CONSIDERATION FOR RARE DISEASES IN THE CONTEXT OF DRUG REIMBURSEMENT PROCESSES

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Thesis submitted to the Faculty of Graduate and Postdoctoral studies in partial fulfillment of the requirements for the MSc degree in Epidemiology

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Abstract

The aims of this thesis were to identify whether justification can be provided for the specialized consideration of drugs for rare diseases (DRDs) within reimbursement decision-making, to understand the processes applied for making coverage decisions for DRDs, and to identify how funding outcomes may differ based on the evaluation process used. The characteristics of DRDs were considered in the frame of developing an ethically acceptable rationale for the differential consideration of DRDs within coverage decision-making. The results revealed that the differing evidence base might provide ethical justification for a specialized process, but this does not justify the use of differential funding criteria. A review of processes applied internationally and within Canadian provinces and territories demonstrated that 13 out of 59 processes consider DRDs distinctively. Finally, two case studies of DRDs, Alglucosidase alfa and Canakinumab, were considered to provide insight into the application of different drug reimbursement processes and associated funding outcomes. The results highlight the heterogeneity in funding outcomes for DRDs, which arises through the application of different funding outcomes. While currently processes exist for the evaluation of DRDs and drugs in general, limitations exist with current approaches. Processes should aim to be fair and jurisdictions should carefully consider the justification underpinning a dedicated process for DRDs.

List of Acronyms

A4R	Accountability for Reasonableness
BC	British Columbia
BIA	Budget impact analysis
CADTH	Canadian Agency for Drugs and Technologies in Health
CAPS	Cryopyrin-associated periodic syndrome
CBA	Cost benefit analysis
CDR	Common Drug Review
CEA	Cost effectiveness analysis
CER	Comparative effectiveness research
CMA	Cost minimization analysis
COPD	Chronic Obstructive Pulmonary Disease
CUA	Cost-utility analysis
DRD	Drugs for rare diseases
DSA	Deterministic sensitivity analysis
EMA	European Medicines Agency
EU	European Union
HRQL	Health related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICUR	Incremental cost-utility ratio
LY	Life years
ODA	Orphan Drug Act
MOHLTC	Ministry of Health and Long-term Care
NICE	National institute for health and care excellence
QALY	Quality adjusted life years
PBAC	Pharmaceutical benefits advisory committee
PNH	Paroxysmal nocturnal hemoglobinuria
PSA	Probabilistic sensitivity analysis
R&D	Research and development
RCT	Randomized controlled trial
SMC	Scottish Medicines Consortium
UK	United Kingdom
WTP	Willingness-to-pay

Acknowledgments

I would like to sincerely thank my supervisor, Dr. Doug Coyle, for his unwavering support and mentorship throughout the entire thesis process. It is difficult for me to overstate my gratitude for all his patience, guidance, and kindness. I would also like to thank my co-supervisor, Dr. Tammy Clifford, for the support and motivation to complete this thesis. A twist of events brought me to this program and I am genuinely appreciative for all the time and energy you invested in training me.

Barry Jones, thank you for always taking the time to provide me with insightful feedback and input at all phases of this thesis. Your perspective was always very helpful in moving this project forward.

Thank you also to Dr. Larry Lynd and the entire CIHR New Emerging Team for Rare Diseases for the funding to complete this thesis and the training that has been provided to me as a member of the New Emerging Team for Rare Diseases. Input from this multi-disciplinary team comprised of experts in various areas of rare disease research including health economics, health policy, priority setting, decision-making and ethics helped provide thoughtful feedback that was very valuable throughout the thesis process.

I am also indebted to my family, friends and colleagues for their everlasting support. To my family, thank you for always being there for me and trusting me. To my fellow students- I am so grateful to have met each of you and developed valued friendships. I am so appreciative of all the perceptive conversations and comic relief that got me through this program. All the difficult and challenging times were always made into fun adventures thanks to all of you.

To all the amazing people in my life who are still not sure if epidemiology has to do with skin, thank you for keeping me grounded and allowing me some distraction from the work. Finally, thank you to the Department of Epidemiology and Community Medicine for the funding support to present my work at the International Society for Pharmacoeconomics and Outcomes Research International Meeting (ISPOR) in Montreal in June 2014.

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Chapter 1- Introduction

Background

Rare diseases are broadly defined as diseases that affect a small number of individuals in the population (1–3). More explicitly, the definition of what constitutes a rare disease is heavily debated and there remains no universal definition. Incidence and prevalence measures are most commonly applied to define rarity, and these range from a prevalence of 1 in 2,000 to 1 in 200,000. Definitions differ not only across jurisdictions, but also in the context in which they are applied; for example, thresholds for rarity may be lower when establishing regulatory incentives than when making coverage (reimbursement) decisions (1). In the Canadian regulatory environment (i.e. relating to the licensing of drug products for market access), rare diseases are defined as those affecting less than 5 in 10,000 individuals; and variation can be noted among the definitions applied within the provincial reimbursement context (4).

Beyond the uncertainty associated with the definition of rarity, the availability of high quality epidemiological data on rare diseases is often limited. In the absence of this information coupled with the limited understanding of many specific rare diseases, the population level burden of these conditions is difficult to estimate. It is estimated that there are between 5000 and 8000 different rare diseases, and that approximately 250 new rare conditions are identified every year (5,6). Drawing on these facts, it is important to recognize that while each rare diseases affects only a small number of individuals in the population, collectively these diseases present an important public health challenge (7).

Drugs for rare diseases (DRDs)

The medications to treat patients with rare diseases are often referred to orphan drugs or drugs for rare diseases (DRDs). They have been labelled as "orphans" because historically, research and development (R&D) into new treatments for rare conditions has been neglected by researchers and the pharmaceutical industry (8). Arguably, this is attributed in part to the challenges of studying rare conditions, and the high costs associated with the R&D into these new products and their limited potential for return on investment (7,9). While this position has traditionally been adopted, there is now growing evidence that pharmaceutical manufacturers are targeting investment into treatments for rare conditions as they are seen to be highly profitable, making them less abandoned (10,11).

In order to encourage interest in developing DRDs, many countries have drafted legislation, such as the U.S. Orphan Drug Act, which afford special incentives to manufacturers for the development of medicines to treat rare conditions. These incentives vary widely across jurisdictions and include extended periods of market exclusivity, fee waivers, and protocol assistance (3,10). The implementation of such policies, and with the application of improved methods in biotechnology, has augmented investigation and investment into drugs to treat rare diseases (12,13). Similarly, in order to promote research and innovation for rare diseases in Canada, in 2012 Health Canada announced that a framework for the designation, authorization and monitoring of orphan drugs is under development (4).

The treatments for rare conditions are often associated with dramatically high costs and have been cited among the most expensive drugs in the world (14,15). Although certainly not all DRDs have dramatic costs, many treatments for rare disorders come at extremely high costs. For example, Elaprase (Idursulfase), a treatment for Hunter's

syndrome, a lysosomal storage disorder affecting 1 in 170,000 live-births, costs approximately $375,000 per patient per year (14). Many factors are suggested to impact the setting of drug prices including: the need to cover investment in R&D, the value of the product to patients, the market conditions, and the country's pricing and reimbursement environments; however, the primary factor in the setting of prices of orphan drugs is similar to drugs for other conditions, in that prices are set to ensure profit (2). It is often noted that the high costs for DRDs are justified on account of the small patient population which limit the potential return on investment (2,15,16).

In addition to the high costs associated with these drugs, there are often difficulties with the evidence available for assessing these treatments. High quality evidence measuring the clinical added value of these medications is often unavailable (2). Sufficient evidence on the efficacy of interventions is restricted by the challenges of conducting adequately powered randomized controlled trials (RCTs) in a reasonable timeframe given the small number of patients affected by each rare condition (17). Additionally, only limited and highly uncertain information related to the natural history, safety, and cost effectiveness of DRDs is typically available, which are also key elements which inform the decision-making process for drugs (15,18,19). Given the high costs and the high uncertainty, treatments for rare conditions present a difficult challenge when making resource allocation decisions (20).

Drug reimbursement decision-making

In many cases, treatments for rare diseases remain inaccessible to patients. The accessibility of medications for patients is often beyond the realm of the regulatory approval of the medication and is affected by decisions related to the allocation of health care resources. However, decisions about where to allocate scarce health care resources are always a difficult task from the perspective of the publicly funded health care system. This problem is particularly salient in the case of expensive DRDs (19,21,22).

In light of the challenges in making resource allocation decisions, decision-makers are forced to establish which therapies should be funded using public resources. Given that it is fiscally impossible to provide funding for all available therapies, jurisdictions make decisions based on a variety of different factors. Many jurisdictions have moved towards the application of evidence informed processes relying on comparative effectiveness research and health technology assessment (HTA) to help inform decision-making processes that are fair and equitable (23). Such processes consider not only the good of individual patients, but also consider the costs and the health benefits at the population level (24).

Many different processes are used for reimbursement decision-making for common conditions in Canada and around the world. Government and HTA agencies mandated to help inform decision-making undertake evaluation processes that consider a range of different factors. Evidence that is often considered within these processes includes: the clinical need for the medication as determined by the severity of the condition and the burden of the illness, and the health impact of the medication based on the evidence (25). The evaluation processes in most countries consider the comparative clinical effectiveness and cost-effectiveness of medications (26,27).

In Canada, the reimbursement of medications is managed by each of the provincial and federal publicly funded drug plans (28). In order to improve efficiency by reducing the duplication of reviews by drugs plans, consolidate the submission process for manufacturers, and to ensure equal access of high quality, timely, and evidence-based information; the process for the evaluation of new drugs has been centralized at the Canadian Agency for Drugs and Technologies in Health (CADTH). CADTH's Common Drug Review (CDR) involves an objective and thorough assessment of the clinical effectiveness, cost-effectiveness, and patient evidence of new drugs, and provides listing recommendations to all participating federal and provincial drugs plans (excluding Quebec) (28). Similar processes are also used in other countries.

Several of the priority-setting processes that are used have been based on the concept of fairness and are intended to align with the framework presented by Daniels and Sabins known as "Accountability for Reasonableness (A4R)" which suggests that four tenets must be satisfied to achieve fairness in resource allocation decisions. The framework proposes that funding decisions and their rationales should be publicly available, they should be relevant, there must be opportunity to, and that the concepts within the processes should be enforceable (29).

Although these processes aim to promote consistency and transparency in the drug reimbursement process, evidence for DRDs rarely meets the routine standards of proven clinical effectiveness, need and cost-effectiveness, used in formal evaluations of health technologies (19). The high costs of many therapies for rare diseases, paired with the limited epidemiological and natural history data available, has led to arguments that existing frameworks for resource allocation decision-making should not be applied to DRDs (14). CDR currently reviews DRDs approved in Canada, in accordance with the

processes applied for other new drugs; however, the CDR process allows for adjustments to the submission requirements and review process to reflect the challenges with making these decisions (30). Due to the limited application of existing processes in Canada, decisions for the funding of DRDs are made on regional and provincial levels largely on the basis of historical and political factors (19).

Statement of problem

With a growing number of DRDs becoming available and the high costs associated with these therapies, processes for reimbursement decision-making that consider the characteristics of rare diseases are needed. In light of the limitations of many of the current decision frameworks, little reflection is given to the cumulative costs or the alternative applications for the resources used to fund DRDs (31,32). In order to support fair resource allocation decisions, processes should be standardized. Consideration should be given to the tenets proposed within the A4R framework which embraces transparency of the decision process, and encourages clearly outlining the criteria on which decisions are based in order to support the defensible use of resources to contribute to maximum population benefit (33).

Note on the structure of the thesis

This thesis addresses multiple research questions that are answered using different methodologies. The thesis has therefore been organized into three chapters, each of which addresses one of the three overarching objectives. Each chapter includes the methodology, results, and conclusions.

Chapter 2- This chapter aims to examine whether an acceptable rationale can be established for the implementation of a differential process for the consideration of DRDs within drug reimbursement decision-making processes.

Chapter 3- This chapter aims to identify processes used for making resource allocation decisions in general, and specifically for rare diseases in Canada and internationally.

Chapter 4- This chapter includes two case studies of different DRDs, to assess how drug reimbursement decisions may vary through the application of different coverage decision-making frameworks.

Chapter 5- This chapter provides a final summary linking together the previous 3 chapters to discuss implications, and future directions.

Chapter 2- Exploration of ethical justifications for a specialized framework for the reimbursement of DRDs

Rationale

In the absence of clear guidance for how DRDs should be considered for reimbursement, jurisdictions make decisions based on a variety of social and political factors (34). There is much debate about whether the same processes and criteria for making drug reimbursement decisions for drugs for common conditions should be applied to the reimbursement of DRDs. While some jurisdictions have moved forward with different strategies on how to address the challenges of making funding decisions for DRDs, whether targeted decision frameworks are warranted remains unclear. Developing an understanding of the characteristics of rare conditions and developing a sound rationale for whether DRDs should be considered uniquely is an important step towards standardized processes for making coverage decisions.

Objective

The purpose of this chapter is to investigate whether there is an evidence-informed rationale for considering DRDs differently in the context of drug coverage decision-making.

Ethical Justifications for the Specialized Consideration of DRDs

In this chapter, sixteen arguments are systematically applied to assess whether a logical justification for a specialized framework for the assessment of DRDs within reimbursement decision-making is ethically defensible. The first 11 arguments were identified by Cookson (35) as potential foundations for the National Institute of Clinical

Excellence (NICE) end-of-life premium. The remaining five arguments were identified from key publications discussing the difficulties of making reimbursement decisions for DRDs (9,15,36,37). Each of these positions is considered independently, and it is examined whether the proposed arguments provide sufficient justification and relevance to the development of a dedicated coverage decision-making process on the basis of the rarity of the conditions and the distinguishing features of rare diseases compared with drugs for common conditions.

Proposed arguments for the differential consideration of rare diseases in resource-allocation decision-making

1. "Rule of rescue" argument, which states that there is a responsibility to save identifiable individuals whose lives are endangered, regardless of the cost.
2. "Fair chances" or "equity" argument, which states that all individuals should be given a fair chance at life.
3. "Ex-post willingness to pay" argument, that individuals will be willing to pay more for treatments after they have been diagnosed with a rare condition.
4. "Caring externality" argument, which states that the family members and caregivers of patients with rare diseases stand to gain important non-health benefits when treatment is provided to a loved one.
5. "Financial protection" argument, that greater value is associated with the funding of high cost treatments such as those to treat rare conditions because of the financial consequences experienced by patients.
6. "Symbolic value" argument, which states that society places special value on funding certain medications such as DRDs

7. "Diminishing marginal value of future life-years" argument, which states that the fewer remaining life years the greater they are valued.
8. "Concentration of benefits" argument, which states that smaller health benefits experienced by patients with rare diseases are valued more highly than larger health benefits experienced by other patients.
9. "Dread" argument, that rare conditions are particularly dreadful and therefore funding for these conditions is valued more highly.
10. "Time to set your affairs in order" argument, which suggests that special value is assigned to the life extension which allows patients the time to set their affairs in order.
11. "Severity of illness" argument, that priority should be given to those with rare diseases because they are worse off and in greater need than other individuals without rare conditions (35).
12. "Complexity of illness" argument that priority should be assigned to those with complex conditions rather than to those with conditions that are not complex.
13. "Vulnerability of the population" (e.g. children) argument that patients with rare diseases are often children, and treatments for children are valued more highly (14).
14. "Differing evidence base for rare diseases" argument, which states that the evidence base for rare conditions is necessarily different from those for common conditions.
15. "Rarity of the illness" argument, which takes the position that rare conditions merit special consideration on account that they affect only a small number of individuals in the population.
16. "Lack of alternatives" argument that more value is ascribed to funding DRDs because they fill an unmet need where no other treatment is available.

1. Rule of rescue argument

The rule of rescue was described by bioethicist Albert Jonsen (1986) to explain the phenomenon where there is a moral impulse to save identifiable individuals that are in immediate danger from avoidable death regardless of the cost (38). Examples include the extreme efforts undertaken to save fishermen lost at sea or skiers trapped by avalanches (39). This principle has also been extended to justify resource allocation for lifesaving health care technologies, and has been cited in the context of reimbursement decision-making for DRDs (40). Proponents argue that despite the high costs associated with many orphan drugs, decision-makers have a responsibility to save identifiable individuals with rare diseases (41). While this argument may be appealing, the rule of rescue cannot be applied as a logical ethical justification for a differential funding framework for DRDs.

In the literature, the rule of rescue has been characterized in terms of four central components: identifiability, endangered lives, opportunity costs, and life-saving rescues (39,41). These aspects will be used to explore the limitations of the rule of rescue as an argument for the distinctive consideration of DRDs when making drug reimbursement decisions.

Identifiability

Among the prominent features of the rule of rescue is the attention to identifiable individuals (41,42). In many cases patients with rare diseases are identifiable due to the rarity and the physical manifestations of their conditions (39,41), and these patients may be particularly discernable as a result of media coverage and publicity (41). Advocates argue that DRDs should be considered uniquely for reimbursement because the benefits experienced by identifiable individuals such as those patients with rare disorders are much

greater than the benefits experienced by the unidentifiable statistical lives (39). Identifiability alone, however, is not sufficient justification for a unique process for reimbursement.

Although identifiability may instill a personal moral obligation among individuals to act towards saving a life, this concept cannot sensibly be applied to decisions taken by public agencies involved in making drug reimbursement decisions (41,43). The role of these organizations is to ensure that resources are allocated to maximize population health (35). This involves consideration for both the lives of identifiable and unidentifiable individuals. A process based on identifiability violates the neutrality in decision-making by favoring the lives of identifiable individuals and ignores the economic principle of making decisions under a "veil of ignorance" (42,44). Furthermore, grounding justification for a unique process for rare diseases should reflect the characteristics of rare diseases. Although some rare diseases are certainly identifiable, rarity does not guarantee identifiability. Among the 5,000-7,000 different diseases that are considered as rare, many are not identifiable. Rationalization for a unique process based on a characteristic that applies only to certain patients with rare diseases is challenging.

Endangered lives

Another central theme of the rule of rescue is that the individuals to be saved must be threatened with imminent death. The argument is that there is a moral obligation to save individuals that are in shocking and in horrifying situations where there is a necessity to act quickly (42). Supporters have argued that the rule of rescue can be invoked not only when a life is endangered but also when there is a substantial decrease in quality of life and that public agencies involved in resource allocation have a moral obligation to act in favor of

those who are the worst-off (41). The transferability of this argument as rationalization for a unique reimbursement framework for DRDs, however, is limited by the characteristics of rare diseases.

Patients with rare diseases may be in immediate danger of death or have significant reductions in quality of life, but rare diseases are not necessarily life threatening. Often, the lives of patients with rare diseases are not threatened in the same way as an individual trapped in a burning building or a patient who has experienced a heart attack. Instead, patients with rare diseases may experience chronic and progressive symptoms, while others may experience mild symptoms. Given the diverse manifestations of rare diseases, justifying a unique funding framework based on this principle presents difficulties.

Furthermore, a specialized framework established on this basis would be vulnerable on account that not only rare conditions place individuals in immediate danger of death or cause substantial reductions in quality of life. For example common conditions such as heart disease, which is among the most prevalent chronic conditions, can place patients at risk of death from heart failure; and chronic obstructive pulmonary disease (COPD), can be associated with dramatic reductions in quality of life. As the lives of patients with both rare and common conditions can be endangered, a specialized reimbursement framework for rare diseases is difficult to rationalize on the basis of this claim.

Opportunity costs

In general, when the rule of rescue is applied there is limited or no consideration for the extraordinary costs or the alternate application of the resources needed to protect the individual at risk (41). In the context of rare diseases, advocates of the rule of rescue argue that costs should not be considered in the framework for funding DRDs, particularly given

that the budget impact of funding these technologies would be minimal (39). A framework for allocating resources for DRDs cannot sensibly be based on disregarding the opportunity costs of funding these technologies.

For one, this goes against the objectives of public agencies who are responsible for improving public health and maximizing health (41). Public agencies have an obligation to appropriately allocate scarce health care resources, which includes consideration for the benefits forgone by making health care resource allocation decisions. This is entirely disregarded by the rule of rescue (42). This if often defended on the basis that the budget impact of funding one expensive drug is often small relative to the pool of resources available for the funding of health care technologies; however, this considers rare diseases in isolation and disregards the collective costs of treatments (39,45). This phenomenon known as isolation bias or budget constraint bias is well documented in studies where individuals are asked how much they are willing-to-pay for an intervention; when presented with one option, individuals are often willing-to-pay more than if they are presented with various groups of options spanning across different diseases(46). The foundations of a specialized reimbursement framework for rare diseases would most appropriately reflect the collective costs of the funding decisions. This is particularly important given the considerably high costs of many of the therapies to treat rare diseases and the growing number of therapies becoming available; completely disregarding the costs of funding these treatments would be unsustainable.

Life-saving rescues

Finally, the rule of rescue is characterized by life-saving rescues, which lead to dramatic improvements in health or save a patient from looming death. Founding a unique

reimbursement decision-making framework for rare diseases based on this principle is difficult given that treatments for rare diseases cannot appropriately be described as "rescues."

It is certain that some patients may experience improvements in quality of life or increases in life expectancy from DRDs, but the currently available treatments are more often incremental and are rarely transformative. Patients receiving treatments for rare diseases seldom have sufficient improvements to health that lead to full restoration of life expectancy (35). Few treatments for rare diseases are transformative or dramatically alter patients life expectancies (46), and this is contradictory to the "rescues" that are traditionally acceptable based on the rule of rescue. For example, saving a fisherman lost at sea would restore his health and life to the status prior to the rescue. The same cannot be said of therapies where the effects experienced by patients may be subtle and therefore this cannot be cited as the reasoning for considering DRDs uniquely for making resource-allocation decisions.

In summary, there are flaws in the arguments that have been presented in favor of the rule of rescue for the justification of a unique process or funding DRDs. The characteristics of rare diseases, coupled with the role of public decision-makers in drug reimbursement are not in line with the principles underlying the rule of rescue.

