing campaigns (e.g. Australian fertility patients) and effective use of the media (e.g., Gaucher patients in Ontario). Alternatively, patients could formally appeal decisions/recommendations made by the US State Medicaid P& T. The US State Medicaid P & T committee allowed its members i.e., patient beneficiaries, to appeal decisions on a case by case basis. And in Israel patient had the ability to re-submit drugs that were not included in the basket.

Members of drug reimbursement committees often believed that a patient’s ability to access rationales on the internet and have public members sit on the committee is sufficient access for patients. Alternatively, patients believed that their testimonials and personal experiences should be considered and they should have access to an appeals mechanism since they are the ones ultimately being denied treatment. In order for the process to be transparent, public membership on committees is insufficient (though it is a positive step towards increased transparency). Patients must also have an opportunity to appeal decisions.

Similarly, industry’s ability to participate in the deliberative decision making process varied by country and committee. Unlike patients, manufacturers were often the initiators of the process because they submitted the drugs to be reviewed. Manufacturers had opportunity to appeal decisions. Nevertheless, they were often not included in the decision making process, with exception of NICE which included industry members on their Technology Appraisal Committee. When asked about the inclusion of industry, committee members were concerned about the conflict of interest they represented. Another reason for lack of industry inclusion in the process was proprietary issues i.e., committee members believed that having an industry member present when discussing innovations made by their competitors was problematic.
Industry representatives believed that these issues could be overcome and there was a definite need for involving them further and encouraging more dialogue.

A central component of a legitimate and fair priority setting process is to make priority setting explicit and to involve pertinent values and stakeholders in decision making. (2) This study has demonstrated that participants believed the involvement of multiple stakeholder groups within the deliberative and appeal/revisions processes would contribute to a fair and legitimate drug reimbursement process.

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