2. Fair chances argument

Consideration of equity issues when making resource allocation decisions in times of resource scarcity continues to be the source of heated debate (47). The equity or fair chances argument is based on the reasoning that all individuals should be given a fair chance of receiving the best treatment available (48,49). Concerns of equity for patients

with rare diseases have been raised on the basis that evidence informed processes may not provide patients with rare conditions a reasonable chance at the best available treatment (9). As a result, the fair chances argument has been cited as a justification for a differential drug reimbursement framework specifically for DRDs. While the evidence base for rare diseases may vary, given the difficulties of applying the equity argument, it cannot be used as justification for a specialized coverage decision framework.

For one, the equity argument is based on the principle that equal access should be provided based on equal needs, and as rarity does not imply need, principles of equity are against the differential consideration of DRDs in resource allocation decision-making (15,36,37). Providing a specialized framework for the reimbursement of rare diseases would imply that patients with rare conditions are valued differently than the patients with more common conditions. From a utilitarian perspective, resources should be allocated in order to provide the greatest good to the greatest number (15,50). From this position, a specialized process for the reimbursement of DRDs would be indefensible, as it would not favor decision-making to benefit the most individuals, and would prioritize patients with rare conditions over patients with more common conditions. The establishment of a dedicated process for rare diseases would be particularly challenging from the utilitarian perspective as a result of the high costs and the modest health benefits associated with many DRDs.

Similarly, a specialized coverage decision-making framework based on equity concerns is indefensible from the rights-based approach, which takes the position that all individuals are entitled to receiving at least a minimum level of health care (13,51). Proponents of this position would argue that a specialized process is justified as current frameworks for decision-making do not allow patients with rare diseases the chance of

receiving a minimum level of health care. The application of this position is challenging as the definition of what is established as the minimum level of health care is ambiguous (13,15). Furthermore, given that a minimum level of care should be given to both patients with rare and common conditions, the prioritization of patients with rare diseases through a specialized process would be unwarranted.

Another popular application of the equity or fair innings argument considers the expected number of QALYs an individual enjoys over a lifetime and states that there is some amount of quality adjusted length of life, which could be deemed as an ethical entitlement (52). Those who receive less than this entitlement are considered as being "cheated, " and those who exceed this entitlement are considered to be "living on borrowed time (52)." When applied in the context of rare conditions, the fair innings argument suggests that patients with rare diseases are "cheated" on the basis that current processes fail to guarantee patients with rare conditions some undefined minimum quality adjusted life expectancy. This reasoning cannot be used to justify the implementation of a specialized reimbursement framework for several reasons. For one, it is unclear what the minimum quality adjusted life expectancy would be, and how this would be established. Additionally, even where a separate process were adopted for funding DRDs, given that many treatments for rare conditions do not lead to dramatic improvements in life expectancy or quality of life, a specialized principle rooted on this basis is difficult to endorse.

The equity argument could also be approached from a vertical equity angle, which promotes differential access on the basis of differential needs. It is argued that a vertical equity perspective is adopted in decision-making, this would justify the differential consideration of rare diseases because patients with rare conditions would be considered to

be a minority, and are entitled to specialized treatment on account that they are different (53). A specialized process on these grounds is difficult to justify on account that the relationship between rarity and need remains unclear. Additionally, in the absence of clear guidance with regards to which equity stance should be taken in resource allocation decision-making, it is difficult to rationalize a differential coverage decision-making process on this basis.

Given the strains of applying the equity argument as the grounds for a unique reimbursement decision-making process for rare diseases, equity cannot be applied as a coherent ethical justification for considering DRDs differently when making resource allocation decisions.

3. Ex-post willingness to pay argument

In many jurisdictions, economic evidence such as cost-effectiveness analyses are an important consideration within the drug reimbursement decision-making process (54). The usefulness of cost-effectiveness to inform decision-making is, however, often called into question. It has been suggested that cost-effectiveness analysis (CEA) would be a more valuable tool for decision-makers with information on willingness-to-pay (WTP) for health benefits or risk reductions (55,56). The rationale for this position is grounded in welfare economics theory, and contends that the value of an intervention should be based on the relevant populations' WTP for the treatment (55).

In general, estimates of WTP are generated through surveys of the general population who have not been diagnosed with the condition of interest; and are referred to as *ex-ante* WTP estimates (57). It has been argued that *ex-post* WTP estimates, which are generated through surveying individuals affected by the disease in question, would be

much higher than *ex-ante* estimates and therefore may provide justification for paying more for treatments for rare conditions (58). While *ex-post* WTP estimates may be higher than those collected *ex-ante*, this cannot be applied as the rationale for the specialized drug reimbursement decision-making process for DRDs.

To begin, it is important to note that the question here is not whether justification can be given for paying a higher cost or premium for DRDs, but whether the *ex-post* WTP argument can rationalize a unique reimbursement decision-making process. Among the challenges of founding a specialized funding framework on the basis of WTP for treatments is that this is inconsistent with the mandate of organizations and decision-makers who are responsible for allocating public resources on the basis of need (35). Patients' WTP for treatment, regardless of rarity, may not appropriately relate to the equitable allocation of resources. Additionally, it is generally expected that decisions taken by the publicly funded health care system should be made under a "veil of ignorance," in that decision-makers should not be aware of those who benefit from the decision. Consideration for *ex-post* WTP in decision-making would compromise the neutrality that is expected from coverage decision-making frameworks. Based on this reasoning, if WTP were considered relevant in the decision-making context, they would most appropriately rely on the *ex-ante* measurement of treatment benefit.

While the relevance of WTP estimates in decision-making remains questionable, in the event that WTP pay was considered to be an appropriate consideration in the decision-making process, this could not be applied to defend a differential reimbursement process for rare diseases for multiple reasons. For one, while it has been suggested that *ex-post* WTP would allow for the approximation of the "Pareto improvement" of a funding decision, by illustrating how much the "winners" would be willing-to-pay the "losers" (35).

This reasoning is flawed in the context of decisions made by publicly funded drug plans given that the "winners" would not actually repay the "losers." For example in the case of rare conditions, if medications for patients with rare conditions were reimbursed, these patients would not repay those whose treatments were not reimbursed. Also, if WTP estimates were to be considered within the decision-process they would most appropriately be collected *ex-ante* in order to estimate how much individuals would be willing to increase their taxes for DRDs to be reimbursed.

Furthermore, a reimbursement process rooted on the fact that *ex-post* measurement of WTP would be higher could not be used to justify a dedicated reimbursement process because *ex-post* estimates of WTP would be higher regardless of the rarity of the condition. As a result, a specialized process would unreasonably consider patients with rare diseases differently.

4. Caring Externality Argument

It is well accepted that the costs and the benefits experienced by patients extend beyond the individual receiving care (59,60). For example, the health status of health care users can afford important non-health benefits to their family members and caregivers (35,61). These external factors are known as "caring externalities." The important benefits that are experienced by the caregivers of individuals receiving end-of-life treatments have been used as a rationale for the alternate consideration of life-sustaining therapies when making coverage decisions (35). Similarly, caring externalities have been applied to justify childhood vaccination programs for infectious diseases such as rotavirus, on account of the significant benefits that are experienced by parents (62). The argument could also be extended toward a unique process for the funding of DRDs based on the non-health gains

that may be extended to the caregivers of patients with rare diseases. Although these important benefits may exist, caring externalities cannot be applied as the rationale for a differential drug reimbursement framework for DRDs.

A differential process for rare diseases based on caring externalities is difficult to defend for several reasons. To begin, this would imply that the gains experienced by the caregivers of patients with rare diseases are unique or preferential to the gains that are experienced by the caregivers of patients with other conditions. For example, caring externalities have been documented in the context of public health interventions and life-sustaining therapies (60,63); a process for rare diseases based on this rationale would therefore unfairly consider patients with rare diseases differently. If caring externalities were established to be a relevant decision-making criterion for drug reimbursement, the QALY gains of caregivers and family members would most fittingly be incorporated into all frameworks for decision-making, as there is no evidence to suggest that the gains experienced by the caregivers of patients with rare diseases would differ from the gains experienced by patients with more common diseases. Another challenge associated with developing a reimbursement process for rare diseases centered on caring externalities is that the process would be biased in favor of patients who have caregivers and discriminate against those who do not have such a support network. Finally, if processes for resource allocation should be made on the basis of health care needs, a different process for rare diseases founded on the basis of caring externalities would violate this principle by focusing on non-health care needs external to the patient.

In summation, although it is well established that non-health benefits are achieved by the loved ones of patients who obtain treatment, coherent ethical justification for a

differential reimbursement process for rare diseases cannot be established based on caring externalities.

5. Financial protection argument

As a result of the substantial financial consequences that can be experienced by patients requiring high cost treatments, individuals may place greater value to the funding of high cost treatments than against low cost treatments (35,64). This argument could be proposed as justification for a dedicated reimbursement decision-making framework for the evaluation of DRDs. The basis of this reasoning is that a differing process is warranted because current processes fail to take into account the financial consequences that are experienced by patients and their caregivers as a result of the high costs of treatments for rare disease.

It is important to clarify that we are not considering what funding decisions should be made under exceptional high cost circumstances, we are considering whether a differential decision-making process is justifiable on the basis of the non-health consequences experienced as a result of high cost therapies. With this clarification, there are two primary challenges associated with applying the financial protection argument as the rationale for a specialized drug reimbursement process.

For one, not all DRDs are associated with high costs. It is true that many of these drugs are expensive; however, a funding process founded on this characteristic would only be relevant for expensive therapies, and therefore could not be generalized towards a process for all rare conditions. Moreover, not only therapies for the treatment of rare diseases are expensive. There are many medications for indications that are not rare which are also subject to dramatically high costs. As a result, a coverage decision-making process

founded on the basis of financial protection would preference rare diseases in comparison with drugs for more common conditions, which are also subject to high costs. Given these challenges, a process for reimbursement cannot be founded on the basis of financial protection.

6. Symbolic value argument

Effectiveness and efficiency are important measures considered when making resource allocation decisions; however, these are not the only factors taken into account by decision-makers (65). Among the additional features that may be considered are society's thoughts and objectives with respect to the decision process (53). Societal values are incorporated into decision-making to reflect the special value that society places on human life (35). Social value judgments have been applied as the justification for deviations from the traditional cost effectiveness threshold and the implementation of the NHS Cancer Drug Fund (66). Similarly, symbolic value could be argued as a justification for the unique consideration of DRDs when making coverage decisions. The argument could be made that a specialized framework for the reimbursement of DRDs may be justified if society places special value to the benefits gained by patients with rare conditions. Notwithstanding the important role that societal values may play in decision-making, symbolic value cannot be applied as the reasoning for a distinctive reimbursement process for DRDs.

Various barriers have been identified to the implementation of a specialized reimbursement process for DRDs based on symbolic value. Although symbolic value may be assigned to the lives of patients with rare diseases, symbolic value is not exclusively a characteristic of rare conditions. Establishing a unique process for rare diseases would therefore be unjustified unless it could be proven that society places greater symbolic value

to the lives of patients with rare diseases than the lives of patients with the other conditions. Although there is a small body of evidence investigating societal views in the context of rare diseases, societal preferences have been explored through population-based studies (51,67,68), and through the engagement of Citizens' Councils (69,70). Results of these studies have suggested that preference is not given to the lives of patients with rare diseases in comparison with the lives of patients with more common diseases, and that similar factors should be considered in the reimbursement decision-making process for both rare and common conditions (51,66,68,70). Given the limited evidence available for societal preferences for the lives of patients with rare diseases, a rationale for a differential funding process based on symbolic value is not defensible.

Furthermore, it is challenging to ground a process for reimbursement based on symbolic value given that symbolic value is subject to interpretation. Symbolic value could be associated with small extensions to the lives of patients with rare diseases, or large improvements to quality of life. This variability in the definition of symbolic value can therefore lead to the distribution of health resources that are not grounded on health need and may not maximize population health, which is inconsistent with the objectives of many reimbursement processes.

Proponents of the symbolic value argument may also reason that precedence has been set through the special treatment of oncology in reimbursement decision-making in many jurisdictions. While justifications have been proposed for many of these dedicated processes, these justifications continue to be debated (71,72). While unique funding mechanisms exist for patients with cancer such as the NHS Cancer Drug Fund in the UK, their remains very little evidence to support whether if all other factors were equivalent, that funding therapies for patients with cancer should be valued more highly than patients

with other conditions (66). Specialized funding has also been allocated towards treatments for rare conditions in Scotland (73); however, given that similarly limited evidence exists to support that symbolic value is associated with the reimbursement of DRDs it is difficult to use the symbolic value argument to support a specialized process.

In brief, although societal values play an important role when making coverage decisions, the symbolic value ascribed to the lives of patients with rare diseases cannot be applied as sufficient justification for a unique reimbursement decision-making process.

7. Diminishing marginal value of future life-years argument

The concept of diminishing marginal value is based on the economic principle that the value of a good is dependent on how many units of the good an individual already possesses. For example, if an individual already has $100,000, the value of an additional dollar to that individual would be less than the value to an individual who has $10. The principle of diminishing marginal value has also been applied in health with respect to life years. The argument can be presented from three different perspectives (35), each of which may be suggested as the rationale underlying a dedicated funding framework for the assessment of DRDs. Each of these positions is explored to illustrate the challenges with the diminishing marginal value of future life-years argument as the ethical rooting for a unique reimbursement process for DRDs.

Life-years from total lifespan at birth

The first interpretation of the diminishing marginal value argument takes into consideration the number of life-years an individual has lived in the context of a patient's total lifespan at birth. This could be brought forward as a potential rationale for the unique consideration of rare diseases founded on the principle that patients with rare diseases have

not lived many life years, and consequently additional life years gained would have added value for these patients. While this argument may be particularly applicable to rare disease patients who are children, this argument cannot be applied as the rationale for a specific process for the funding of DRDs.

Two challenges arise from the application of the diminishing marginal value of future life-years argument in the context of providing justification for a process devoted to the reimbursement of DRDs. To begin, this argument could be applied equally to all patients with conditions that lead to a reduction in life expectancy, regardless of whether the condition is rare or common. As there is no reason to believe that the value of additional life years would vary on the basis of the rarity of the condition, a unique coverage process on this grounding would be unwarranted.

The other difficulty with the diminishing marginal value argument stems from the heterogeneity that can be observed in the manifestation of rare diseases. While there are certainly many rare diseases which are life threatening and lead to substantial reductions in life expectancy, this is not the case for all rare conditions. Additionally, consideration of life years in the context of patients' total lifespan would suggest that life extension gains by children are more valuable than life extension gains by adults because adults have had the opportunity to experience more life-years. Given that rare diseases are observable among all age groups with varying lifespans, a unique reimbursement process for rare diseases could not be founded on this basis.

Life-years gained through treatment

The diminishing marginal value argument can also be interpreted in the context of the life years gained from the intervention of interest. From this perspective it is argued that

small life extensions from treatments should be prioritized over large life extensions on account that greater value is associated with the smaller life extensions. This position may be used to advocate for a specialized process for rare diseases that reflects the value of small life expectancy gains from treatments for rare conditions; however, there are several barriers with the implementation of a focused framework for evaluating DRDs on this basis.

Among the difficulties with this position is that it is at odds with the role of decision-makers who have the responsibility of maximizing health and allocating resources based on health needs. From a utilitarian perspective, this would be particularly difficult to justify on account that a specialized process for rare diseases based on this position would not lead the resource allocation that maximizes the health of the population, as it would prioritize treatments with incremental benefits in a small patient population as opposed to prioritizing treatments with large health benefits in a larger patient population. Furthermore, given that DRDs vary widely in their effectiveness, a process based on the diminishing value of future life years could not be applied to all DRDs, and would lead to the prioritization of treatments for rare conditions that cause incremental increases in life expectancy over those that contribute larger health benefits.

It is also once again important to note that both treatments for common conditions and those for rare conditions can lead to small extensions in life expectancy. A dedicated process for rare diseases based on the small health gains experienced through treatment would only be acceptable if the value placed on these gains varied between patients with common conditions and patients with rare conditions. Given that there is no reason to believe that this would be the case, a process founded on this argument is unjustifiable.

Future remaining life-years

Finally, the diminishing marginal value argument could be considered based on the patients remaining life years. This position was presented as a possible justification for the NICE end-of-life premium on the grounds that patients at the end of their lives value each additional life year more on account that they do not have many more life years to live (35). Similarly to the other applications of the diminishing marginal value of future life-years argument, this cannot be applied as the ethical basis of a distinctive process for making drug funding coverage decisions for DRDs.

Once again, this argument presents a challenge because this reasoning could not be applied to all rare conditions. In this context, the diminishing marginal value argument could only be applied as the reasoning for a process for patients with rare diseases who do not have many life years left to live. Given that there are many rare conditions where this is not the case, a process for DRDs on this grounding would have limited applicability in the consideration of the many rare diseases such as those that affect children or rare conditions that are not associated with reductions in life expectancy. As with the other two applications of the diminishing marginal value of future life-years arguments, this one also applies to both rare and common conditions. As there is no evidence to suggest that the value of life extension would vary between patients with rare conditions from those with common conditions, a unique funding framework cannot be rationalized.

In conclusion, regardless of the perspective taken, the diminishing marginal value of future life-years argument cannot be applied as the logic supporting a specialized process for the reimbursement of DRDs.

8. Concentration of benefits argument

The “concentration of benefits” argument is grounded in the belief that resources should be preferentially allocated to yield large health benefits in a small number of individuals as opposed to small health benefits in a large number of individuals (35,74). This argument could be applied as a potential rationale for the unique consideration of DRDs when making coverage decisions as societal preferences support allocating resources to interventions that yield a large health benefit in patients with rare conditions as opposed to small health benefits in patients with more common conditions. However, the application of this argument presents difficulties when establishing a specialized reimbursement process.

For one, the health benefits that are experienced by patients with rare diseases would need to be large for this argument to apply. Many of the therapies provide incremental benefits to the quality-of-life of patients and may not lead to dramatic improvements in life expectancy or quality-of-life. As a result establishing the foundation for a differential process is challenging, as it would apply to some DRDs but not all. Additionally, if decision-makers are tasked with allocating resources efficiently, the large health benefits experienced by the small populations with rare diseases would need to be proportional to the small health benefits experienced by patients with more common conditions. While it could be argued that when rare diseases are considered collectively, they affect a large number of individuals, and the overall benefits experienced by these patients would be significant, it is unclear whether the relative effects of DRDs will exceed those of more common conditions.

In summation, the concentration of benefits argument cannot be applied to a logical reasoning for a unique process for funding DRDs.

9. Dread argument

It has been suggested that deaths and conditions that are viewed as horrible and involuntary induce feelings of empathy that may affect societies willingness-to-pay (WTP) for interventions to prevent against these dreaded situations (75). The dread argument has been applied to justify the implementation of a "bad-death" premium for conditions that are notably alarming. The principles underpinning the dread argument may also be extended as a rationalization for a differential reimbursement process for rare diseases on the grounds that rare diseases are particularly dreadful. Although rare conditions may have some similar characteristics to other dreaded diseases, the dread argument cannot be used as the rationale justifying a specialized process for the reimbursement of DRDs.

Firstly, if dread were noted to be a pertinent consideration within the decision process for making coverage decisions, a process differentiating rare diseases would require evidence indicating that rare diseases are especially dreadful. The feelings of dread that accompany different conditions vary widely on account of a variety of factors (76–78), including the potential for premature death, and the lack of voluntariness and control(75). While rare diseases may have many of these characteristics and have commonalities with other dreaded conditions, it is possible that rare diseases do not invoke the same feelings of dread to justify their special consideration. For example, dread may be affected by baseline perceptions of risk (79,80); which may differ for rare diseases in comparison with more common conditions such as cancer. This is further complicated by the fact that patients have a difficult time understanding risk (81). Prior to the implementation of a specialized reimbursement process for rare diseases on the basis of the dread argument, it would be necessary to establish that rare diseases are indeed dreadful. In the absence of this

evidence, it is difficult to accept a differential drugs reimbursement framework based on this rationale.

The establishment of a differential decision-making process for rare diseases becomes increasingly problematic when the diversity among rare diseases is considered. The characteristics that contribute to feelings of dread may vary widely across the spectrum of conditions considered to be rare, thus some rare conditions may be dreaded while others are not. As a result, the dread argument cannot be used to form the basis for a focused reimbursement process for all DRDs. It is also important to note that diseases that are common can also lead to feelings of dread on the part of society, consequently a process for rare diseases would unjustly provide special consideration to DRDs. Where dread is considered to be an applicable decision-making criterion for resource allocation, it is difficult to defend its role in the justification for a funding framework for rare diseases.

While evidence may suggest that dread can influence societal preferences for reimbursement, the dread argument cannot be used as the ethical justification for the differential consideration of rare diseases in resource allocation decision-making.

10. Time to set your affair in orders argument

It has been suggested that special value is attributed to life extension at the end-of-life as compared with the beginning or at the middle of life, as it provides patients with the opportunity to set their affairs in order before the end of their lives. The additional life extension would allow patients to sort out financial details, say goodbyes to friends and family members, and finalize projects. This principle has been brought forward as a justification for the NICE end-of-life premium (35). This argument may also be proposed as the reasoning for a specialized reimbursement process for DRDs on the basis that these

drugs provide patients with rare diseases valuable life extension at the end of their lives, which will provide them the opportunity to set their affairs in order. Many challenges can be noted with basing a specialized reimbursement process for rare diseases on the benefits of time to put affairs in order.

The consideration for providing patients with the time to set their affairs in order is arguably beyond the scope of what should be considered by decisions makers of publicly-funded programs, who are tasked with allocating resources on the basis of health care needs. Moreover, although it is possible that patients, their families, and caregivers may gain important non-health benefits as a result of the opportunity to set their affairs in order, valuing these benefits would not provide a suitable rationale for a specialized process on account that the same benefits would be observed in patients with both rare and common conditions. The establishment of a specialized process for rare diseases established on these grounds would therefore suggest that the benefits gained by the patients and loved ones of patients with rare diseases are unique or favored relative to those experienced by patients with more common conditions. As there is no reason to suggest that the benefits experience by the loved ones of patients with common conditions would vary from those benefits experienced by the loved ones of patients with rare diseases; therefore, a process established on this footing would be unwarrantable.

Another challenge here is that the principle that patients with rare diseases would benefit from life extension to set their affairs in order is inconsistent with many of the common characteristics of rare conditions. For one, rare diseases are often chronic and progressive in nature, and as a result, patients would often have the opportunity to set their affairs in order during the progression of their illness. While this may have applicability to situations where patients receive sudden news that they will die soon; this would only

apply to a small subset of patients with rare diseases, and thus this argument has limited application as the foundation for considering rare diseases uniquely when making coverage decisions. Additionally, rare conditions can affect both children and adults. As the time to set affairs in order is intended for activities such as organizing finances and preparing a will, the value added for the approximately 80% of rare disease patients who are young children may be limited. As the characteristics of rare diseases are incompatible with the rationale that patients should be given time to set their affairs in order, this cannot be used as the underpinning of a differential decision-making process for rare diseases.

The value of patients gaining the time to set their affairs in order cannot be applied as the rationale for the specialized consideration of DRDs when making resource allocation decisions.

11. Severity of illness argument

Decision-making strategies for allocating resources to health care technologies have been criticized for relying heavily on factors such as cost-effectiveness and clinical-effectiveness, and failing to take into account societal values for factors such as the severity of the illness (82–84). The severity of illness argument is built on the paradigm that resources should be allocated on the basis of equity, and those with severe illness are in the greatest need (35,83,85). This argument could be extended as a potential basis for the unique consideration of rare diseases when making coverage decisions, as it is argued that patients with rare diseases are often more severely ill than patients with other conditions. Although arguments may be made in favor of considering disease severity when making resource allocation decisions, it is difficult to justify a specialized reimbursement process specifically for rare diseases grounded on severity of these conditions

Societal preferences for the prioritizing of patients on the basis of disease severity have been investigated using empirical studies. Result of these studies have demonstrated that society places greater value to the health gains experienced by patients with worse lifetime health prospects(82,83,85,86). This preference holds true even when the health improvement observed in the more severe patients is small but meaningful (82). This suggests that society places value on funding health care for those who are in greatest need, and may justify incorporating considerations for severity in decision-making processes. However, the question here is not whether or not severity should be a consideration within the reimbursement process, but whether it could be utilized as the foundation for a differential reimbursement process for DRDs. There are several challenges with the application of the disease severity argument as the basis for a differential drug reimbursement decision-making process.

The first relates to the fact that disease severity applies to a range of conditions some of which are rare while others are common. As a result, if societal values support the differential consideration of technologies on the basis of the severity of the indication, a reimbursement process that is grounded on the severity of the condition would most appropriately be applied to the consideration of all drugs for severe conditions, and not only those for rare conditions. In addition, rare conditions fall along a continuum of severity, where some may lead to significant reductions in life expectancy or quality of life, and others may be associated with minor symptoms or may remain asymptomatic. Grounding a process based on disease severity could therefore only be applied to the rare conditions that are deemed to be severe, and would not be applicable to a process for the evaluation of all DRDs.

Another obstacle associated with applying severity as the basis for a differential reimbursement process is the conceptualization of disease severity. Although the definition of disease severity is most often based on a reduction in quality of life or reduction in length of life, definitions of severity often lack clarity and consensus (87). Additionally, clinical perceptions of severity may not be reflective of patients perceptions (88). A process built on the severity of illness would therefore require an agreed upon standard for what constitutes a severe condition.

In conclusion, although evidence supports that severity of illness is a valuable consideration when making funding decisions, the application of the disease severity argument as the basis for a specialized process for DRDs is difficult to rationalize.

12. Complexity of illness

Rare diseases and their treatments are often characterized as complex on account that they can affect multiple systems, and frequently require highly involved clinical care plans spanning different medical specialties. In addition to their complicated disease trajectories, the treatments for rare conditions often involve intricate manufacturing and development (89,90). The complexity of rare conditions and their treatments can present difficulties from the perspective of evidence-based drug reimbursement decision-making processes because the natural history is seldom well understood, and may require the development of complex economic models that are subject to high uncertainty (91,92). Additionally, given that complex interventions include multiple components, the assessment of effectiveness may rely on intricate statistical models that complicate assessments for drug reimbursement (92,93).

As a result of the obstacles that disease and treatment complexity can cause while applying current reimbursement processes, complexity could be argued as the basis for a specialized process for the reimbursement of DRDs. However, while the complicated nature of many rare diseases and their treatments can make reimbursement decisions arduous, several obstacles exist with the development of a dedicated process for rare diseases centered on the complexity argument.

The first hurdle is that complexity is not a defining characteristic of rare diseases and thus, centering a drug reimbursement process on this basis is difficult to rationalize. While some rare diseases such as lysosomal storage disorders can be highly complex in their manifestations and their treatments, this is certainly not the case for all rare conditions. For example, the condition phenylketonuria (PKU) is a simple monogenetic condition where affected patients are unable to produce the enzyme to metabolize the amino acid phenylalanine (94). The condition has a well-understood disease progression, is easily diagnosed, and can be managed through adherence to a strict diet (95). In light of the heterogeneity in the expression of rare diseases, a reimbursement process reflecting the complexity of conditions would unfairly preference the patients with complex disease.

Additionally, complexity is not a characteristic unique to rare diseases and their treatments. There are many common conditions that are also highly complex on account of their symptomologies and treatments. For example, diabetes is a common condition, which has multisystemic symptoms and patients often require highly involved treatment plans. While it is unclear whether the complexity of a condition or its treatments should be a relevant consideration when making resource allocation decisions, given that complexity could apply equally to patients with rare diseases as it could for patients with rare

conditions, a specialized funding process grounded on the complexity argument would be unwarranted.

13. Vulnerability of the population (e.g. children)

Although opinions concerning the consideration of age as a decision-making criteria are polarized, many justifications have been presented in favor of the preferential consideration of children when making resource allocation decisions (96). Among the proposed explanations include that children have more productive years ahead of them, have more years left to live, and have not yet lived their fair share of life (97). From an equity perspective, it can be argued that there is a minimum quality adjusted life expectancy that all individuals are entitled too, and children have not reached this minimum and therefore have been "cheated (52)." These arguments could be extended as a rationale for the differential consideration of rare diseases when making coverage decisions given that rare diseases affect a vulnerable population due to the high volume of children who suffer from rare diseases. It is estimated that approximately 75% of rare diseases affect children and 30% of patients with rare diseases die before the age of 5 (98). Although rare diseases may disproportionately affect the young, a differential decision-making process for rare diseases constructed on the vulnerability of the patients is indefensible.

The first challenge with applying a different process for rare diseases on the basis of age is that age-based rationing and the specialized consideration of children are inconsistent with the role of decision-making organizations that aim to allocate resources on the basis of health care needs. As the age of a patient is not associated with their need for treatment, it can be argued that decisions should be made independently of the age of

patients (99). A second challenge with the differential consideration of rare diseases is that not all patients with rare diseases are children; therefore, a process routed on the vulnerability of the patient population would unfairly prioritize the patients with rare diseases who are children and could not be applied as justification for the unique consideration of all DRDs.

In spite of these challenges, the consideration of age as a relevant criterion in reimbursement decision-making continues to be debated. Many of the arguments used as support for the specialized consideration of younger patients cannot be applied to back a differential process for the reimbursement of DRDs due to the characteristics of rare diseases and their treatments. These arguments will be examined to establish the limitations in the context of reimbursement decision-making for rare diseases.

For one, it is argued that allocating resources towards the young allows for the maximization of their opportunity to achieve a normal life span, and as a result fewer resources would be extended to them later in life to provide the same benefit (99). Advocates of this position would argue that through expending resources early on, this could prevent the expenditure of resources to treat the complications and the worsening of symptoms associated with disease progression. The challenge with this position in the context of DRDs is that treatments for rare conditions are rarely curative and although symptoms may progress more slowly, the resources needed to treat the patient may increase overtime. It is also important to note that for some expensive DRDs such as enzyme replacement therapies, the dosing is based on the weight of the patients, which would lead to an increase in drug cost as patients' ages; therefore, resources expended later in life may increase overtime. Given these obstacles this argument cannot justifiably be

applied as the rationale for a unique decision-making process in the context of rare diseases.

Another reason that has been applied for the prioritization of children is based on the rationalization that children have more years of productive life ahead, which contributes to increased economic productivity that benefits society (100,101). The challenge with applying this argument as the justification for a different reimbursement process draws on the incremental effects of many treatments for rare conditions, which lead to small changes in quality of life and may not allow for substantial increases in the productive life of patients. Furthermore, older patients with rare conditions could continue to provide years of productive life; therefore, a specialized process on this basis is difficult to defend.

While the debate about the consideration for age in reimbursement continues, it has been stated that as a result of resource scarcity and changes in population demographics, programs will be forced to make decisions that prioritize patients explicitly or implicitly on the basis of age (102). As a result, arguments have been made that decisions should reflect societal preferences for the prioritization of age (101). While some evidence from studies of societal preferences support the prioritization of children over older adults (52,103,104), the application of this as the basis for a specialized process specifically for rare diseases is limited. In the event that age is established as relevant decision-making criteria, consideration would need to be applied equally while considering rare and common conditions. As a result, a process for rare diseases based on age may unfairly prioritize children with rare diseases over children with common conditions.

In conclusion, given the limited applicability of arguments for the prioritization of children in the context of the reimbursement of DRDs the vulnerability of the patient

cannot be applied as the logical ethical rationalization for a differential reimbursement process.

14. Differing evidence base for rare diseases

In order to improve efficiency and the availability of high quality treatments for patients, evidence-based methods such as health technology assessment (HTA) and comparative effectiveness research (CER) are now widely used in Canada and many other jurisdictions to help inform reimbursement decision-making. The evidence available to evaluate treatments for rare diseases is arguably different from therapies for more common conditions (14). Due to the small patient populations that suffer from each rare disease, the availability of high quality, adequately powered studies on the natural history and the efficacy of treatments for rare diseases can be limited or absent (105–108). The differing evidence-base for DRDs has therefore been suggested as justification for a varying reimbursement decision-making framework. While continuing to acknowledge the importance and necessity for high quality evidence, the differing evidence-base for rare diseases provides a plausible defense for a differential decision-making framework.

Evidence-informed practices for the reimbursement of health care technologies are often based on the assessment of four types of evidence: safety and efficacy, clinical effectiveness, and cost-effectiveness (15). The clinical and economic evidence-base available for rare diseases will be explored to provide justification for a unique reimbursement process.

Clinical Evidence

A specialized process for the funding of DRDs based on the differing clinical evidence may be acceptable given that it is unreasonable and often impossible to collect the

same level of clinical data for rare diseases as for other therapies. The preferred gold standard for the evaluation of the clinical benefit of pharmaceuticals is the randomized controlled trial (RCT), and in the case of rare conditions, it would be extremely difficult to conduct an RCT with a sufficient number of patients in a reasonable timeframe (17,109,110).

Although new developments in clinical trial designs and statistical analysis have improved the ability to study rare diseases and have been accepted by some regulatory agencies, these approaches are at odds with the evidentiary standards routinely applied in the assessment of clinical benefit. For example, trials on rare diseases often rely on the application of short-term surrogate markers (15). Surrogate endpoints are applied to improve trial efficiency and practicality, and they are particularly attractive in the context of rare diseases because they can allow for shorter trials with smaller patient populations. However, surrogate outcomes present a challenge when the evidence is considered to inform reimbursement decisions, as there can be uncertainty with respect to the relationship between the surrogate outcome and the final clinically relevant endpoint (111). Although, surrogate endpoints may be validated for common diseases, the small numbers of patients with rare diseases make it difficult to provide the required evidence to link short term surrogate outcomes to long term meaningful patient related outcomes. In the absence of processes that acknowledge the differing clinical evidence-base for rare diseases, there will continue to be uncertainty -surrounding DRDs, which can have an important impact on the final reimbursement decision.

Economic Evidence

In addition to the challenges associated with the clinical evidence surrounding DRDs, the assessment of economic evidence in the evaluation of DRDs is also challenging. Economic evaluations of health care technologies assess whether a technology provides good value for money by considering the relative costs and benefits of the treatment compared to treatment alternatives. DRDs are unlikely to meet commonly-applied standards of cost-effectiveness used in decision-making due to their high costs and the uncertainty with regards to clinical outcomes (33,112). A specialized process for the reimbursement of DRDs may be defensible as it would not be possible for DRDs to meet the standards of cost-effectiveness routinely applied for assessing economic evidence.

To begin, economic evaluations rely on data gathered from various sources including clinical trials and observational studies to generate estimates of the clinical benefit of a health care technology relative to its costs. In light of the limited clinical evidence available related to treatments for rare diseases, this translates to significant uncertainty in the economic evidence. Furthermore, cost-effectiveness studies often rely on the creation of decision models that reflect the natural history of a condition; however, the natural history data for rare diseases is frequently unavailable, which further increases the levels of uncertainty within the economic evidence (33). Decision modeling for rare conditions can also be further complicated by the complex and multi-systemic nature of many of these conditions (108). While some economic evaluations of interventions to treat rare diseases appear in the literature, the lack of quality data inputs contributes to significant uncertainty within the results of the economic analysis (113,114).

In addition to the high levels of uncertainty in the economic evidence, due to the high price point on many drugs to treat rare diseases; the cost-effectiveness estimates are often much greater than the cost-effectiveness thresholds traditionally applied in

reimbursement decision-making (9). In the absence of specialized processes for the reimbursement of DRDs, it is arguable that these medications are very unlikely to receive positive funding recommendations.

The challenges associated with both the clinical and economic evidence for rare diseases are largely as a result of the rarity of the conditions that are being studied. Although arguments could be made that a specialized process for the reimbursement of DRDs would promote poor quality evidence and unfairly advantage DRDs. It should be noted that consideration for the differing evidence-base would not need to imply that poor quality evidence is acceptable. It would acknowledge that the evidence-base for rare diseases is necessarily different and that alternate sources of evidence may be the most informative for the evaluation of these technologies. For example, the traditional clinical studies may fail to take into account such things as the significant clinical heterogeneity that may manifest in patients with rare conditions (115). A continued emphasis on quality of evidence could be maintained through the application of alternate forms of critical appraisal and the development of new methodologies (3,106). For example, increasingly complex Bayesian analyses have been applied to help address some of the challenges of traditional clinical trial designs and innovative trial designs have been developed (3,110).

The differing clinical and economic evidence base for rare diseases may provide a valid justification for an alternate reimbursement process for the assessment of DRDs but would not necessarily validate the use of a different threshold for coverage. Where differential standards for demonstrating cost effectiveness are used, consideration for whether a different threshold would be justifiable is important, as this would imply that funding DRDs is of greater value than funding drugs for common conditions. For example, in the case of eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria

(PNH), the valuation of each quality adjusted life year (QALY) would be 40 times greater than for patients with a common condition (113). This example highlights just one example where the threshold for establishing cost-effectiveness would need to be loosened significantly in order for a positive funding outcome. Finally, is important to note that funding DRDs which do not meet established criteria for cost effectiveness, necessarily impose opportunity costs on other patient groups due to the inability of funding an alternate more cost effective use of scarce resources (113).

15. Rarity of the condition

The defining characteristic of rare conditions is that they affect a small number of individuals in the population. The infrequency of these conditions has been applied as a reasoning to justify a specialized drug funding reimbursement framework. Two rationales could be brought forward as explanations favoring the establishment of a unique reimbursement process for DRDs based on rarity. The first being that society places greater value to the health benefits gained by patients with rare diseases compared to patients with common diseases, and the other being that rare diseases affect so few individuals that the impact of a differential process would be minimal. Challenges exist with both these positions, and rarity alone cannot be applied as the groundwork for a dedicated reimbursement decision-making process.

The first challenge is that a reimbursement process for DRDs would imply that the value of the health outcomes experienced by patients with rare conditions differs as a result of the rarity of their condition (36). For this to be justifiable, societal preferences for rarity would need to be established. However, studies that have investigated these preferences have shown that rarity is not valued within the decision-process, and that society would not

favor the allocation of resources towards patients with rare diseases at the expense of patients with common conditions (68,116). Moreover, ascribing a single weight to the additional value that is associated with funding treatments for rare conditions would be difficult given observed heterogeneity in rare conditions and difficulties in defining rarity. The argument could also be raised that rarity is associated with greater uncertainty in the funding decision, and decision-makers may ascribe less value to treatments with greater uncertainty in comparison with where there is more certainty. In the absence of evidence that societal preferences favor rarity, a specialized reimbursement process on this basis would be indefensible.

A specific process for rare diseases rooted on the assumption that the impact of a unique reimbursement framework would be limited, is reflective of isolation bias caused by considering each disease independently (113). While rare conditions individually affect a small number of individuals, given that there are over 5000 different rare conditions (117), collectively a differential reimbursement process would affect a large number of individuals. A specialized reimbursement process would thus unfairly consider patients with rare diseases as special on the basis of the small number of individuals affected, which is inconsistent with the position that resources should be allocated according to need. Furthermore, it is important to consider that the decision to fund any treatment has an impact on two groups; the patients who stand to benefit from the funding of treatments and the patients who bear the opportunity cost of the decision (118). If funding treatments for rare conditions is considered appropriate based solely on the grounds of rarity, this fails to consider the impact on the patients without rare diseases who do not receive treatments as a result of the funding decision.

Finally, rarity cannot be applied as the root of a specialized reimbursement process because considering rarity in the context of reimbursement would require defining rarity (119). This is difficult as, no standardized definition has been established for what constitutes a rare disease in Canada, and there is a great deal of heterogeneity in definitions applied internationally. Even where a definition of rare diseases is established, the development of the threshold would be inefficient as rarity is not a binary concept and would continue to be subject for interpretation. Furthermore, definitions of rarity vary based on the context in which the definition is being applied, for example differing definitions may be applied in the regulatory environment than the realm of reimbursement decision-making. Given the varied definitions of rarity, in the absence of an established threshold, a unique reimbursement process would be difficult to justify.

In light of the limitations of the reasoning underlying the rarity argument, rarity cannot be applied as the reasoning for a special process for rare diseases.

16. Lack of alternatives

Historically, investment in niche products such as those for the treatment of rare conditions has been limited for several reasons; however, recent developments in biotechnology and regulatory incentives for manufacturers have been applauded for promoting advancements towards novel treatments for rare conditions(117,120). These new medications are perceived as filling a therapeutic gap where no alternative therapies exist. This has become the basis for an argument in favor of the implementation of an alternate reimbursement process for treatments for rare diseases rooted on the principle that DRDs fill an unmet need, which is not addressed by new treatments for more common conditions where alternatives are often available. While medical necessity may be a

consideration when making drug-funding decisions, the lack of alternatives argument cannot be applied as the ethical justification for a differential drug reimbursement process for rare diseases for several reasons.

One of the problems with the lack of alternatives argument is that it is based on the misperception that in the absence of a drug treatment, patients with rare conditions have no other treatments options (37,113). In reality, this is often not the case. The proponents of the lack of alternatives argument refer to the absence of disease modifying agents, and fail to consider the other care strategies that may be available to patients. In many cases, alternate treatments targeting the symptoms and complications of conditions may be available and can have a significant impact on a patients' quality of life (37,113). Given that alternate care strategies are often available, a specialized reimbursement process based on the lack of alternatives argument is difficult to justify.

Another problem with applying the lack of alternatives argument as the basis for an alternate reimbursement process is that therapeutic gaps are not exclusive to rare conditions. Unmet needs may also apply to patients with more common conditions; therefore, special consideration grounded on this principle is difficult to rationalize. The implementation of a unique reimbursement process on this basis would unjustifiably preference patients with rare conditions based on a characteristic that may be a relevant consideration in all decision-processes.

Moreover, although the vast majority of DRDs are the first medication specifically for the indication they treat, there are examples of rare conditions where more than one drug treatment option exists; therefore, the lack of alternatives argument could not rationally be applied to justify a specialized process within this context. This may also be further complicated by the fact that some orphan drug therapies are nearing the end of their

period of market exclusivity, which may introduce the potential for competitive treatments to be developed and marketed. To date, much uncertainty remains with regards to whether the end of the market exclusivity period for DRDs will lead to competition; however, this should be considered as a relevant obstacle in the establishment of a unique process for the reimbursement of DRDs based on the lack of alternatives argument (90).

As a result of the challenges with the application of the lack of alternatives argument, a unique reimbursement process grounded on this basis is not reasonable.

Discussion

Sixteen arguments have been investigated as the possible reasoning behind the specialized consideration of DRDs when making drug reimbursement decisions: (1) rule of rescue, (2) fair chances, (3) ex-post willingness to pay, (4) caring externalities, (5) financial protection, (6) symbolic value, (7) diminishing marginal value for future life years, (8) concentration of benefits, (9) dread, (10) time to set your affairs in order, (11) severity of illness, (12) complexity of illness, (13) vulnerability of the population, (14) differing evidence base, (15) rarity, and (16) lack of alternatives. There are three overarching difficulties with the proposed arguments for a specialized decision-framework for funding drugs to treat rare conditions.

The first major problem with developing a process on the basis of the arguments presented is that the differential consideration of rare diseases is not in line with the fundamental principles on which decisions for the publicly funded health care system should be based. Decision-makers are tasked with making decisions to promote population health by supporting the efficient allocation of resources on the basis on health care need. For example, the application of the fair chances, financial protection, and caring

externalities arguments to justify a unique reimbursement framework is at odds with the core principles that underline decision-making processes as they fail to consider the efficient allocation of resources by disregarding opportunity costs, and do not reflect the allocation of resources based on health care needs. Additionally decision-makers tasked with making reimbursement decisions are responsible for making decisions at a population level, which should be done without identifying the patients who would benefit. This ensures fairness and neutrality within the process, and these principles are violated by arguments such as the rule of rescue and the ex-ante willingness-to-pay argument.

Another major obstacle with applying these arguments as the ethical grounding of a specialized reimbursement process is that they fail to acknowledge the variability that exists in rare conditions. While some arguments may have a role in justifying the unique consideration of certain rare conditions, these arguments could not similarly be applied to other rare conditions. For example, while the severity argument may provide reasoning to consider lysosomal storage disorders differently for reimbursement, it could not equally be applied to the rare conditions whose manifestations are less severe. The rationale for funding DRD based on an argument that justifies a specialized process for some rare conditions could lead to the prioritization of certain rare conditions over others. A suitable rationale for the specialized consideration of DRDs would most appropriately reflect the characteristics of all rare conditions.

An additional concern with the proposed arguments is that many of them could also be brought forward to defend the special consideration of patients with common conditions within coverage decision frameworks. Characteristics such as complexity and severity certainly apply to some rare conditions but they also reflect the characteristics of common conditions such as diabetes, which is associated with a multitude of secondary conditions

arising both from disease progression and treatment. Similarly, the lack of alternatives and need for financial protection arguments are not concerns unique to patients with rare conditions. A unique decision process for funding DRDs routed on these arguments is vulnerable as it would preference patients with rare diseases over patients with similar characteristics who have common conditions.

While the differing evidence base available for rare diseases may provide a possible argument for rationalizing a differential decision framework for the reimbursement of DRDs, there may continue to be challenges with the development of a standardized process for the funding of DRDs. While it could be argued that while a specialized funding framework for rare diseases is defensible, it is unclear whether this provides sufficient justification for the consideration of different criteria when making drug coverage decisions. Even where a specialized framework is defensible, the use of alternate thresholds for decision-making may not be defensible, and it could be reasoned that the limited evidence base contributes to increased uncertainty, which would warrant stricter thresholds with respect to cost-effectiveness. It is also arguable that while a specialized decision framework for DRDs maybe justifiable, consideration for the challenges of funding DRDs could be reflected within existing frameworks for coverage decisions making.

Conclusion

Given the challenges with the arguments favoring a differential decision-making process for DRDs, in conclusion, a differential process for reviewing the evidence for rare diseases may be warranted which could feed into the current processes for making funding decisions. It is apparent that many challenges exist with founding a process for the evaluation of rare diseases on the grounds of the arguments presented. Further investigation

would be required to assess whether these arguments could be used to justify the implementation of differential thresholds for evidence, and where a strong argument could be made investigation surrounding what threshold would be most appropriate within the decision-making framework would be warranted. Additionally these arguments could be considered as the defense for one off decisions pertaining to the reimbursement of medications to treat rare conditions.

Chapter 3- Frameworks for the reimbursement of DRDs in Canada and Internationally

Rationale

Formal techniques are applied in Canada and internationally to support informed decisions about which health care technologies to cover through the publicly-funded health care system; however, the applicability of these frameworks to reimbursement decisions for DRDs has been limited (14). While it is known that some jurisdictions have implemented special processes for decision-making for DRDs, a comprehensive understanding of these processes remains limited. A review of processes for making coverage decisions aims to provide insight into the strategies currently employed for making coverage decisions for drugs in order to understand how DRDs are considered in the context of reimbursement decision-making. An understanding of these processes may serve to identify gaps within existing frameworks for making rationing decisions in order to inform the development of processes that encourage fair resolutions for the funding of DRDs in Canada.

Objectives

There are three objectives of this review, the first is to identify what funding systems exist for making coverage decisions for drugs internationally and to identify what considerations are given to DRDs within these reimbursement decision-making frameworks. Where jurisdictions apply formal techniques for reimbursement, the review aims to identify whether the same process is applied for the evaluation of all drugs in order to assess whether DRDs are considered distinctively. Finally, the review investigates what criteria are considered within coverage decision-making processes for DRDs.

Methods

Literature Review

A systematic search of published and grey literature was used to identify the processes applied for making coverage decisions.

Sampling frame

The G20 nations were selected as the sampling frame in order to represent current drug reimbursement decision-making processes applied internationally. The G20 is made up of 18 countries (Argentina, Australia, Brazil, Canada, China, France, Germany, India, Indonesia, Italy, Japan, Republic of Korea, Mexico, Russia, Saudi Arabia, South Africa, Turkey, and the United States), the United Kingdom and the European Union. The member countries vary in size, population, economies, health care systems, and cultures; therefore, provide a comprehensive representation of reimbursement decision-making in developed countries.

Search Strategy

In order to capture publicly available strategies for making health care reimbursement decisions, a comprehensive search was conducted. Peer-reviewed literature was systematically searched using electronic databases. A strict protocol driven search strategy focused on standard electronic databases was deemed to be insufficient to address the research questions due to the complex policy driven nature (121,122). It has been noted that traditional strategies are inefficient and inappropriate as may fail to identify key evidence when addressing policy questions (122). This was identified as a particular concern in this study, given that many processes for reimbursement decision-making are

dictated by government and HTA agencies and may not be available in the published literature. Therefore, a database search was supplemented with a grey literature search and hand searching to ensure key sources were identified. All searches were run between November 1st, 2013 and February 1st, 2014.

Database search

A variety of databases were included within the search. The electronic database search included the following databases: Medline, Scopus, CINHAL, EconLit and PsychInfo. Search terms included a combination of keywords and MESH terms. The following search terms were used: priority setting, resource allocation, rationing, cost allocation, reimbursement, funding, decision-making, and health priorities. Country and agency specific search terms were also used within the search. Search terms were combined with Boolean operators, and truncation was used to maximize search results.

Grey literature search

An extensive grey literature search was also completed in order to capture unpublished processes for reimbursement decision-making. The grey literature search was conducted concurrently with database searches to identify frameworks used for drug reimbursement decision-making. The search included both Canadian and international sources, and focused primarily on the websites of decision-making authorities and HTA agencies. Each website was searched systematically. The site maps were identified and web pages related to the public drug plan and decision-making processes were identified. This was supplemented with in site searching via in site search bars. Search terms used were: drug reimbursement, drug funding, formulary, coverage, insurance, drug plan, orphan drugs, orphan, rare diseases, and drugs for rare diseases. HTA specific resources were also

used to help direct the search and included the Health Technology Assessment International (HTAi) Vortal which is a centralized database of HTA resources (123), and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Global Health Care Systems Roadmaps which provides an overview of country specific decision-making processes applied for the approval, evaluation, and reimbursement of health care technologies (124).

Hand-searching/Snowballing

Due to the unique nature of the research question and known challenges of conducting systematic reviews to answer policy questions, the electronic search was supplemented with hand searching. Finally, additional citations were retrieved through a "snowballing" approach, which consisted of manually searching the bibliographies of key publications identified within the initial searches. This has been suggested as an effective strategy for reviews addressing policy questions (121,122). In cases where uncertainties remained based on the review of the published and grey literature, individuals with expertise in the drug reimbursement decision-making process within these jurisdictions were contacted to provide additional insight and clarification surrounding the employed drug reimbursement decision processes.

Eligibility criteria

Inclusion criteria

The review included processes applied for making coverage decisions for outpatient drugs within the national (macro-level) publicly funded health care systems within G20 countries and the Canadian provinces and territories. Given the fragmented reimbursement

decision-making processes applied in the UK and the EU, frameworks applied within the member countries were considered within the review; therefore, a total of 28 countries were considered.

The processes from each of the UK countries (England, Northern Ireland, Scotland, and Wales), and selected EU member countries were included within the analysis (Belgium, Spain, The Netherlands, Sweden, and Switzerland). EU member countries were identified to reflect jurisdictions that are likely to have challenges similar to the Canadian reimbursement decision-making context, and therefore, may help inform the development of funding processes in Canada. Finally, given that reimbursement decisions in Canada are made at the provincial/territorial level and informed by a central HTA process, both national and provincial processes applied in Canada were included in the review.

The processes employed by HTA agencies within these jurisdictions were included where HTA is an integral component of the drug reimbursement decision-making process. HTA processes were determined to be integral to the decision-making process in jurisdictions where the role of the HTA process is clearly indicated by the decision-maker.

Exclusion criteria

With the exception of the Canadian provinces, reimbursement decision-making strategies applied at the regional levels (meso- level) were excluded from the analysis due to feasibility of collecting high quality data. Any drug reimbursement mechanisms applied at the level of clinical programs (micro- level) were not included in this analysis, and drug reimbursement systems applied by private insurers were also excluded. Although similarities exist between the reimbursement decision-making processes at the varying levels of the health care system, decisions at the meso- and micro- level, and by private

insurers were determined to be beyond the scope of this review, as these processes would involve consideration for factors beyond the goals of national decision-making (125). Finally, publicly funded plans exclusively for the funding of inpatient drugs were also excluded from this analysis.

Data extraction and synthesis

The synthesis takes the form of a narrative review, to identify the elements of decision-making processes. Due to the scope of the review, a quantitative synthesis with formal meta-analysis was neither appropriate nor possible. In order to capture relevant decision-making considerations in the processes applied within different jurisdictions, various characteristics of the reimbursement decision-making process were acknowledged. In order to provide an understanding of the processes applied by publicly funded drug reimbursement decision-making bodies, several characteristics of the processes were identified. For each process, the funding program, the objectives of the funding process, the expert committee involved in decision-making, and the technologies appraised were identified (Table 1, Table 3). Similarly, for the processes applied by HTA agencies, information was extracted on the agency involved in the reimbursement decision-making, the objective used by the process, the expert committee involved in the evaluation process, and the technologies appraised (Table 2).

Within each of identified reimbursement processes, it was noted whether DRDs were considered through the same reimbursement framework as drugs for common conditions, or whether any special consideration was given within the review of these medications. Where it was not indicated, it was noted that this was not reported and it was assumed that the review of DRDs were not evaluated using a distinctive process or

framework. A process was defined as distinctive where it was explicitly indicated that DRDs are given unique consideration within the implemented reimbursement framework for the evaluation of drugs, or where a differing framework is used for the assessment of DRDs. Specialized frameworks for DRDs were described as those designed specifically for the review of DRDs and are used exclusively for the review of medications to treat rare conditions.

To provide insight into the definition of rarity applied within the reimbursement environment, the definitions for rarity were extracted from each of the frameworks. Definitions applied in other contexts such as the regulatory framework were not considered in the analysis. Additionally, to provide insight into the reasoning grounding the specialized consideration of DRDs when making coverage decisions, the rationale was extracted.

In order to gain a comprehensive understanding of the decision processes for the reimbursement of DRDs, a comparative framework was adapted from McMahon et al. (26); which draws upon central elements considered within coverage decision-making. For one, within each of the processes, it was identified whether the evaluation included an assessment of the clinical evidence. Subsequently, details of the process for the evaluation of clinical evidence were also extracted, including the types of clinical evidence assessed, the comparators included, and the outcome measures considered. Furthermore, within each of the processes, it was considered whether economic evidence was assessed within the decision-making framework. Details on the process for the evaluation of economic evidence were also gathered, including the perspective used in the evaluation, the analytical technique(s) applied, the measures of health benefit used, and whether a threshold for cost-effectiveness is stated.

Assessment of Fairness

Additionally, with the objective of evaluating each of the decision-making processes, the Accountability for Reasonableness framework (A4R) theorized by Daniels and Sabin's was used to appraise the decision-making processes for the evaluation of DRDs(29). The framework was selected as it forms the basis for the processes implemented by several HTA agencies, and is often used for the evaluation and comparison of decision-making processes (25–27).

The framework highlights four conditions that should be met in fair priority-setting: transparency, relevance, a process for appeals, and enforceability (29). Similarly to the analysis by Barnieh et al. (27), frameworks for decision-making were evaluated using three of the four A4R criteria (transparency, relevance, and mechanism for appeals).

The enforceability criterion was not considered within this analysis. Enforceability refers to whether there is either voluntary or public regulation of the process to ensure that the conditions of fair priority-setting are met (29). While this is central component of the A4R framework, given that some frameworks are used as the basis of recommendations and others to inform final decisions; meaningful comparisons across processes may not be possible and thus consideration for enforceability would not provide an eloquent basis on which to assess decision-making processes.

The three criteria from the A4R framework considered within the review were transparency, relevance, and mechanisms for appeal; each criterion and how they are defined in the analysis are described here:

Transparency

Transparency refers to the public availability of coverage decisions for new technologies and their rationales (29). Each process for drug reimbursement decision-making was assessed to determine whether the decisions and the rationales for the decisions were publicly available. Processes where the final decision or recommendation, and the rationale justifying the position were available on the website of the agency, the process met the criterion for transparency.

Relevance

The relevance criteria refers to whether the criteria considered within the priority setting process and their rationales would be considered acceptable by fair minded individuals (29). Relevance was assessed among frameworks for the reimbursement of DRDs based on whether the rationale for the specialized consideration of DRDs was clearly outlined. Processes where the rationale was described were considered to meet the criteria for relevance, and where the rationale was not provided these processes were considered not to meet this criterion for fair priority setting.

Mechanism for appeals

A mechanism for appeals refers to the ability for decisions to be challenged and modified (29). This analysis includes both decision processes where the outcome is the final decision and those where the outcome is a recommendation to inform the decision. It is recognized that a mechanism for appeals would only apply to decisions; however, while recommendations cannot be appealed, these processes should include a step that allows for the clarification of errors and omissions. To reflect the differences in the two type types of processes, this criterion was assessed differently for processes where the outcome is a

decision and where the outcome is a recommendation. For processes where the outcome of the evaluation is the final reimbursement decision, a process was considered to meet this criterion if it is clearly indicated that the coverage decision could be challenged or disputed. For processes where the outcome of the evaluation is a recommendation, a process was considered to meet the criterion for mechanism of appeal where the process includes a step that allows for the clarification of errors or omissions.

Results

The final analysis considered processes from the following countries: Canada, South Africa, the United States, Mexico, Brazil, Argentina, China, Japan, South Korea, Russia, Turkey, Germany, France, Italy, Saudi Arabia, Australia, Belgium, Spain, the Netherlands, Switzerland, Sweden, Scotland, England, Wales, and Northern Ireland (Table 1). India, Indonesia, and Saudi Arabia were excluded from the analysis, as these countries do not have a national publicly-funded drug reimbursement system or an agency which helps support the coverage decision-making process at a national level (126–128). The frameworks applied by both the English Advisory Group on National Specialized Services (AGNSS) and NICE were considered in the analysis. While the remit for the evaluation of DRDs was recently transferred from AGNSS to NICE, both processes were included because the framework applied by AGNSS represents an evidence informed decision-process, which may provide important insight into possible considerations when making funding decisions for DRDs. To reflect the structure of the health care system within the United States, the process used by the Medicaid/Medicaid Program, as well as, the process applied by the Veterans Affairs were considered. To reflect the five federal publicly funded drug plans in Canada, the processes used by Health Canada, Correctional Services of

Canada, Department of National Defense, Royal Canadian Mounted Police, and Veterans Affairs were all included. Finally, processes applied in the ten Canadian provinces and three territories were also all included within the analysis (Table 3).

HTA was determined to play an integral role within 17 formulary decision-making processes, each of the processes used by these agencies is considered in this analysis (Table 2). The final analysis included a review of 59 processes which included processes applied by 42 publicly funded drug plans (29 national level processes and 13 processes applied within Canadian provinces and territories) and 17 HTA agencies within 25 countries.

Table 1: Country specific processes for the evaluation of drugs at the national level

Jurisdiction	Agency involved in reimbursement decision-making	Funding program	Objective of process	Expert Committee	Technologies appraised	References
Canada*	Health Canada (HC)	Non-Insured Health Benefits Program	To provide the First-Nations and Inuit with medications, which are medically necessary and are not otherwise covered.	Federal Pharmacy and Therapeutics Committee	Prescription drugs, over-the-counter medications, medical supplies and equipment	(129)
Canada*	Correctional Service of Canada (CSC)	-	To provide prescription drug coverage for Federal inmates.	-	Prescription drugs.	(130)
Canada*	Department of National Defense (DND)	Canadian Armed Forces Drug Benefit list	To provide prescription drug benefits to members of the Forces and Reserve Force.	Canadian Forces Pharmacy and Therapeutics Committee	Prescription and over the counter medications	(131)
Canada*	Royal Canadian Mounted Police (RCMP)	-	To provide prescription drug benefits to members of the RCMP	-	Prescription drugs	(130)
Canada*	Veterans Affairs (VA)	Prescription Drug Program	To provide drug products and other pharmaceutical benefits to those who demonstrate financial need.	-	Prescription drugs, over-the-counter medications	(132)
South Africa	Department of Health	Essential Drugs Programme	Provide equal access to medicines, improve supply of limited items, and lower the costs of medications	National Essential Medicines List Committee	Pharmaceuticals	(133)
United States	US Centers for Medicare and Medicaid Services	Medicare	To cover all reasonable and necessary services.	-	Pharmaceuticals	(134,135)
United States	Department of Veterans Affairs	Veteran's Affairs Pharmacy Benefits Management Services; Veteran's Affairs Drug Formulary	To improve the health of veterans through the encouragement of appropriate medication use; To provide evidence-based and reliable information to veterans in an efficient manner; To ensure that all veterans across the country have access to the same medications at all VA facilities	National formulary committee with is supported by the Pharmacy Benefits Management group	Pharmaceuticals	(136)

Jurisdiction	Agency involved in reimbursement decision-making	Funding program	Objective of process	Expert Committee	Technologies appraised	References
Mexico	Consejo De Salubridad General Ministry of Health	Basic Formulary (for primary care) and Catalogue of Inputs (for secondary and tertiary care), Health Sector's National Formulary	To promote quality and rational use of medications based on evidence-based and transparent methods.	Comisión Interinstitucional del Cuadro Básico y Catálogo	Pharmaceuticals	(137–139)
Brazil	Ministry of Health Brazil's Sistema Unico de Saude	Relação National de Medicamentos Essenciais (RENAME)	To ensure the essential and rational use of medications by the Sistem Unico de Saude (SUS).	-	Pharmaceuticals	(139–141)
Argentina	Ministry of Health and Social Action	Remediar+Redes	-	Comite de Medicamentos (Committee of Medicinal Products)	Pharmaceuticals	(139)
China	Ministry of Human Resources and Social Security	National Basic Medical Insurance Drug Formulary List	To provide coverage for medications which are clinically necessary, safe for use, effective, convenient for use, reasonably priced, and available in sufficient market supply	-	Medicines	(139,142–144)
Japan	Ministry of Health, Labor, and Welfare	Employees Health Insurance (EHI) and National Health Insurance (for non-employees)	-	-	Pharmaceuticals	(144–146)
South Korea	Ministry of Health and Welfare	Korean National Health Insurance	To ensure improved efficiency and access to health care.	Health Insurance Policy Review Committee	Pharmaceuticals	(139,143,147)
Russia	Ministry of Health	Federal Drug Reimbursement Program - Programme for Supplementary Pharmaceutical	To provide free access and coverage to prescription drugs to the Russian Federation's most vulnerable social groups.	-	Pharmaceuticals	(148,149)

Jurisdiction	Agency involved in reimbursement decision-making	Funding program	Objective of process	Expert Committee	Technologies appraised	References
		Provision [Dopolnitelnogo Lekarstvennogo Obespecheniya (DLO)]				
Turkey	Social Security Institute (part of the Ministry of Labor and Social Security)	Health insurance funds (all have a unified, positive drug list)	To ensure an equal level of care to the entire population	Sosyal Sigortalar Kurumu (SSK) Drug Committee	Pharmaceuticals	(139,150,151)
Spain	Ministry of Health	The Spanish Catalogue	The purpose may be to recognize and state the rights of citizens, move towards equality between regions, reducing inequalities, and controlling health care costs.	-	Pharmaceuticals	(152)
Belgium	Ministry of Public Health and Social Affairs	National Institute for Health and Disability Insurance (INAMI/RIZIV)	To ensure the access to high quality health care at appropriate prices for the largest population.	Drug Reimbursement Commission (CRM/CTG)	Pharmaceuticals	(27,153)
Sweden	Dental and Pharmaceutical Benefits Agency-TLV	Pharmaceutical Reimbursement Scheme	To promote quality service and accessibility of pharmacies.	Pharmaceutical Benefits Board	Pharmaceuticals	(154)
Switzerland	Federal Office of Public Health	List of Pharmaceutical Specialties (SL)	To increase equality, increase transparency, and the quality of care.	Federal Drug Commission	Pharmaceuticals	(155)
The Netherlands	Dutch Ministry of Health	Dutch Medicine Reimbursement Registry (GVS)	To reduce the growth in pharmaceutical costs without losing the quality of pharmaceuticals	-	Pharmaceuticals	(156–158)
Germany	Federal Ministry of Health	Statutory Health Insurance (SHI)	To ensure that insured medicines have access to adequate, expedient and cost-effective therapies which do not exceed what is necessary.	Federal Joint Committee	Pharmaceuticals	(159–161)
France	French Ministry of	-	-	-	Pharmaceuticals	(158,162,16

Jurisdiction	Agency involved in reimbursement decision-making	Funding program	Objective of process	Expert Committee	Technologies appraised	References
	Health Ministère des affairs sociales, de la santé et des droits des femmes					3)
Italy	National Health Service (SSN)	National Pharmaceutical Formulary (Prontuario Farmaceutico Nazionale -PFN)	-	AIFA Technical Scientific Committee and the Pricing and Reimbursement Committee	Pharmaceuticals	(27,164–166)
Scotland	National Health Service- Scotland	-	-	-	-	(167,168)
England	National Health Service England	-	-	-	-	(26,169,170)
Wales	National Health Service	-	-	Welsh Pharmaceutical Committee	-	(169,171,172)
Northern Ireland	Department of Health, Social Services, and Public Safety	-	-	-	-	(173)

Jurisdiction	Agency involved in reimbursement decision-making	Funding program	Objective of process	Expert Committee	Technologies appraised	References
Australia	The Department of Health (Australia)	Pharmaceutical Benefits Scheme	To improve health through focusing on health outcomes.	Pharmaceuticals	Generic Equivalents, Dosing/regimen changes of existing products, New chemical entities for listing on the PBS	(174,175)[1]

*Reimbursement decisions in Canada are made at the provincial and territorial level; details on these processes are included in Table 3.

Table 2: Country specific processes for the evaluation of drugs applied by health technology assessment agencies

Jurisdiction	Agency involved in reimbursement decision-making	Objective of process	Expert Committee	Technologies appraised	References
Canada-Common Drug Review	Canadian Agency for Drugs and Technologies in Health	To reduce duplication, maximize the use of resources and expertise, improve the quality and consistency among drug reviews.	Canadian Drug Expert Committee (formerly Canadian Drug Expert Advisory Committee)	Pharmaceuticals	(28)
Canada-Quebec	Institut national d'excellence en santé et services sociaux	To make recommendations to the Minister as to whether medications should be listed on the provincial formulary (RAMQ)	Comité Scientifique de l'évaluation des medicaments aux fins d'inscription (CSEMI)	Pharmaceuticals	(176)
Canada-Atlantic Provinces	Provincial- Nova Scotia, New Brunswick, Newfoundland and Labrador	-	Atlantic Expert Advisory Committee	Pharmaceuticals	(177)
Mexico	Center of National Health Technology (Centro Nacional de Excelencia Tecnologica en Salud)	To produce and disseminate information on the appropriate use and adoption of medical technologies through consideration for their safety, effectiveness and efficiency, for the benefit of the population and the advancement of medical practice	N/A	Pharmaceuticals	(137,178)
Brazil	Comissao Nacional de Incorporacaode Tecnologies (CONITEC)	-	-	Pharmaceuticals	(137)
South Korea	Health Insurance Review Agency	To contribute to improved health through quality improvement and cost control.	Drug Benefit Coverage Assessment Committee (DBCAC)	Pharmaceuticals, treatments and medical materials	(147,179)
Spain	Instituo de Salud Carlos III	To assess new technologies to be included in the national catalogue.	-	Pharmaceuticals, devices, procedures, programmes and settings in health care	(180,181)

Jurisdiction	Agency involved in reimbursement decision-making	Objective of process	Expert Committee	Technologies appraised	References
Belgium	Belgian Health Care Knowledge Centre (KCE)	To produce studies and reports that will aid the policy-makers on issues related to health care and health care insurance	-	New clinical technologies and medications	(182)
Sweden	Swedish Council on Technology Assessment in Health care (SBU)	Assessing health care related interventions comprehensively by considering clinical, economic, social, and ethical factors	-	Methods for prevention, diagnosis and treatment of health conditions-technologies for comprehensive review are selected by the SBU board	(183,184)
The Netherlands	Institute of Health Care Quality (within CVZ)	Critically assessed whether the basic health care package provides good quality of care and continues to be accessible and affordable	Medicinal Products Reimbursement Committee	Pharmaceuticals	(185)
Germany	Institute for Quality and Efficiency in Health Care (IQWIG)	To objectively assess the advantages and the disadvantages of health care interventions for patients	-	Pharmaceuticals, non-drug interventions, diagnostic and screening tests, clinical practice guidelines and disease management programs	(160,186)
France	Haute Authorité de Santé (HAS)	To ensure access to that the best available care is durable and equitable.	Commission de la Transparence and La Commission evaluation economique et de la sante publique (Economic evaluation)	Pharmaceuticals	(187,188)
Italy	National Agency for Regional Health care Services	To provide technical and operational support to aid the Ministry of Health to make policy decisions that improve the efficiency and quality of health services	Pricing and Reimbursement Committee	Biomedical equipment, medical devices, drugs, clinical procedures, organizational models, prevention programs for	(189,190)

Jurisdiction	Agency involved in reimbursement decision-making	Objective of process	Expert Committee	Technologies appraised	References
				health promotion	
Scotland	Scottish Medicines Consortium	to ensure that drugs that provide good value for money are accepted by the NHS so they can benefit patients and to reduce local variability in decisions	New Drugs Committee	Pharmaceuticals	(191)
England	National Institute for Health and Care Evidence	To eliminate the variability in the availability of medicines and health technologies across the National Health Service (NHS)	Technical Appraisal Committee	Pharmaceuticals, medical devices, diagnostic techniques, surgical procedures, health promotion activities	(192)
Wales	All Wales Medicines Strategy Group	To provide guidance on the use of new medications in Wales	New Medicines Group	Pharmaceuticals	(193,194)
Australia	The Department of Health (Australia)	To improve health through focusing on health outcomes	Pharmaceutical Benefits Advisory Committee with two sub committees-- Drug Utilization Sub Committee, and the Economics Sub-committee	Pharmaceuticals	(174,175)

Table 3: Province and Territory specific processes for the evaluation of drugs in Canada

	Agency involved in reimbursement decision-making	Funding program	Objective of process	Expert Committee	Technologies appraised	References
Ontario	Ministry of Health and Long-term Care	Ontario Drug Benefit	-	Committee to Evaluate Drugs	Pharmaceuticals, Food & Supplements (Inherited Metabolic Diseases)	(195)
Quebec	Quebec Ministry of Health	Public Prescription Drug Insurance Plan (RAMQ)	To provide the First-Nations and Inuit with medications that are medically necessary which are not otherwise covered	-	Pharmaceuticals	(176)
Alberta	Alberta Health	Alberta Drug Benefit	-	Alberta Expert Committee on Drug Evaluation and Therapeutics	Pharmaceuticals	(196)
Saskatchewan	Saskatchewan Ministry of Health	Drug Plan	To provide coverage of quality pharmaceuticals to Saskatchewan Residents, reduce the cost of medications to residents, to reduce the cost of drug materials, and to encourage the rational use of medications	Drug Advisory Committee of Saskatchewan	Pharmaceuticals	(197)
British Columbia	British Columbia Ministry of Health Services	B.C. Pharmacare Program	To provide coverage for drugs, which support the health and the well-being of B.C. residents, and to ensure that covered drugs are affordable while providing good value for money.	Drug Benefit Council	Pharmaceuticals	(198)
Manitoba	Manitoba Health	Manitoba Pharmacare	Provides income based drug coverage to Manitoba residents	Manitoba Drug Standards and Therapeutics Committee	Pharmaceuticals	(199)
Nova Scotia	Nova Scotia Department of Health and Wellness	Nova Scotia Pharmacare	-	Nova Scotia Drugs and Therapeutics Committee	Pharmaceuticals	(200)
New	New Brunswick	New Brunswick	-	-	Pharmaceuticals	(201)

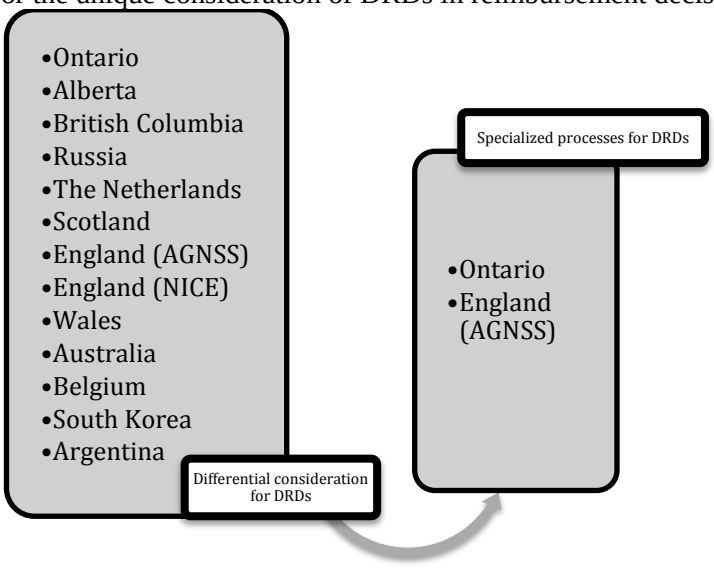
	Agency involved in reimbursement decision-making	Funding program	Objective of process	Expert Committee	Technologies appraised	References
Brunswick	Department of Health	Prescription Drug Program				
Newfoundland and Labrador	Department of Health and Community Service	The Newfoundland and Labrador Prescription Drug Program (NLPDP)	-	-	Pharmaceuticals	(202)
Prince Edward Island	Health PEI	PEI Pharmacare	-	PEI Pharmacy Advisory Committee	Pharmaceuticals	(203)
Yukon	Yukon Department of Health and Long-term care	Pharmacare	To provide coverage for drugs which are proven to be highly effective and have been approved for use.	Yukon Formulary Working Group	Pharmaceuticals	(204)
Northwest Territories	Northwest Territories Health	-	To provide coverage for patient's medical conditions which are not otherwise covered.	No provincial advisory committee. Medications covered under the non-insured health benefits program are eligible for reimbursement	Pharmaceuticals	(205)
Nunavut	Department of Health	Extended Health Benefits Full Coverage Plan	To provide coverage for patients with chronic health conditions.	No provincial advisory committee. Medications covered under the non-insured health benefits program are eligible for reimbursement.	Pharmaceuticals	(206)

Unique consideration for rare diseases in reimbursement decision-making

Among the processes for reimbursement decision-making that considered DRDs uniquely, some processes provided special considerations within the existing framework for reimbursement decision-making, while others considered DRDs through a specialized reimbursement framework. Distinctive processes for informing coverage decision-making for DRDs were identified within 13 of the 59 processes reviewed (

Figure 1) (14,108,143,207–219). Internationally, 10 countries apply specialized consideration for the funding of DRDs (14,143,208–219) (Table 4, Table 5). In Canada, DRDs are evaluated distinctively in three provinces (ON, AB, BC) (Table 6) (14,108,207,208). Among processes applied by HTA agencies, four processes consider DRDs uniquely (Table 5). Finally, among the frameworks where rare diseases were considered differently, two jurisdictions (ON, England) adopted specialized reimbursement frameworks for the evaluation DRDs (14,207,214,215) (Figure 1).

Figure 1: Processes for the unique consideration of DRDs in reimbursement decision-making



Definition of rarity

Different definitions of rarity are applied within frameworks for the evaluation of DRDs for coverage. Incidence and prevalence thresholds are commonly used to define rarity. Within frameworks for the evaluation of DRDs, the threshold ranged from an incidence of less than 1 in 2,000 to less than 1 in 150,000 individuals in the population. Among processes used by publicly funded drug plans, the definition of rarity was indicated among four processes (South Korea, Russia, Belgium, England (AGNSS)) (Table 4) (142,214,215,218,219,222). Belgium and England (AGNSS) applied the EMA definition, where rare diseases are defined as conditions with a prevalence of less than 5 in 10,000 individuals (214,215,218,219). In South Korea, within the context of drug reimbursement, rarity is defined as a condition affecting less than 20,000 people in South Korea, and where there is no other existing therapies to treat the condition (142). Within processes for reimbursement applied by HTA agencies, rarity was defined within three of the decision-making frameworks (the Netherlands, Scotland, Wales) (Table 5). These agencies have all adopted the EMA definition, where rare diseases are defined as conditions affecting less than 5 in 10,000 individuals (157,171,172,193,212,213). Within Canadian processes, the definition of rarity is described within two reimbursement frameworks (Table 6). In Alberta, a condition is considered rare if it affects less than 1 in 50,000 people in Canada or less than 1 in 50 people in Alberta (208), while in Ontario, rarity is defined based on an incidence of less than 1 in 150,000 (223).

Rationale for the specialized consideration of DRDs

Among the 13 processes where rare conditions are considered uniquely, the rationale applied to justify the unique consideration of DRDs was stated within seven

decision processes (South Korea, England (AGNSS), Australia, Scotland, Wales, ON, AB) (14,108,142,171,172,193,207,208,212–216,220). The rule of rescue is cited as the justification for the specialized processes applied in South Korea and Australia (142,216,220). The differing evidence base for DRDs is the reasoning provided within four jurisdictions (England, Scotland, Wales, ON) (142,171,172,193,212–216,220). In the province of Alberta, the specialized consideration of DRDs is routed on the financial protection argument, as the cost of these medications would not be affordable by most Albertans (208). Finally, in England, the AGNSS provided multiple justifications for the specialized consideration of DRDs including vulnerability of the population, limited availability of alternative treatments, and the differing evidence-base (221).

Table 4: Country specific assessment of the specialized consideration of DRDs within national formulary processes

Jurisdiction	Same framework applied for the review of DRDs	Distinctive consideration for DRDs	Specialized framework for the consideration of DRDs	Definition applied to rare diseases.	Rationale for the specialized consideration of rare diseases	References
Canada (NIHB)	Yes	No	No	-	-	-
Canada (CSC)	Yes	No	No	-	-	-
Canada (DND)	Yes	No	No	-	-	-
Canada (RCMP)	Yes	No	No	-	-	-
Canada (VA)	Yes	No	No	-	-	-
South Africa	NR	No	No	-	-	-
United States (Medicare and Medicaid)	NR	No	No	-	-	-
United States (Department of Veterans Affairs)	NR	No	No	-	-	-
Mexico	NR	No	No	-	-	-
Brazil	NR	No	No	-	-	-
Argentina	No	Yes	No	-	NR	(217,222)
China	NR	No	No	-	-	-
Japan	NR	No	No	-	-	-
South Korea	Yes	Yes	No	Condition affecting less than 20,000 people in South Korea, or where there is no available treatment for the disease in Korea.	Rule of Rescue	(142)
Russia	NR	Yes	Unclear	No more than 10 cases in 100,000	NR	(222)
Turkey	Yes	No	No	-	-	(224)

Jurisdiction	Same framework applied for the review of DRDs	Distinctive consideration for DRDs	Specialized framework for the consideration of DRDs	Definition applied to rare diseases.	Rationale for the specialized consideration of rare diseases	References
Spain	NR	No	No	-	-	-
Belgium	Yes	Yes	No	A prevalence of 50 or fewer in 100,000 (EMA definition)	NR	(12,219,225)
Sweden	Yes	No	No	-	-	-
Switzerland	Yes	No	No	-	-	-
The Netherlands	Yes	No	No	-	-	(226)
Germany	Yes	No	No	-	-	-
France	Yes	No	No	-	-	-
Italy	Yes	No	No			(12,164)
Scotland	Yes	No	No	-	-	(212)
England (AGNSS)	No	Yes	Yes	500 patients and/or four centres in England	The vulnerability of the population, limited availability of alternative treatments, and the differing evidence base.	(214,215)
Wales	Yes	No	No	-	-	(171,172,193)
Northern Ireland	Yes	No	No	-	-	-
Australia	Yes	Yes	No	No incidence or prevalence cut-off is indicated.	Rule of Rescue	(216,220)

*Reimbursement decisions in Canada are made at the provincial and territorial level; processes for the evaluation of DRDs are reviewed in Table 6.

NR-Not reported

Table 5: Country specific assessment of the specialized consideration of DRDs applied by HTA agencies

Jurisdiction	Same framework applied for the review of DRDs	Distinctive consideration for DRDs	Specialized process for the review of DRDs	Definition applied to rare diseases.	Rationale for the specialized consideration of rare diseases	References
Canada-CDR	Yes	No	No	-	-	(227)
Canada-INESSS	Yes	No	No	-	-	-
Canada-ACDR	NR	No	No	-	-	-
Mexico	NR	No	No	-	-	-
Brazil	NR	No	No	-	-	-
South Korea	Yes	No	No	-	-	-
Spain	NR	No	No	-	-	-
Belgium	Yes	No	No	-	-	-
Sweden	Yes	No	No	-	-	-
The Netherlands	Yes	Yes	No	EMA definition of rare diseases is applied - life threatening conditions affecting less than 5 in 10,0000 people in the European Union	NR	(157,213)
Germany	Yes	No	No	-	-	-
France	Yes	No	No	-	-	-
Italy	Yes	No	No	-	-	-
Scotland	Yes	Yes	No	EMA definition of rare diseases is applied - life threatening conditions affecting less than 5 in 10,0000 people in the European Union	The evidence base for DRD differs due to smaller clinical trial programs and these medications are unlikely to meet the thresholds of cost-effectiveness.	(212,213)
England (NICE)	Yes	Yes	No	-	-	-
Wales	Yes	Yes	No	Condition affecting less than 1 in 50,000 individuals in the EU (at the time of orphan designation)	Recognizes that the evidence base used to assess these drugs is weaker	(171,172,193)

Table 6: Province and territory specific assessment of the specialized considerations of DRDs in Canada

Jurisdiction	Same framework applied for the review of DRDs	Distinctive consideration for DRDs	Specialized framework for the review of DRDs	Definition applied to rare diseases.	Rationale for the specialized consideration of rare diseases	References
Ontario	No	Yes	Yes	A clearly defined diseases, with an incidence of less than 1 in 150,000	Differing evidence base-The evidence available for the assessment of the effectiveness and cost-effectiveness is limited by the inability to conduct adequately controlled RCTs- therefore in the absence of a process, these medications will likely have negative listing recommendations	(14,108,207)
Quebec	Yes	No	No	-	-	-
Alberta	No	Yes	No	Genetic Disorders, with an incidence of less than 1 in 50,000 in Canada or 50 in Alberta	Financial protection	(108,208)
Saskatchewan	Yes	No	No	-	-	(108)
British Columbia	Yes	Yes	NR	NR	NR	-
Manitoba	Yes	No	No	-	-	-
Nova Scotia	Yes	No	No	-	-	-
New Brunswick	Yes	No	No	-	-	-
Newfoundland and Labrador	Yes	No	No	-	-	-
Prince Edward Island	Yes	No	No	-	-	-
Yukon	Yes	No	No	-	-	-
Northwest Territories	Yes	No	No	-	-	-
Nunavut	Yes	No	No	-	-	-

Requirement for Clinical Evidence

Clinical evidence is often an important component of the decision-making process for drugs, and often an assessment of clinical evidence is required beyond the requirements for regulatory approval, as licensing agencies do not typically reflect on the added value of the drug for patients and society (228). Among the frameworks in which DRDs are considered uniquely, ten processes (ON, AB, Scotland, England (AGNSS), England (NICE), Wales, Belgium, South Korea, Australia, the Netherlands) explicitly indicated that consideration is given to the clinical evidence-base within the decision framework (14,142,143,171,172,193,207,212–216,218,219,229). While none of the frameworks indicate that clinical evidence is not considered within the process, it is unclear within three of the processes how or whether clinical evidence is assessed within the evaluation process (BC, Argentina, Russia) (208,210,211,217). While Australia considers DRDs uniquely for reimbursement, the process stipulates that DRDs are required to maintain the same standards of clinical evidence as drugs for other conditions (216).

Types of clinical evidence reviewed

Where details on the process and guidance for the evaluation of clinical evidence for treatments for rare conditions is given, a preference for evidence from head-to-head randomized controlled trials (RCTs) has been noted within some frameworks. Explicit consideration for expert opinion is noted within the processes applied in Ontario, Alberta, and England (AGNSS) (208,221,230). Processes in Ontario, Australia, and the Netherlands also indicate the inclusion of observational studies within the assessment of clinical evidence (213,216,230). The details of the types of studies used within the assessment of clinical

evidence are not available for the processes used in British Columbia, England (NICE), Wales, South Korea, Argentina, and Russia (139,168,190,210,216,223,225,232,233).

Comparators

The selection of comparators plays a central role in the outcome of clinical and economic evaluations (228). Within the evaluation frameworks that consider DRDs distinctively, three processes (Scotland, Wales, the Netherlands) provide clear direction with regards to the selection of comparators (171,212,213). In Scotland, the recommends comparators are treatments for the same indication (212,213). The evaluation process in Wales suggests that the most appropriate comparator is the current standard of care in the NHS Wales, and that the selection of multiple comparators is often appropriate including unlicensed comparators (171). Finally, the evaluation framework used in the Netherlands indicates that the comparator should be other interventions for the same indication, and that the comparison with standard or usual treatments is required (157,213).

Outcome measures

Various different outcome measures can be used in the assessment of clinical evidence. Details of acceptable outcomes within the evaluation are provided within three of the frameworks for the consideration of DRDs (14,205,211,222,236). Generally, the preferred outcome assessed within the clinical evidence was the final endpoint within the analysis. A preference for final outcomes was noted within the process used for the assessment of DRDs in Scotland (212,213). Many processes also allow for the consideration of surrogate endpoints where the final outcomes cannot easily be measured. The Ontario framework highlights that where surrogate outcomes are used in the analysis, their validity must be assessed. Within the framework, the Bradford-Hill criteria (237) are applied to

assess whether the treatment (exposure) of interest is related to the health benefits (outcome)(14). While the Scottish guidance indicates a clear preference for final outcomes, surrogate outcomes may be considered where the association between the surrogate outcome and a meaningful patient outcome is provided (212,213). Finally, the evaluation process in the Netherlands indicates that all necessary outcomes should be considered during the evaluation (229,236).

Table 7: Consideration for clinical evidence in reimbursement decision-making processes for DRDs

Jurisdiction	Consideration for clinical evidence	Types of clinical evidence considered	Comparators	Outcome measures	References
Ontario	Yes	All relevant clinical evidence -- considered in the assessment of clinical value including expert opinion and medical literature to establish the natural history.	-	Surrogate markers are assessed for their validity. Where there is question about the impact of the therapy on the health outcomes, the Bradford-Hill Criteria maybe applied to assess whether the treatment (exposure) leads to health benefits (outcome). Clinical effectiveness may also involve decision modelling, adopting a Bayesian perspective.	(14,207)
Alberta	Yes	Details unclear— expert opinion is considered within the decision process	-	-	(208,210)
British Columbia	Unclear	-	-	-	(211)
Scotland	Yes	Head-to-head trials (preferred)	Existing treatments	Final outcomes. If surrogate markers are used- An explanation of the association between the surrogate marker and the effect on the patient must be provided.	(212,213)
England (AGNSS)	Yes	Data submitted by manufacturers, comments from independent academic groups; submissions by consulters; views of clinical specialists; opinions of experts and carers on the patient experience; uncertainty generated by the evidence; and differences in risks. The weight given to different forms of evidence is dependent on the discretion of decision-making committees.	-	-	(214,215)
England (NICE)	Yes	-	-	-	(229)
Wales	Yes	-	Current standard of	-	(171,172,193)

Jurisdiction	Consideration for clinical evidence	Types of clinical evidence considered	Comparators	Outcome measures	References
			care in NHS Wales. Multiple comparators may be acceptable. Unlicensed comparators may be considered in some cases.		
Argentina	Unclear	-	-	-	(217)
Belgium	Yes	Head-to-head superiority trials (preferred)	-	-	(12,219,225)
South Korea	Yes	-	-	-	(139,233)
Australia	Yes	Epidemiological and other studies.			(234)
Russia	Unclear	-	-	-	(217)
The Netherlands	Yes	Head-to-head comparisons (preferred); all relevant data from RCTs, observational studies, guidelines, etc. are considered within the assessment of clinical benefit.	Other treatments for the same indication. Comparison with standard or usual treatments is essential	All necessary outcomes to determine therapeutic value should be considered	(229,236)

Requirement for Economic Evidence

The consideration for economic evidence is often an important element within frameworks for reimbursement decision-making (Table 8). Few jurisdictions explicitly indicate whether economic evidence is considered within the processes for the reimbursement of DRDs. Within the processes that considered DRDs uniquely, consideration for economic evidence is given within six of the funding processes (ON, Scotland, England (AGNSS), Wales, South Korea, Australia) (14,139,168,190,205,206,211–214,222,223,233,234). Within five frameworks (AB, BC, England (NICE), Argentina, Russia), whether consideration is given to economic evidence within the evaluation process is unclear (208,210,211,217,222,229). In Belgium economic evidence is not required for the appraisal of DRDs (45,46). In the Netherlands, while an economic submission is required when a manufacturer seeks for a medication to be reimbursed, DRDs may apply and qualify for an exemption for the consideration of economic evidence within the reimbursement decision-process (213). Where frameworks indicate the consideration of economic evidence, details on how the economic evidence is judged within the evaluation process are limited.

Perspective

The perspective within an economic evaluation guides the costs and benefits that are considered within the evaluation. Guidance surrounding the perspective of the economic evaluation was provided within few frameworks for the reimbursement of DRDs. Only two reimbursement frameworks (the Netherlands, Scotland) indicated a preferred perspective within the evaluation. The Netherlands recommends adopting the societal

perspective (213). The Scottish Medicines Consortium (SMC) recommends adopting the perspective of the NHS Scotland, as well as, the societal perspective (212,213).

Analytical techniques

Various analytic techniques can be applied when conducting an economic evaluation including cost-benefit analysis (CBA), cost-utility analysis (CUA), cost-effectiveness analysis (CEA), and cost consequence analysis (CCA). Among processes that considered DRDs differently which take into consideration cost evidence, only Scotland, Wales, and Australia indicated the acceptable forms of economic evaluations used in the evaluation framework (168,190,211,212,222,223,234). The SMC indicated a preference for CUA for the economic submission (212,213). In Wales acceptable forms of economic evaluations to review of DRDs are the CUA, CMA, and CEA (171,172,193). Finally, in Australia (PBAC) economic submissions may take the form of CUA, CEA, or CBA (234).

Measures of health benefits

Only two frameworks provided details about the preferred outcome to measure health benefits within the economic analysis of DRDs (211,212,222,234). The measure of health benefit preferred by SMC is the QALY, and where the QALY is not applied, justification must be provided for the use of another measure (212,213). The process used in Australia indicates that the preferred outcome for a CUA is the QALY and monetary outcomes are appropriate where a CBA is performed(234).

Threshold of cost-effectiveness

Some jurisdictions have implemented explicit cost per QALY thresholds for cost-effectiveness in order to establish whether a treatment is cost-effective or not cost-effective (118). The analysis assessed whether a threshold for cost-effectiveness was indicated within the systems that considered DRDs uniquely. No explicit threshold was indicated to establish cost-effectiveness for DRDs in any of the jurisdictions, which were included within the analysis. While the Ontario Ministry of Health and Long-term Care acknowledges that drugs are typically considered cost-effective where the ICER is between $40,000-$60,000; the process for the evaluation of DRDs recognizes that DRDs are unlikely to meet this threshold (14).

Table 8: Consideration for economic evidence in reimbursement decision-making processes for DRDs

Jurisdiction	Consideration for economic evidence	Perspective	Analytical technique	Measure of health benefits	Threshold for cost-effectiveness	References
Ontario	Yes	-	-	-	Drugs are in general, considered to be cost-effective if they have an ICER between $40,000-60,000 or lower--- but it has been recognized that DRDs are unlikely to fall within this threshold	(14,108,207)
Alberta	Unclear	-	-	-	-	(208,210)
British Columbia	Unclear	-	-	-	-	(211)
Scotland	Yes	NHS in Scotland and societal	CUA preferred	QALY preferred. (Justification for not using QALY must be provided)	No formal threshold	(212,213)
England (AGNSS)	Yes	-	-	-	-	(214,215)
England (NICE)	Unclear	-	-	-	-	(229)
Wales	Yes	-	CUA, CMA, or CEA			(171,172,193)
Argentina	Unclear	-	-	-	-	(217)
Belgium	No**					(12,219,225)
South Korea	Yes					(139,233)
Australia	Yes	-	CEA, CUA, or CBA	QALY-base case (CUA), monetary (CBA)	None stated	(234,238,239)
Russia	Unclear	-	-	-	-	(217,222)
The Netherlands	No**	-	-	-		(213)[2]

**In Belgium and the Netherlands, while economic submissions may be submitted, for DRDs this maybe excluded from the decision process.

Accountability for Reasonableness

The A4R Framework was applied to assess processes applied to assess whether processes for the reimbursement of DRDs met the criteria for fairness as described by Daniels and Sabins (29). Processes were judged based on three of the four tenets of the accountability for reasonableness framework. Table 9 provides an overview of whether the processes where DRDs were considered distinctively subscribe to the tenets of fairness in priority setting as outlined by the A4A framework(29).

Table 9: Appraisal of frameworks for the reimbursement decision-making processes for DRDs based on the Accountability for Reasonableness Framework

Jurisdiction	Transparency	Relevance	Process for Appeals
Ontario	Yes	Yes	Yes
Alberta	No	Yes	No
British Columbia	No	No	No
Scotland	Yes	Yes	No
England (AGNSS)	Yes	Yes	Yes
England (NICE)	No	No	No
Wales	Yes	Yes	No
Argentina	No	No	No
Belgium	Yes	No	No
South Korea	No	Yes	No
Australia	Yes	Yes	No
Russia	No	No	No
The Netherlands	Yes	No	No

Transparency

Specific to the process for rare diseases, transparency was assessed based on whether recommendations/decisions and their rationales were publicly available. While the rationales for the decisions made through some reimbursement processes were publicly available, several were not. The decisions made and the rationale supporting these decisions is indicated within seven of the processes.

Relevance

A process was deemed to be relevant where the rationale for the specialized consideration for DRDs was clearly indicated. Within seven frameworks for the funding of DRDs, the criterion for relevance is met(14,108,142,171,172,193,207,208,212–216,220). Within the remaining processes, there is no clear explanation justifying the specialized consideration of DRDs.

Process for appeals

A process for appeals was considered to be in place where a mechanism is clearly outlined to change or review the decision or recommendation. Among the processes identified for the reimbursement of DRDs, a process for appeals was clearly outlined within two of the frameworks (14,108,207,214,215).

Discussion

While structured comparisons of funding processes are available within the published literature (25,27); the scope of these studies is focused on drugs in general. This review adds an understanding of the processes presently used for informing the reimbursement of DRDs and considers processes applied the internationally at the national level, by HTA agencies, as well as Canadian provinces and territories. Publications pertaining to reimbursement processes for DRDs have described individual frameworks (14,240), or have compared processes within a narrow group (139,212,228,241).

The G20 countries are representative of a diverse range of health and social care systems and provide a comprehensive overview of reimbursement processes applied in developed nations which can help inform reimbursement decision-making processes in Canada, particularly in the context of funding therapies for rare conditions. The majority of

these countries have national formulary systems or centralized processes for the evaluation of drugs for reimbursement, and ministries of health and HTA agencies are noted as the organizations typically involved in drug coverage decision-making. While the structure of each system and the processes used vary, the challenges experienced by the various jurisdictions regarding the funding of DRDs are likely to be similar.

This analysis demonstrates observable similarities and differences among the processes applied by the jurisdictions included within the review. Within the 59 frameworks (29 national-level processes, 17 HTA processes, and 13 provincial and territorial processes) considered in this analysis, the differential consideration of DRDs was clearly indicated within 13 frameworks (23%). This currently represents a small proportion of processes; but this may reflect the changing landscape of reimbursement decision-making for DRDs as the number of new drugs for rare conditions coming to market continues to grow(242,243).

Where processes consider rare diseases uniquely, the majority of jurisdictions implemented special considerations within the existing process as opposed to adopting a dedicated funding framework for the evaluation of DRDs. The limited number of specialized frameworks may reflect challenges for justifying an alternate process and the difficulties in the development and operationalization of dedicated reimbursement decision-making frameworks.

Where specialized processes and considerations are applied for the funding of DRDs, whether a rationale is provided was noted. A justification for the specialized consideration of DRDs was clearly outlined within seven processes; but was not clearly

outlined in the six others. Where a rationale for a unique process is not provided this reveals concerns of transparency, and questions of whether a dedicated process is relevant.

When considering rare diseases exceptionally, it would be advisable that the rationale is clearly indicated and consideration should be given to whether the rationale is justifiable in order to promote transparency and relevance of the decision process. The rationale for a differing process stated in both South Korea and Australia is the rule of rescue, which has important limitations as the grounding for a dedicated reimbursement process. Among the key challenges noted with the application of the rule of rescue as the basis for a specialized reimbursement process includes its limited applicability to all rare diseases, and its inconsistency with allocating resources to maximize health by disregarding the opportunity cost of funding decisions. The rationale for the process applied in Alberta is based on the financial protection argument, which similarly provides insufficient justification for a differing process on account that concerns over the financial strain would also be applicable to many drugs for common conditions, making it difficult to justify a process specifically for rare diseases. The other four jurisdictions apply the most convincing justification for a separate process for DRDs by noting the limited evidence base given that the rarity of these conditions limits the availability of a the same levels of evidence that can be generated for more common conditions. Jurisdictions should carefully reflect on the justifications for an alternate process for DRDs, Chapter 2 provides an assessment of the justifications, which have been proposed for a dedicated reimbursement framework for DRDs.

The publicly available information on the details of the clinical and economic review processes used for the evaluation of DRDs is limited. No detailed information is

provided on the relative weights applied to the different criteria considered within each of the evaluation processes.

Among processes for the evaluation of DRDs, the majority explicitly indicated that the clinical evidence was considered in the decision-making framework. This indicates that while a different evidence-base may be available for the evaluation of DRDs, jurisdictions continue to value attention to clinical effectiveness. This is consistent with the recent findings of a review of valued decision-making factors in the evaluation of DRDs, which revealed that the effectiveness and magnitude of benefit are important factors within the decision process (244). A complete understanding of how the evaluation of clinical evidence is considered in evaluation processes and how the evaluation differs for rare diseases is limited. Although this information is not publicly available, an in depth understanding of the types of clinical evidence considered, acceptable comparators, and outcome measures used in designated processes for rare diseases would provide a more comprehensive understanding of the unique attention given to DRDs within decision processes.

Attention to economic evidence is not addressed within all frameworks for reimbursement decision-making and in several cases the consideration and details of the process are not available. Belgium and the Netherlands have allowed for the exemption of an economic submission for evaluations of treatments for rare diseases. This may reflect position that treatments for rare conditions are unlikely to meet standard thresholds of cost effectiveness and the difficulties with conducting these analyses (15,245). Although it is argued that methodological challenges exist in the assessment of cost-effectiveness for technologies to treat rare conditions, several examples exist of fully completed evaluations

(113). Similarly to the details of the clinical evidence, little information is provided on the details of the evaluation of the economic assessment, where economic evidence is considered. Further details on the perspective, analytical techniques accepted, the measures of health benefit would provide a more comprehensive understanding of the processes currently applied for reimbursement decision-making of DRDs.

This analysis also identified whether frameworks for the evaluation of DRDs met the criteria outlined within the widely used A4R framework, which described the tenets of fair priority setting processes. Based on this assessment, only two processes (ON, England (AGNSS) meet the three criteria assessed in this analysis (transparency, relevance, process for appeals). Both processes are dedicated frameworks developed specifically for the consideration of DRDs. Transparency varies widely across the frameworks identified for the reimbursement of DRDs. In order to be transparent any developed processes for the reimbursement of DRDs, it is important that the funding outcomes and rationales supporting decisions are publicly available. Similarly variability is noted in the relevance of the dedicated reimbursement processes; in many cases the rationale supporting the process for rare diseases process is not outlined. A limitation of several of the reimbursement frameworks was the absence of a defined process to appeal or revise a recommendation. Only 2 of the 13 processes explicitly indicate that a process for appeals or a mechanism by which to review the recommendation exists. The A4R framework is widely used in the context of reimbursement decision-making and each of the tenets should be considered in the development of new processes for the funding of DRDs.

Limitations

This study is subject to limitations. For one, although a systematic and comprehensive search was conducted to identify the processes available for the reimbursement of drugs, the nature of the research questions addressed within this review did not allow for the application of traditional systematic review methodologies. While efforts were made to conduct a comprehensive search including grey literature, it is possible that searches were not sufficiently sensitive to identify all processes, particularly those in languages other than English. Where there was uncertainty within the processes, contacts within the HTA community were emailed for feedback and clarifications. Additionally, with the changing rare disease market and reimbursement processes, the considerations made within reimbursement processes for rare conditions are continuing to evolve and changes that occurred to processes after February 1st, 2014, are not reflected within this analysis.

Another limitation of this study is that it does not provide a complete assessment of the context in which reimbursement decisions are made. Although this was considered outside the scope of this work, coverage decision-making is a complex process and a broader understanding of the health care system in which these decisions are made and other contextual factors would be valuable in understanding the reimbursement processes. Additionally while this analysis considers the processes and criteria considered in the decision-making of DRDs, decision-makers are forced to take into account additional factors beyond the standardized evaluation. These additional factors may be jurisdictional and as a result may explain variation that may occur between the funding outcomes within different jurisdictions.

Conclusion

Current processes for the reimbursement of DRDs are varied. This analysis demonstrates that there are limitations within the current processes applied for reimbursement decision-making for DRDs. It is intended that this in depth analysis of current processes for reimbursement will help provide insight into inform the development of fair processes for the funding of DRDs, and could be used in discussions with decision-makers concerning strategies for making coverage decisions for DRDs.

Chapter 4- Funding outcomes for DRDs-Case studies of Alglucosidase alfa (Pompe Disease) and Canakinumab (Cryopyrin-Associated Periodic Syndrome (CAPS))

Rationale

Different processes are used for making drug coverage decisions, and these differing processes may lead to differing funding outcomes (246). Case studies of two DRDs are used to provide insight into the different reimbursement outcomes that may arise through the application of differing processes and alternate criteria for making drug reimbursement decisions. An improved understanding of the rationales guiding current decision-making processes in Canada and internationally may aid in identifying gaps in current frameworks and to advance the processes for the funding of DRDs.

Objectives

To assess what funding decisions emerge through the application of different frameworks for making coverage recommendations or decisions through the application of two case studies.

Methods

Two case studies of orphan drugs were selected to investigate whether differences in funding outcomes may result from the application of differing processes for the assessment of DRDs. The first drug considered within this assessment is Alglucosidase-alfa (Myozyme) for the treatment of Pompe disease, and the other is Canakinumab (Ilaris) for the treatment of Cryopyrin-Associated Period Syndrome (CAPS). Case studies were selected to feature two different DRDs, with differing characteristics, costs, and patient

populations; details of the differences are stipulated below. This was done with the objective of highlighting the heterogeneity across differing rare diseases.

Using the G20 countries as a sampling frame the funding status, appraisal status, and rationale supporting the recommendations and decisions made by government agencies and HTA agencies were considered.

Sampling frame

Search strategy

The search was focused on a grey literature search including HTA agencies, and government agencies responsible for making reimbursement recommendations and decisions. In-site searching of key words was used to identify the formulary and/or documents pertaining to the reimbursement decision-making process and rationale supporting the coverage decision. All searches were done between September 1st, 2014 and November 12th, 2014.

Eligibility Criteria

For each of the identified processes used in the G20 countries (Chapter 3), the funding outcomes were determined based on publicly listed formulary listings of the medications and publicly available documentation of the evaluation for coverage. Additionally, in jurisdictions where HTA was determined to be integral to the reimbursement decision-making process, the outcome of the evaluation was included in the analysis. In order to help inform reimbursement decision-making within the Canadian context and account for the differential processes within provinces and territories, funding outcomes within each of the Canadian provinces and territories were also considered.

Similarly, to Chapter 3, funding outcomes taken at the regional level (excluding Canadian provinces and territories), within clinical programs, and private payers were not included.

Data extraction and synthesis

For each of the processes identified (processes used at the national level, processes used by HTA agencies, and processes applied by Canadian provinces and territories), it was noted whether the medication was considered for reimbursement through the process and the date where the appraisal occurred. It was assumed that an appraisal was completed where the medication was listed on the formulary or where documentation of the funding outcome was available. Where it was unclear whether an appraisal was done, it was indicated that the appraisal status was not reported.

For each of the country specific national processes and within Canadian provinces and territories included in the analysis, data on whether the medication is listed for general benefit (access to all under the drug plan), restricted benefit (access to a restricted population covered under the drug plan meeting specific criteria), or not for benefit was extracted. A medication was considered to be for benefit where no explicit restrictions were noted for reimbursement, restricted benefit was noted for medications where patients are required to meet explicit eligibility criteria in order to be eligible for reimbursement; finally, a medication was noted not for benefit where the outcome of the appraisal explicitly indicated that the medication is not listed for benefit. Where the medication was not listed on the formulary and no documents identifying the appraisal status were noted, it was noted that the funding outcome was not reported. It was not assumed that the medication was not for benefit on account that while the medication may not be listed on

the formulary, the medications maybe funded through specialized funding programs. Given that many HTA agencies play an integral role within the reimbursement decision process in many jurisdictions, the appraisal outcome for each process was extracted. Categories of funding outcomes were not explicitly defined a priori in order to reflect the varying roles and outcomes of appraisals conducted by HTA agencies.

Where reported, information on the status of the appraisal and the date of the completion of the appraisal were noted. Where an appraisal was done, and the details of the justification supporting the outcome were available this was noted to provide insight into the considerations made and the transparency in the decision process. Where multiple appraisals were noted through the reimbursement decision-making process, the final outcome of the most recent appraisal was used to define the funding outcome, and it was acknowledged within the comments that multiple appraisals were conducted.

Results

Case study 1: Alglucosidase Alfa (Myozyme) for the treatment of Pompe Disease

Background

Pompe disease is an autosomal recessive condition where the a mutation in the gene encoding α-1,4-aglucosidase leads to a deficiency or absence of the enzyme acid-α-glucosidase (GAA) (247,248). The enzyme deficiency results in a lysosomal storage disorder where lysosomal glycogen accumulates in various organs and tissues (247). The incidence of Pompe disease varies across different ethnic groups and is estimated to range between 1 in 20,000 and 1 in 300,000 (248).

Symptoms of the condition vary by the organs affected, most commonly skeletal, cardiac, and smooth muscle are affected (247). Significant phenotypic variability has been observed among patients with Pompe disease, patients are often categorized with respect to the age of disease onset and the extent of organ involvement. These classifications; however, are quite inconsistent (247). Patients generally follow the same disease course whereby glycogen will steadily accumulate within tissues, which leads to debilitation, organ failure, and ultimately death (247). In the absence of treatment, among patients with severe form of disease, the condition can lead to death within 2 years (247).

Alglucosidase alfa is an enzyme replacement therapy that was approved in 2006 as the first treatment for a Pompe disease (249). Prior to its approval Pompe disease was treated with supportive measures and interventions such as bone marrow and heart transplantation were attempted; however, offered limited success (247). The annual treatment cost with Alglucosidase alfa is approximately $300,000 per patient per year (14).

The clinical evidence for Alglucosidase alfa suggests that the treatment is beneficial if started as soon as possible after birth (250). Among infants with Pompe disease, treatment with Alglucosidase alfa has been associated with the reversal of cardiac symptoms which has been linked to an altered natural history of the disease and prolonged survival (250,251). Limited clinical benefit has been observed among patients with late-onset Pompe disease relating primarily to improvements in walking distance while disease progression often continues (250).

This medication and illness was selected as a case study because it highlights many of the important challenges associated with the evaluation of medications for the treatment of rare conditions. Pompe is a severe disease, with a low prevalence, where there is a great

deal of heterogeneity among patients, limitations exist with regards to the levels of evidence available, and the high treatment costs.

Country specific funding outcomes for Alglucosidase Alfa at the national level

Within the 29 national funding systems included within this analysis, Alglucosidase alfa was considered for funding within eight jurisdictions (United States, Brazil, Belgium, Switzerland, Italy, Scotland, Wales, and Australia)(Table 10)(252–258). Within six jurisdictions, Alglucosidase alfa is funded for restricted benefit (Belgium, Switzerland, Italy, Scotland, Wales, Australia) (254–259). In Italy, Alglucosidase alfa is listed for restricted benefit under Class H of the formulary, where drugs are only funded in the hospital environment (256). Brazil is the only jurisdiction where the medication was appraised but not listed for benefit; the assessment indicated that consideration was given to the price, clinical evidence base, and the reimbursement status of the medication internationally(246). In the United States, Alglucosidase alfa is listed for benefit through the Medicare program(245). The rationale grounding the funding decision is not stated by any of the jurisdictions included in the analysis.

Table 10: Country specific funding outcomes for the reimbursement of Alglucosidase Alfa within national drug plans

Country	Agency involved in reimbursement decision-making	Funding program	Appraisal Status	Availability on Publicly funded drug formulary	Rationale Supporting Decision/ Recommendation Publicly Available	Comments	References
Canada*	Health Canada	Non-Insured Health Benefits Program	NR	NR	No	NA	(129)
Canada*	Correctional Service of Canada	NR	NR	NR	No	NA	(130)
Canada*	Department of National Defense (DND)	Canadian Armed Forces Drug Benefit list	NR	NR	No	NA	(131)
Canada*	Royal Canadian Mounted Police (RCMP)	NR	NR	NR	No	NA	(130)
Canada*	Veterans Affairs	Prescription Drug Program	NR	NR	No	NA	(132)
South Africa	Department of Health	Essential Drugs Programme	NR	NR	No	NA	(253)
United States	US Centers for Medicare and Medicaid Services	Medicare	Completed	Benefit	No	Listed on Medicare Part D formulary	(245)
United States	Department of Veterans Affairs	Veteran's Affairs Pharmacy Benefits Management Services; Veteran's Affairs Drug Formulary	NR	NR	No	NA	(254)
Mexico	Consejo De	Basic Formulary	NR	NR	No	NA	(255)

Country	Agency involved in reimbursement decision-making	Funding program	Appraisal Status	Availability on Publicly funded drug formulary	Rationale Supporting Decision/ Recommendation Publicly Available	Comments	References
	Salubridad General/ Ministry of Health	(for primary care) and Catalogue of Inputs (for secondary and tertiary care), Health Sector's National Formulary					
Brazil	Ministério da Saúde/ Ministry of Health	SUS Pharamceutical Services List	Completed May/2012	Not for benefit	No	• Consideration for the price, clinical evidence base, and the reimbursement status internationally were noted within the appraisal.	(246)
Argentina	Ministry of Health and Social Action (Ministerio de Salud de la Nacion)	Remediar+Redes	NR	NR	No	NA	(256)
China	Ministry of Human Resources and Social Security	National Basic Medical Insurance Drug Formulary List	NR	NR	No	NA	(257)
Japan	Ministry of Health, Labor, and Welfare	Employees Health Insurance (EHI) and National Health Insurance (for non-employees)	NR	NR	No	Formulary not publicly available online	(258)
South Korea	Ministry of Health and	Korean National Health Insurance	NR	NR	No	Formulary not publicly available online	(259)

Country	Agency involved in reimbursement decision-making	Funding program	Appraisal Status	Availability on Publicly funded drug formulary	Rationale Supporting Decision/ Recommendation Publicly Available	Comments	References
	Welfare						
Russia	Ministry of Health	Federal Drug Reimbursement Program/ Programme for Supplementary Pharmaceutical Provision [Dopolnitelnogo Lekarstvennogo Obespecheniya (DLO)]	NR	NR	No	• Formulary not publicly available online • Unclear which medications are eligible through the DLO drug fund covering treatment for 7 expensive drugs	(260)
Turkey	Social Security Institute (part of the Ministry of Labor and Social Security)	Health insurance funds	NR	NR	No	NA	(261)
Spain	Ministry of Health	The Spanish Catalogue	NR	NR	No	NA	(262)
Belgium	Ministry of Public Health and Social Affairs	National Institute for Health and Disability Insurance (INAMI/RIZIV)	Completed 01/May/2007	Restricted benefit	No	NA	(247)
Sweden	Dental and Pharmaceutical Benefits Agency-TLV	Pharmaceutical Reimbursement Scheme	NR	NR	No	NA	(263)
Switzerland	Federal Office of Public Health (FOPH)	List of Pharmaceutical Specialties (SL)	Completed 01/Nov/2011	Restricted benefit	No	NA	(248)

Country	Agency involved in reimbursement decision-making	Funding program	Appraisal Status	Availability on Publicly funded drug formulary	Rationale Supporting Decision/ Recommendation Publicly Available	Comments	References
The Netherlands	Dutch Ministry of Health	Dutch Medicine Reimbursement Registry (GVS)	NR	NR	No	NA	(264)
Germany	Federal Ministry of Health GBA-Gemeinsamer Bundesausschuss	Statutory Health Insurance (SHI)	NR	NR	No	NA	(265) (266)
France	French Ministry of Health Ministère des affairs sociales, de la santé et des droits des femmes	-	NR	NR	No	Medication was reviewed by the Haute Autorité de Santé	(267)
Italy	National Health Service (SSN)	National Pharmaceutical Formulary (Prontuario Farmaceutico Nazionale -PFN)	Completed	Restricted benefit	No	Medication is listed for reimbursement only under Class H of the drug plan (Drugs which are fully reimbursed only in hospital)	(249)
Scotland	National Health Service- Scotland	-	Completed	Restricted benefit	No	• Reimbursed on a case-by-case basis • Reviewed by the SMC. Not recommended by the SMC for funding through the NHS but may be funded under exceptional case review.	(252)

Country	Agency involved in reimbursement decision-making	Funding program	Appraisal Status	Availability on Publicly funded drug formulary	Rationale Supporting Decision/ Recommendation Publicly Available	Comments	References
England	National Health Service England	-	NR	NR	No	NR	(268)
Wales	National Health Service	-	Completed	Restricted benefit	No	• Reimbursed on a case-by-case basis in accordance with Specialized Services Policy. • The medications covered through the program must be approved by the All Wales Medicines Strategy Group (AWMSG)	(250)
Northern Ireland	Department of Health, Social Services, and Public Safety	-	NR	NR	No	NA	(269)
Australia	The Department of Health (Australia)	Pharmaceutical Benefits Scheme	Completed	Restricted benefit	No	• Not listed for benefit on the PBS • Eligible for restricted benefit through the life-saving drugs program (LSDP).	(251)

*Reimbursement decisions in Canada are made at the provincial and territorial level; funding outcomes of provincial and territorial processes in Table 12.

Evaluation outcomes for Alglucosidase alfa completed by HTA agencies

Among the 17 HTA processes identified as integral to the reimbursement decision-making processes, Alglucosidase alfa was evaluated and the outcome of the review was provided in seven jurisdictions (Canada, Quebec, Netherlands, France, Scotland, Wales, Australia) (Table 12) (174,175,270–277). The outcome of all seven HTA processes was a recommendation to list for restricted benefit (174,175,270–277). The details of the evaluation and rationale are provided by all seven HTA agencies (174,175,270–277).

In Canada, the rationale for recommendation to list for restricted benefit among patients with the infantile form was based on the clinical and economic evidence (31) The restricted benefit listing by the HTA agency in Quebec, the Institut national d'excellence en santé et en services sociaux (INESSS), indicated that the recommendation was based on consideration for the therapeutic value and economic factors as outlined by the law (271). The Institute of Health Care Quality (the Netherlands), recommended the medication for restricted benefit because it is the first medication available for the treatment of Pompe disease, the medication has been proven to have therapeutic value, and the medication is generally well tolerated by patients (272). The recommendation to list for restricted benefit in France was based on the rarity of the condition (273–275). Finally, the recommendation for restricted benefit in Australia, Scotland and Wales was based on the clinical effectiveness of the medication among patients with the infantile form of the condition (276,277).

Table 11: **Evaluation outcomes for Alglucosidase alfa completed by HTA agencies**

Jurisdiction	Agency involved in reimbursement decision-making	Appraisal Status	Outcome of evaluation	Rationale Supporting Decision/ Recommendation Publicly Available	Comments	References
Canada-Common Drug Review	Canadian Agency for Drugs and Technologies in Health	Completed 10/Oct/2006	Recommended for restricted benefit	Yes	• The review considered clinical and cost effectiveness when making recommendation. • Recommended for coverage for infantile Pompe disease- based on the onset of symptoms and the confirmed presence of cardiomyopathy before 12 months. CDR recommends that each province develop their own monitoring criteria, which includes consultation with experts in the management of lysosomal storage disorders.	(270)
Canada-Quebec	Institut national d'excellence en santé et services sociaux	Completed 12/Dec/2009	Recommended for restricted benefit	Yes	• Based on consideration for the therapeutic value and economic factors as outlined by the law. Medication is reimbursed for patients with Pompe disease who are less than 12 months of age.	(271)
Canada-Atlantic Provinces	Provincial-Nova Scotia, New Brunswick, Newfoundland and Labrador	Not appraised	NR	NA	Medication evaluated through the CDR process are not considered through the Atlantic Common Drug Review	(177)
Mexico	Center of National Health Technology (Centro Nacional de Excelencia	NR	NR	No	NA	(178)

Jurisdiction	Agency involved in reimbursement decision-making	Appraisal Status	Outcome of evaluation	Rationale Supporting Decision/ Recommendation Publicly Available	Comments	References
	Tecnologica en Salud)					
Brazil	Comissao Nacional de Incorporacaode Tecnologies (CONITEC)	NR	NR	No	NA	(278)
South Korea	Health Insurance Review Agency	NR	NR	No	NA	(279)
Spain	Instituo de Salud Carlos III	NR	NR	No	NA	(280)
Belgium	Belgian Health Care Knowledge Centre (KCE)	NR	NR	No	NA	(281)
Sweden	Swedish Council on Technology Assessment in Health care (SBU)	NR	NR	No	NA	(282)
The Netherlands	Institute of Health Care Quality (within CVZ)	Completed Nov/12	Recommended for restricted benefit	Yes	• Rationale for recommendation: this drug is the first medication to treat Pompe disease, it has been established to have therapeutic value and is generally well tolerated by patients. • Reimbursement restricted to patients with infantile Pompe disease, as there is limited evidence of effectiveness among patients with Adult-onset disease. • It is noted that the reimbursement status should be reviewed based upon the	(272)

Jurisdiction	Agency involved in reimbursement decision-making	Appraisal Status	Outcome of evaluation	Rationale Supporting Decision/ Recommendation Publicly Available	Comments	References
					availability of new information.	
Germany	Institute for Quality and Efficiency in Health Care (IQWIG)	NR	NR	No	NA	(283)
France	Haute Authorité de Santé (HAS)	Completed 16/Jun/2010	Recommended for restricted benefit	Yes	• While the public health and actual benefit of the drug was determined to be low. • The French Pompe registry indicates that there are approximately 60 patients that would be eligible for the treatment; therefore, the HAS recommended that it be listed for benefit.	(273–275)
Italy	National Agency for Regional Health care Services	NR	NR	No	NA	(284)
Scotland	Scottish Medicines Consortium	Completed 9/Feb/2007	Not recommended for benefit	Yes	• The SMC considered the medication within the context of its orphan drug policy • Assessment considered clinical and cost effectiveness, in addition to whether the drug could reverse the condition or bridge the gap to a definitive therapy. • While evidence supports the improvements among patients with the infantile form of Pompe, the effectiveness among patients on ventilator support and patients with the late onset form of the disease remains unclear.	(276)
England	National Institute for Health and Care	No appraisal completed	NR	No	NA	(285)

Jurisdiction	Agency involved in reimbursement decision-making	Appraisal Status	Outcome of evaluation	Rationale Supporting Decision/ Recommendation Publicly Available	Comments	References
	Evidence					
Wales	All Wales Medicines Strategy Group	Complete 8/Dec/2006	Recommended for restricted benefit	Yes	• Recommended to the Minister of Health and Social Services for benefit for only the infantile form of Pompe disease on the grounds that there is insufficient evidence of clinical effectiveness for the adult form of Pompe disease.	(277)
Australia	Pharmaceutical Benefits Advisory Committee (PBAC)	Complete Nov/2012	Recommended for restricted benefit	Yes	• Recommended for benefit for patients Infantile Pompe Disease • Several resubmissions have been made to PBAC for reimbursement for the adult form through the LSDP. Recent submission rejected on November 2012 on the grounds that there remains insufficient evidence to support the effectiveness of Myozyme in patients with late-onset Pompe diseases.	(174,175)

Province and territory specific funding outcomes for the reimbursement of Alglucosidase Alfa in Canada

Within the context of Canadian provincial drug reimbursement processes, the funding outcomes for Alglucosidase alfa is explicitly indicated in seven provinces (ON, QC, AB, SK, BC, NS, NB) (Table 12) (196,200,201,286–291). These seven provinces provide the medication under restricted coverage. The coverage criteria differ across provinces, in 4 provinces (QC, SK, NS, NB) it is clearly indicated that the coverage of the medication was restricted to patients with the infantile form of Pompe disease (200,201,289,290). While it is indicated that the Alglucosidase is eligible for coverage in AB and BC, the coverage criteria are not publicly available (196,291). ON is the only province where coverage is provided for both adult/late onset Pompe disease and infantile/early onset Pompe disease. Additionally, ON is the only province to clearly outline the rationale supporting the reimbursement decision (286–288). Alglucosidase alfa is funded in ON given the high fatality rate experienced by untreated patients, the high survival benefits and reduction in ventilator support reported in clinical trials, and the lack of alternative treatment options available (286–288).

Table 12: Province and territory specific funding outcomes for the reimbursement of Alglucosidase alfa in Canada

Province/ Territory	Agency involved in reimbursement decision-making	Funding program	Appraisal Status	Availability on Publicly drug formulary	Rationale Supporting Decision/ Recommendation Publicly Available	Comments	References
Ontario (ON)	Ministry of Health and Long-term Care	Ontario Drug Benefit	Completed Nov/09	Restricted benefit	Yes	• Rationale for recommendation: the high fatality rate observed among untreated patients, the reported high survival benefits and the reduction in ventilator dependence within clinical trials, and the lack of treatment alternatives. • The committee noted that it was unlikely that the medication would meet the conventional standards applied as a result of the rarity of the condition making it difficult to collect strong clinical and economic evidence • Appraisal highlighted that more long term evidence is needed on the effectiveness of the medication • A complete cost analysis was not submitted by the manufacturer, which prevented the committee from determining whether the intervention presents good value for money • Myozyme was originally reviewed for adult Pompe disease prior to the implementation of the DRDs evaluation framework and the committee recommended against reimbursement on the grounds that	(286–288)

Province/ Territory	Agency involved in reimbursement decision-making	Funding program	Appraisal Status	Availability on Publicly drug formulary	Rationale Supporting Decision/ Recommendation Publicly Available	Comments	References
						the evidence was limited and difficult to interpret	
Quebec (QC)	Quebec Ministry of Health	Public Prescription Drug Insurance Plan (RAMQ)	Completed 11/Dec/09	Restricted benefit	No	Covered on the Liste des Medicaments under exceptional drug status.	(289)
Alberta (AB)	Alberta Health	Alberta Drug Benefit	Completed Apr/09	Restricted benefit	No	• Patients with Pompe disease are eligible for drug coverage through Alberta Health- where the Alberta Rare Disease Clinical Review Panel makes funding decisions on an individual basis	(196)
Saskatchewan (SK)	Saskatchewan Ministry of Health	Drug Plan	Completed	Restricted benefit	No	• Coverage for patients with infantile Pompe disease. Monitoring and withdrawal criteria were based on CEDAC recommendation • All patients considered for reimbursement of Alglucosidase alpha must be willing to participate in the long-term evaluation of treatment efficacy and failure to comply may result in the withdrawal of financial support for the treatment.	(290)
British Columbia (BC)	British Columbia Ministry of Health Services	B.C. Pharma-care Program	Completed 14/Jun/07	Restricted benefit	No	While Myozyme is not listed for regular benefit, it is available through the EDRD program	(291)
Manitoba (MB)	Manitoba Health	Manitoba Pharma-care	NR	NR	No	NA	(292)

Province/ Territory	Agency involved in reimbursement decision-making	Funding program	Appraisal Status	Availability on Publicly drug formulary	Rationale Supporting Decision/ Recommendation Publicly Available	Comments	References
Nova Scotia (NS)	Nova Scotia Department of Health and Wellness	Nova Scotia Pharma-care	Completed	Restricted benefit	No	The drug is covered under exceptional drug status. The medication is covered for patients with infantile Pompe disease with confirmed symptoms and cardiomyopathy before the age of 12 months. Patients must agree to participate in the evaluation of the long-term efficacy of the intervention as described in the monitoring of therapies guidelines.	(200)
New Brunswick (NB)	New Brunswick Department of Health	New Brunswick Prescription Drug Program	Completed	Restricted benefit	No	Only reimbursed for patients who meet the New Brunswick Drug Plan Special Authorization Criteria.	(201)
Newfoundland and Labrador (NL)	Department of Health and Community Service	The Newfoundland and Labrador Prescription Drug Program (NLPDP)	NR	NR	No	NA	(293)
Prince Edward Island (PE)	Health PEI	PEI Pharma-care	NR	NR	No	NA	(294)
Yukon (YT)	Yukon Department of Health and Long-term care	Pharma-care	NR	NR	No	NA	(295)

Province/ Territory	Agency involved in reimbursement decision-making	Funding program	Appraisal Status	Availability on Publicly drug formulary	Rationale Supporting Decision/ Recommendation Publicly Available	Comments	References
Northwest Territories (NT)	Northwest Territories Health	Funding based on Non-Insured Health Benefits (NIHB) Formulary	NR	NR	No	NA	(296)
Nunavut (NU)	Department of Health	Funding based on NIHB Formulary	NR	NR	No	NA	(297)

Table 13: **Provincial reimbursement restrictions Alglucosidase alfa**

Province/Territory	**Reimbursement criteria**
Ontario (ON)	Adult/late onset patients must meet the following criteria: • A diagnosis confirmed using enzymology or mutation analysis, and have clinical features consistent with the adult onset of the condition • Patient is not eligible under the criteria defined for the infantile/early form in Ontario • Patient is not on chronic invasive mechanical ventilation • Eastern Cooperative Oncology Group Performance group of grade 1-3 • Patient must not have other life-threatening disease where prognosis is likely to be influenced by Enzyme Replacement Therapy [ERT] • Treatments must be provided in centers with an expertise in the treatment of Pompe disease • The maximum funded dosage is 20mg/kg body weight, administered through IV every 2 weeks Infantile/early onset patients must meet the following criteria: • A diagnosis confirmed using enzymology or mutation analysis, and have clinical features consistent with the adult onset of the condition • Eastern Cooperative Oncology Group Performance group of grade 1-3 • Patient must not have other life-threatening disease where prognosis is likely to be influenced by Enzyme Replacement Therapy [ERT] • Treatments must be provided in centers with an expertise in the treatment of Pompe disease • The maximum funded dosage is 20mg/kg body weight, administered through IV every 2 weeks
Quebec (QC)	• Funding provided only for patients with the infantile form of the condition where symptoms are observed prior to the age of 12 months • Authorization is provided for 6 months at which time it must be proven that the patients' condition has deteriorated significantly (noted through a requirement for invasive ventilator support or an increase in ventricular hypertrophy).
Alberta (AB)	Coverage criteria not specified.
Saskatchewan (SK)	• Funding provided only for patients who demonstrate symptoms and cardiomyopathy prior to 12 months of life • Severity of symptoms must be monitored and are withdrawn where the patients' condition deteriorates significantly (withdrawal criteria defined through a need for ventilator support after the initiation of ERT and the deterioration of cardiac function as defined by left ventricle hypertrophy).
British Columbia (BC)	Coverage criteria not specified.
Manitoba (MB)	N/A

Nova Scotia (NS)	• Funding provided only for patients who demonstrate symptoms and cardiomyopathy prior to 12 months of life • Authorization is provided for 6 months and continued coverage is determined on the basis of the efficacy of treatment.
New Brunswick (NB)	• Funding provided only for patients who demonstrate symptoms and cardiomyopathy prior to 12 months of life • Patients must be monitored and treatment may be withdrawn if patients fail to comply with medical assessments or where the condition deteriorates significantly (withdrawal criteria defined through a need for ventilator support after the initiation of ERT and the deterioration of cardiac function as defined by left ventricle hypertrophy).
Newfoundland and Labrador (NL)	N/A
Prince Edward Island (PE)	N/A
Yukon (YT)	N/A
Northwest Territories (NT)	N/A
Nunavut (NU)	N/A

Case study 2: Canakinumab for the treatment of Cryopyrin-Associated Periodic Syndrome

Background

Cryopyrin-Associated Periodic Syndrome is used to describe a group of rare autosomal dominant syndromes caused by a mutation in the NLRP3 gene, which encodes the protein cryopyrin (NALP3) (298–300). Recurrent inflammatory episodes are among the common symptoms associated with CAPS and these episodes are suspected to be driven by the over-production of the protein interleukin-1β (301,302).

CAPS has been classified into three different phenotypes which fall along a continuum of severity(303,304). The mildest phenotype is known as familial cold auto-inflammatory syndrome (FCAS) and typically presents with recurrent urticaria (hives), arthralgia (joint pain), and fevers following general exposure to cold(303,305). The intermediate phenotype is known as Muckle-Wells Syndrome (MWS) and the symptomology is similar to FCAS but patients may experience addition symptoms such as partial hearing loss and migraines. In contrast with FCAS, the symptoms may be triggered in the absence of an exposure (305–307). Finally, the most severe phenotype of CAPS is known as neonatal onset multisystem inflammatory disease (NOMID) which is also referred to as chronic infantile neurologic, cutaneous, articular syndrome (CINCA) has a similar clinical profile as MWS; however, patients may experience additional symptoms such as visual and cognitive impairment. Mortality among patients with NOMID is approximately 20% before adulthood(305,306).

Canakinumab is a human, monoclonal antibody that binds with circulating interleukin-1β to prevent the inflammatory episodes that occur among patients with CAPS. Although other treatments have been used in patients with CAPS, this is the first treatment specifically indicated for the treatment of patients with CAPS. Canakinumab is administered through subcutaneous injection every 6 weeks (308). For patients requiring six vials the cost it is approximated that the cost of the medication is $96,000 per patient per year(309).

The safety and efficacy of Canakinumab have been assessed using a Phase I/II dosing study and a 48-week phase III trial (310). The phase I/II trial demonstrated that within 1-day urticarial rashes disappeared, and there was complete absence of symptoms within 1 week. The remission of symptoms on average lasted 185 days (310). In the placebo controlled clinical trial of Canakinumab, where the primary outcome was the percentage of patients with disease flares, it was shown that only small differences were noted the in quality of life of patients, and no differences were observed in the patients' global assessment of symptoms in patients receiving treatment in comparison with those receiving placebo (311).

Country specific funding outcomes for Canakinumab at the national level

Within the 29 national funding systems included within this analysis, the funding outcome for Canakinumab was openly indicated for four of the processes (United States-Medicare, Brazil, Switzerland, Italy) (245,248,249,312) (Table 14). The medication is covered for benefit by in the United States under the Medicare program (245). In Brazil, the medication is not listed for benefit and this is the only jurisdiction where the rationale

supporting the funding decision is provided. The rationale for the negative listing is that the medication treats only palliative symptoms where the effectiveness has not been adequately proven with appropriate scientific quality (312). In Switzerland and in Italy, Canakinumab is covered for restricted benefit (248,249). Specifically, in Switzerland, funding is provided to patients who have a confirmed NLRP3 mutation (248). Finally, in Italy, the medication is restricted to benefit within the hospital setting (Class H of the Prontuario Farmaceutico Nazionale) (249).

Table 14: **Country specific funding outcomes for the reimbursement of Canakinumab within national drug plans**

Country	Agency involved in reimbursement decision-making	Funding program	Appraisal Status	Availability on Publicly-funded drug formulary	Rationale Supporting Decision/Recommendation Publicly Available	Comments	References
Canada*	Health Canada	Non-Insured Health Benefits Program	NR	NR	No	NA	(129)
Canada*	Correctional Service of Canada	NR	NR	NR	No	NA	(130)
Canada*	Department of National Defense (DND)	Canadian Armed Forces Drug Benefit list	NR	NR	No	NA	(131)
Canada*	Royal Canadian Mounted Police (RCMP)	NR	NR	NR	No	NA	(130)
Canada*	Veterans Affairs	Prescription Drug Program	NR	NR	No	NA	(132)
South Africa	Department of Health	Essential Drugs Programme	NR	NR	No	NA	(253)
United States	US Centers for Medicare and Medicaid Services	Medicare	NR	Benefit	No	Listed on Medicare Part D formulary	(245)
United States	Department of Veterans Affairs	Veteran's Affairs Pharmacy Benefits Management Services; Veteran's Affairs Drug Formulary	NR	NR	No	NR	(254)

Country	Agency involved in reimbursement decision-making	Funding program	Appraisal Status	Availability on Publicly-funded drug formulary	Rationale Supporting Decision/Recommendation Publicly Available	Comments	References
Mexico	Consejo De Salubridad General; Ministry of Health	Basic Formulary (for primary care) and Catalogue of Inputs (for secondary and tertiary care), Health Sector's National Formulary	NR	NR	No	NR	(255)
Brazil	Ministério da Saúde/ Ministry of Health	SUS Pharmaceutical Services List	Completed May/2012	Not for benefit	Yes	Based on CITEC (now replaced by CONITEC) decision that the drug should not be reimbursed because it treats only palliative symptoms where the effectiveness has not been adequately proven with appropriate scientific quality. Consideration for the price, clinical evidence base, and the reimbursement status internationally were noted within the appraisal.	(312)
Argentina	Ministry of Health and Social Action	Remediar+Redes	NR	NR	No	NA	(256)
China	Ministry of Human Resources and Social Security	National Basic Medical Insurance Drug Formulary List	NR	NR	No	NA	(257)
Japan	Ministry of Health, Labor, and Welfare	Employees Health Insurance (EHI) and National Health	NR	NR	No	Formulary not publicly available online	(258)

Country	Agency involved in reimbursement decision-making	Funding program	Appraisal Status	Availability on Publicly-funded drug formulary	Rationale Supporting Decision/Recommendation Publicly Available	Comments	References
		Insurance (for non-employees)					
South Korea	Ministry of Health and Welfare	Korean National Health Insurance	NR	NR	No	Formulary not publicly available online	(259)
Russia	Ministry of Health	Federal Drug Reimbursement Program - Programme for Supplementary Pharmaceutical Provision [Dopolnitelnogo Lekarstvennogo Obespecheniya (DLO)]	NR	NR	No	• Formulary not publicly available online • Unclear while medications are eligible through the DLO drug fund covering treatment for 7 expensive drugs	(260)
Turkey	Social Security Institute (part of the Ministry of Labor and Social Security)	Health insurance funds	NR	NR	No	NA	(261)
Spain	Ministry of Health	The Spanish Catalogue	NR	NR	No	NA	(262)
Belgium	Ministry of Public Health and Social Affairs	National Institute for Health and Disability Insurance (INAMI/RIZIV)	NR	NR	No	NA	(247)
Sweden	Dental and Pharmaceutical Benefits Agency- TLV	Pharmaceutical Reimbursement Scheme	NR	NR	No	NA	(263)

Country	Agency involved in reimbursement decision-making	Funding program	Appraisal Status	Availability on Publicly-funded drug formulary	Rationale Supporting Decision/Recommendation Publicly Available	Comments	References
Switzerland	Federal Office of Public Health	List of Pharmaceutical Specialties (SL)	Completed 25/Jun/10	Restricted Benefit	No	Treatment is funded exclusively for patients with a confirmed NLRP3 mutation.	(248)
The Netherlands	Ministry of Health, Welfare, and Sport	Dutch Medicine Reimbursement Registry (GVS)	NR	NR	No	NA	(264)
Germany	Federal Ministry of Health	Statutory Health Insurance (SHI)	NR	NR	No	NR	(265) (266)
France	French Ministry of Health Ministère des affairs sociales, de la santé et des droits des femmes	-	NR	NR	No	Medication reviewed by HAS	(267)
Italy	National Health Service (SSN)	National Pharmaceutical Formulary (Prontuario Farmaceutico Nazionale - PFN)	NR	Restricted Benefit	No	Medication is listed for reimbursement under Class H (Drugs which are fully reimbursed only in hospital)	(249)
Scotland	National Health Service-Scotland	-	NR	NR	No	NA	(252)
England	National Health Service England	-	NR	NR	No	NA	(268)
Wales	National Health Services	-	NR	NR	No	The manufacturer did not submit for appraisal through the AWMSG	(313)
Northern Ireland	Department of Health, Social	-	NR	NR	No	NR	(269)

Country	Agency involved in reimbursement decision-making	Funding program	Appraisal Status	Availability on Publicly-funded drug formulary	Rationale Supporting Decision/Recommendation Publicly Available	Comments	References
	Services, and Public Safety						
Australia	The Department of Health (Australia)	Pharmaceutical Benefits Scheme	NR	NR	No	NA	(251)

*Reimbursement decisions in Canada are made at the provincial and territorial level; funding outcomes of provincial and territorial processes in Table 16.

Evaluation outcomes for Alglucosidase alfa completed by HTA agencies

Among the 17 HTA processes identified as integral to the reimbursement decision-making process, the funding outcome for Canakinumab was reported by 4 HTA agencies (Canada, Netherlands, France, Scotland) (Table 15). In Wales, it was identified that Canakinumab was not appraised by the AWMSG on account that the holder of market authorization did not submit for review (314). In two of the included jurisdictions, Canakinumab was given a do not list recommendation (Canada, Scotland) (309,315,316). A negative funding recommendation was issued through the Canadian HTA process because the clinical evidence did not demonstrate an improvement in the quality of life of the patients (309). In Scotland, the SMC issued a recommendation not to list the medication for benefit because the holder of market authorization did not submit for review (315,316). Finally, two agencies issued recommendations indicating that Canakinumab should be listed for restricted benefit (France, Netherlands) (317–319). The rationale justifying the recommendation for France is that the alternative available treatment for CAPS (Anakinra) is not reimbursed (317,318). Finally, the recommendation in the Netherlands was grounded on the fact that Canakinumab has therapeutic value compared with existing treatment (Anakinra) and because given the small number of patients, it meets the cost criterion for medication reimbursed within the hospital setting (319).

Table 15: **Evaluation outcomes for Canakinumab completed by HTA agencies**

Country	Agency involved in reimbursement decision-making	Appraisal Status	Outcome of Appraisal	Rationale Supporting Decision/ Recommendation Publicly Available	Comments/Basis of the decision	References
Canada-Common Drug Review	Canadian Agency for Drugs and Technologies in Health	Completed 26/Jan/11	Do not list recommendation	Yes	• Medication was not recommended for listing on the grounds that although clinical results demonstrated a decrease in disease flares among patient, their results of clinical trials did not demonstrate an improvement in the quality of life of patients.	(309)
Canada-Quebec	Institut national d'excellence en santé et services sociaux	NR	NR	No	NR	(271)
Canada-Atlantic Provinces	Provincial-Nova Scotia, New Brunswick, Newfoundland and Labrador	NA	NR	No	Medications evaluated through the CDR process are not considered through the Atlantic Common Drug Review.	(177)
Mexico	Center of National Health Technology (Centro Nacional de Excelencia Tecnologica en Salud)	NR	NR	No	NA	(178)
Brazil	Comissao Nacional de Incorporacaode Tecnologies (CONITEC)	NR	NR	No	NA	(278)

Country	Agency involved in reimbursement decision-making	Appraisal Status	Outcome of Appraisal	Rationale Supporting Decision/ Recommendation Publicly Available	Comments/Basis of the decision	References
South Korea	Health Insurance Review Agency	NR	NR	No	NR	(279)
Spain	Instituo de Salud Carlos III	NR	NR	No	NR	(280)
Belgium	Belgian Health Care Knowledge Centre (KCE)	NR	NR	No	NR	(281)
Sweden	Swedish Council on Technology Assessment in Health care (SBU)	NR	NR	No	NR	(282)
The Netherlands	Institute of Health Care Quality (within CVZ)	Completed 09/Dec/2011	Recommended for restricted benefit	Yes	• Canakinumab has therapeutic value in comparison with Anakinra • Annually, approximately 39 patients would be eligible for treatment with Canakinumab. The cost forecast for Canakinumab meets the cost criterion and therefore was recommended for reimbursement in hospitals.	(319)
Germany	Institute for Quality and Efficiency in Health Care (IQWIG)	NR	NR	No	NA	(283)
France	Haute Authorité de Santé (HAS)	Completed 5/Feb/2010	Recommended for restricted	Yes	• While the public health benefit of the drug was determined to be low, the actual benefit to	(317,318)

Country	Agency involved in reimbursement decision-making	Appraisal Status	Outcome of Appraisal	Rationale Supporting Decision/ Recommendation Publicly Available	Comments/Basis of the decision	References
			benefit		patients is substantial. • Alternative treatment (Anakinra) is not reimbursed. • Previous appraisal (10/Feb/2010), most recent appraisal (5/Feb/2010) was to extend benefit to children over the age of 2, original appraisal assessed coverage in patients over the age of 4	
Italy	National Agency for Regional Health care Services	NR	NR	No	NA	(284)
Scotland	Scottish Medicines Consortium	Completed 10/May/2013	Not recommended for benefit	Yes	No submission filed by the holder of market authorization. Previous review with same recommendation in 08/June/2010.	(315,316)
England	National Institute for Health and Care Evidence	NR	NR	No	NA	(285)
Wales	All Wales Medicines Strategy Group	No appraisal completed	NR	NA	No submission filed by the holder of market authorization.	(314)
Australia	Pharmaceutical Benefits Advisory Committee (PBAC)	NR	NR	No	NA	(174,175)

Province and territory specific funding outcomes for the reimbursement of Canakinumab in Canada

Within the context of the Canadian drug reimbursement processes the funding outcomes within each province and territory were considered. The reimbursement status for Canakinumab was explicitly indicated for four provinces (ON, AB, SK, BC) (Table 16) (196,291,320–322). The status of the appraisal and reimbursement outcome was not stated for nine provinces and territories (QC, MB, NS, NB, NL, PE, YT, NT, NU) (292–297,323–325). Canakinumab is funded for restricted benefit in ON and BC (291,320,321). In ON, Canakinumab was reviewed using the Ontario Drug for Rare Diseases evaluation process (320,321), and funding is provided to patients who meet specified criteria as outlined by the exceptional access program. The rationale supporting the decision is not publicly available through the ministry of health and long-term care. No details on the funding restrictions are highlighted for the BC process. In Alberta and Saskatchewan, Canakinumab is not listed for benefit (196,322). None of the provinces outline the rationale to support the funding decision.

Table 16: Province and territory specific funding outcomes for the reimbursement of Canakinumab in Canada

Province/Territory	Agency involved in reimbursement decision-making	Funding program	Appraisal Status	Availability on Publicly drug formulary	Rationale Supporting Decision/ Recommendation Publicly Available	Comments	References
Ontario	Ministry of Health and Long-term Care (MOHLTC)	Ontario Drug Benefit	Completed Apr-2012	Restricted benefit	No	• Funded through the Exceptional Access Program (EAP). • Funding may be considered it patients meet criteria outlined by the MOHLTC • This drug was evaluated through the Ontario Drug for Rare Diseases (DRDs) evaluation process. • No transparency bulletin issued by the MOHLTC to highlight the rationale grounding the reimbursement decision	(320,321)
Quebec	Quebec Ministry of Health	Public Prescription Drug Insurance Plan (RAMQ)	NR	NR	No	NA	(323)
Alberta	Alberta Health	Alberta Drug Benefit	Completed 01-May-2011	Not for benefit	No	Medication is not considered through the Alberta Rare Diseases Drug Program through Alberta Health and Wellness.	(196)
Saskatchewan	Saskatchewan Ministry of Health	Drug Plan	Completed 01-Apr-2011	Not for benefit	No	NA	(322)
British Columbia	British Columbia Ministry of Health Services	B.C. Pharmacare Program	Completed 26-Jan-2011	Restricted benefit	No	Not listed for regular benefit, it is available through the EDRD program.	(291)

Province/Territory	Agency involved in reimbursement decision-making	Funding program	Appraisal Status	Availability on Publicly drug formulary	Rationale Supporting Decision/ Recommendation Publicly Available	Comments	References
Manitoba	Manitoba Health	Manitoba Pharmacare	NR	NR	No	NA	(292)
Nova Scotia	Nova Scotia Department of Health and Wellness	Nova Scotia Pharmacare	NR	NR	No	NA	(324)
New Brunswick	New Brunswick Department of Health	New Brunswick Prescription Drug Program	NR	NR	No	NA	(325)
Newfoundland and Labrador	Department of Health and Community Service	Newfoundland and Labrador Prescription Drug Program (NLPDP)	NR	NR	No	NA	(293)
Prince Edward Island	Health PEI	PEI Pharmacare	NR	NR	No	NA	(294)
Yukon	Yukon Department of Health and Long-term care	Pharmacare	NR	NR	No	NA	(295)
Northwest Territories	Northwest Territories Health	Funding based on NIHB Formulary	NR	NR	No	NA	(296)
Nunavut	Department of Health	Funding based on NIHB Formulary	NR	NR	No	NA	(297)

Table 17: Provincial reimbursement restrictions Canakinumab

Province/Territory	Reimbursement criteria
Ontario (ON)	Patients must meet the following criteria in order to be eligible for coverage: *Muckle Wells Syndrome (MWS):* • Confirmed diagnosis of MWS based on clinical symptoms AND NLRP3 mutation AND SAA levels ≥ 10mg/L AND an assessment of the patients disease activity • Initial coverage is provided to patients for a period of 1 year. *Neonatal-Onset Multisystem Inflammatory Disease (NOMID) Syndrome:* • Confirmed diagnosis of NOMID based on clinical symptoms AND NLRP3 mutation AND an assessment score of the patients disease activity • Initial coverage is provided to patients for a period of 6 months. Where no NLRP3 mutation is noted, the medication is funded on a case-by-case basis Patients who meet the following criteria will not be eligible for coverage: • Patients must not be bedridden • Patients has no other life-threatening disease • Patients with Familial Cold Auto-Inflammatory Syndrome (FCAS) are not eligible for coverage.
Quebec (QC)	NA
Alberta (AB)	NA
Saskatchewan (SK)	NA
British Columbia (BC)	Coverage criteria not specified.
Manitoba (MB)	NA
Nova Scotia (NS)	NA
New Brunswick (NB)	NA
Newfoundland and Labrador (NL)	NA
Prince Edward Island (PE)	NA
Yukon (YT)	NA
Northwest Territories (NT)	NA
Nunavut (NU)	NA

Discussion

Similarities and differences are evident between the funding outcomes of Canakinumab and Alglucosidase alfa based on the evaluation processes applied. Equally, comparisons can be made surrounding the funding outcomes across the two case study medications. Canakinumab and Alglucosidase alfa are both treatments for rare conditions, which have received regulatory approval from Health Canada for use (326,327). Pompe disease and CAPS are both genetic conditions, with multisystemic representations, with clinical presentations that can vary widely across patients diagnosed with the conditions.

Within reimbursement it is clearly indicated that Alglucosidase alfa was reviewed by 8 out the 29 processes (32%) included within this review, and Canakinumab by 4 out of the 29 processes (16%). Whether an evaluation was completed is unclear within the remaining processes. While it may be suggested that this represents a limited number of appraisals for DRDs and could possibly be ascribed to the challenges of using accepted evaluation processes, this cannot be concluded; as it cannot be assumed that an appraisal was not completed where the appraisal outcome is not reported. The numerous not reported funding outcomes may be attributed in part to the fact that reimbursement outcomes were often determined by consulting national formulary listings, which often only document positive listings. The base supporting the final funding outcome for the medications was rarely provided. This highlights the limited availability of publicly documented appraisals for medications and a lack of transparency within many reimbursement decision-making processes.

Among HTA processes, it was clearly indicated that Alglucosidase alfa was appraised within 7 of the 17 processes (41%) and Canakinumab was appraised within 4 of the 17 processes (23%). There does not appear to be a large difference in the proportion of HTA agencies that evaluated these medications in comparison with publicly funded systems at the national level. HTA processes were more transparent in the rationales grounding reimbursement recommendations and decisions. The justification for the decision was provided for all evaluation outcomes provided by HTA agencies, indicating transparency and an effort to demonstrate relevance within the decision process. This is in line with the tenets described in the described by the A4R framework (29).

Within the Canadian provinces and territories, it is distinctly indicated that Alglucosidase alfa was evaluated for reimbursement in seven provinces and Canakinumab was evaluated in four provinces. In all seven provinces (ON, QC, AB, SK, BC, NS, NB) where Alglucosidase alfa was appraised, it is listed for restricted benefit and the Canakinumab is funded under restricted benefit in both provinces (BC, ON) where it is funded (Table 17). The rationale supporting the funding decision in ON was clearly outlined in a Transparency bulletin; published by the MOHLTC in December 2009, for Alglucosidase alfa. While Canakinumab is also funded through the Exceptional Access Program and evaluated using the Ontario framework for Drugs Rare Diseases, a transparency bulletin was not published by the MOHLTC. This emphasizes efforts that have been made for reimbursement processes and their rationales to be transparent (328), there remains gaps within the most developed reimbursement decision-making framework for DRDs in Canada. No other provinces provided a rationale justifying the reimbursement decision.

Differences among funding restrictions are also observed across provinces and territories. The restricted benefit of Alglucosidase alfa to patients with the infantile/early onset form of Pompe disease may be attributable to the differential evidence of effectiveness among patients with adult/late onset form of the disease. This is likely attributed to the limited clinical benefit which has been linked with the use of Alglucosidase alfa among patients with the later on-set form of the condition in comparison with the improved outcomes associated with treatment among patients with the early on-set form of the condition (243). This cannot however be concluded with certainty as the justification for the reimbursement criteria is not publicly available.

It is also apparent that more appraisals were done for Alglucosidase alfa in comparison with Canakinumab, and generally, Alglucosidase alfa had more positive funding recommendations then Canakinumab. Negative funding outcomes maybe attributable to the limitations of the clinical evidence supporting the use of Canakinumab. Negative funding outcomes may also explain the fewer reported appraisals, as these are not likely to be listed on formularies. While there are numerous possible explanations could be proposed for the different funding outcomes and number of appraisals, it is difficult to conclude what factors drove these decisions as details of the rationales are rarely available, and even where they are available the weight given to various criteria are often unclear.

The comparison of this study with others is difficult given that few other analyses have considered funding outcomes for DRDs. This is the only known analysis that considered funding outcomes for two DRDs systematically across national level funding processes, HTA agencies, and Canadian provinces. These case studies highlight not only the heterogeneity which can arise from the application of differing funding process on funding outcomes but also how funding outcomes of two different drugs to treat rare

conditions may vary. A review of funding outcomes by Vegter et al. (2010) similarly highlighted the heterogeneity that is observed among the funding outcomes across jurisdictions (213). A survey on the funding outcomes for the medication Laronidase for the treatment of mucopolysaccharoidosis type 1 (MPS1) in Europe also highlighted heterogeneity within the funding outcomes and appraisals of the medications across the included jurisdictions (15). This analysis differs from the case study conducted by Hughes et al. (2005) as this review only considered funding outcomes publicly available.

These case studies are subject to limitations. To begin, as this review relied on publicly available information on the funding outcomes of medications, this may not have captured funding available to patients through special authorization programs where the details are not available within the public domain. Additionally, this review does not necessarily provide insight the accessibility of these medications to patients, as it is possible that patients are eligible for coverage through alternate funders such as private drug plans. Furthermore, the results of this work cannot be generalized to other medications for rare illness, as each system and medication differs on factors that may be relevant to the decision process. Future research would be helpful in identifying how different funding criteria applied within different funding frameworks can contribute to varying funding outcomes.

Conclusion

Two case studies of different DRDs in the context of processes applied for reimbursement decision-making reveal that different funding outcomes may arise through the use of differing processes and for different medications. Current processes offer limited transparency and therefore it is difficult to determine how different characteristics of the processes and medications effect the funding decision.

Chapter 5- Conclusions

Summary

Drugs for the treatment of rare conditions present a particular challenge for the allocation of health care resources, and questions remain about how best to address these challenges. This thesis studies the characteristics of DRDs within the environment of reimbursement decision-making in order to provide an understanding of possible considerations to be made within coverage decision-making processes.

In Chapter 2, a series of ethical arguments were explored to provide insight into whether a coherent justification could be developed for the application of differential funding frameworks for DRDs. Limitations were prominent within the majority of the proposed arguments to support a unique decision process; including that it is difficult to apply these arguments universally to all rare conditions given the wide variability within rare diseases, and that many of the arguments would apply similarly to both common and rare conditions. Only the differing evidence base argument may be applied as the logical basis for a specialized reimbursement process; however, further consideration should be given to whether alternate thresholds are warranted and whether evaluation criteria should vary.

In Chapter 3, a comprehensive overview of the current landscape of reimbursement decision-making for DRDs is provided. Various elements of the decision processes were explored, including the rationales applied to support a devoted framework for DRDs. The results emphasize the differences in the processes used for making drug reimbursement decisions for DRDs. Where processes considered DRDs uniquely from drugs for common conditions, similarities and differences were observed with respect to the definition of

rarity applied, the rationale used to support the specialized process, and the evaluation of the clinical and economic evidence. Each process for the evaluation of DRDs was assessed based on the tenets of the A4R framework, drawing attention to limitations in current frameworks and possible areas of improvement for future processes.

Finally, in Chapter 4, case studies of two DRDs, Alglucosidase alfa and Canakinumab, were studied to explore how reimbursement outcomes may vary through the application of different funding outcomes. Variability was noted in the funding outcomes across the two case studies, as well as, across the differing evaluation frameworks applied in decision-making. It was unclear from this analysis which factors drove the final funding outcomes.

Significance of the thesis

The purpose of this thesis was to better understand the characteristics of DRDs in the context of drugs reimbursement decision-making, and to better understand the environment in which decisions for funding DRDs are currently made. Various different criteria are traditionally applied in the assessment of health care interventions, and it is important to consider whether a differential consideration of rare conditions is warranted.

Future directions

The challenges of making drug reimbursement decisions with scarce health care resources are well established; these difficulties are particularly salient when reimbursement decisions for DRDs are considered. As more DRDs are approved, HTA agencies and decision-makers should reflect on the rationales being used to support differential processes based on the characteristics of rare conditions. Where warranted, decision-makers and HTA agencies should apply a transparent and coherent rationalization for any dedicated processes. Researchers and decision-makers should explore how and whether the criteria, and standards applied in evaluations should differ for DRDs and common conditions. This should include consideration for the processes presently applied in Canada and internationally to identify possible elements that should be reflected the in decision processes. Agencies involved in decision-making should strive to develop standardized processes that meet the tenets of fair priority setting. Finally, future research should consider how different decision-criteria drive funding outcomes for rare conditions in order to improve consistency and to inform the development of processes for the allocation of resources.

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