A Multi Criteria Approach for The Assessment of Drugs for Rare Diseases

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A thesis submitted to

The Faculty of Gradute and Postdoctoral Studies

In partial fulfillment of the requirements

For the degree of

Master of Science in

Systems Science

University of Ottawa

Canada

Abstract

Evaluating Drugs for Rare Diseases (DRDs) for the purpose of reimbursement and beyond represents a tremendous challenge for most health care priorities. A consensus is set about the irrelevance of cost effectiveness analysis to evaluate such drugs. The appeal for multi criteria decision aid models seems reasonable as the evaluation of DRDs is indeed multifaceted. However, the application of MCDA for the purpose of evaluating DRDs is yet primitive and simplistic. The present work tries to tackle the issue of evaluating DRDs from a decision maker angle by adopting an innovative robust ordinal regression MCDA method, UTADIS-GMS, that helps the decision maker discern between the DRDs based on their multi criteria value.

Acknowledgements

This work would have not seen the light without Dr. Sarah Ben Amor as supervisor. Sarah, for all your patience...for all the freedom i enjoyed in my research...for all the intercontinental collaboration...for every single word in this thesis...Thank You.

*My dear Mother..You who were waiting for this moment a very long
time..You whom i am sure i will not disappoint.. You who have always seen
my success as Your success...I dedicate this work to You.*

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Chapter 1

Introduction

1.1 General Background

Diseases characterized by a relatively small prevalence among the whole population are called rare diseases. Medicines intended to treat these diseases are known as orphan drugs. We shall call them Drugs for Rare Diseases (DRDs). DRDs are not always available and they are counted among the most expensive drugs in the world. Hence their funding is probematic

Economically speaking, patients with rare diseases are considered as 'consumers' for pharmaceutical companies. For these companies, like any lucrative organization, making monetary profit is always on top of their goals. This makes the situation more critical. But, the characteristics of drugs for rare diseases and the nature of their sponsors make their market far from

being in a perfect equilibrium: We are talking about a market where few producers are struggling to innovate products to sell them on a non-well regulated market yet to a relatively very small number of buyers. This description is true for luxury product markets. In fact, luxury products are extremely customized, nay, unique. Sellers are very few due to the high level of specialization required and buyers are very few due to the disinterestedness of the majority of the vast population in regard of these products. Unfortunately, drugs for rare diseases differ from luxury products. While luxury products show a positive price elasticity, drugs for rare diseases are characterized by a low elasticity level because they are products serving to treat needy people affected by chronic, life threatening and extremely infrequent diseases.

Usually governments as health care payers should guarantee the access to health care services to all the public equally. Nevertheless, due to budgetary constraints (scarcity of resources), they are unable to meet all the demand for health care in general and the access to drugs for rare diseases in this case in particular. To adjudicate on the dilemma of resource allocation, health care payers base their decisions in part on the effectiveness and the cost effectiveness of health care programs. However, besides their high cost, effectiveness of drugs for rare diseases is doubtful as they are lacking of sufficient reliable epidemiological data that could argue positively for their medical effectiveness. The relatively high cost of drugs for rare diseases in conjunction with the uncertainties about their level of effectiveness will disqualify them on any

resource allocation decision based on the cost effectiveness criteria.

Because rare diseasses are severe, life threatning and affects not only patients but also their caregivers, advocates of the right to access healthcare equally find discriminatory and unfair how DRDs are disqualified from any funding or reimbursement plan while the drug exisits in the market and governments susbsidized their development. Healthcare payers turn are more and more aware about the social burden of rare diseases as well as the challenges of the economical appraisal of orphan drugs. The National Institute for Health and Care Excellence (NICE), and particularly its citizens council, was asked to advise the National Health Service (NHS) , the authority regulating the health system in the United Kingdom, on whether or not the NHS should be prepared to pay premium prices for drugs to treat patients with very rare diseases. The council in its majority concluded that paying premium prices for ultra orphan drugs is justifiable. However, the council pointed out that the NHS has to adopt a different strategy for the assessment of cost effectiveness to decide funding or not expenditure on ultra orphan drugs(NICE Citizens Council, 2004). Moreover, in Canada, in 2010 the Ontario Citizen's Council prepared a report on the considerations for funding drugs for rare diseases (Ontario Citizen Council, 2010). The council was asked under what situations and/or conditions should the Ontario government (i.e. taxpayers) pay for drugs for rare diseases? The council admitted that orphan drugs cannot meet the usually employed criteria for effectiveness and efficacy. As

a consequence their funding will be denied under the current funding model for common (non-rare) drugs. The council stated that a specific framework is needed to evaluate drugs for rare diseases for funding and reimbursement purposes.

It turns out that due to the medical, economical and societal specificities of DRDs, there has been a consensus that decisions about reimbursement or funding of drugs for rare diseases should be performed out of the regular drug evaluation framework since rare diseases are relatively neither effective nor affordable compared to common drugs. Multi Criteria Decision Analysis (MCDA) could be a promising way to achieve this goal. In fact, recent studies (Sussex et al., 2013; Shire, 2012) have supported the argument of the effectiveness of MCDA techniques for the assessment of DRDs. However, MCDA techniques have been so far applied whether in an experimental environment to gauge the feasibility of such techniques or in a simplified environment (where the importance of the criteria are weakly defined). Indeed, many relevant criteria have been employed by health technology assessment agencies around the world to assess DRDs. Literature is also pregnant with potential criteria. Yet, while we know that the incremental cost effectiveness ratio constitutes the golden decision rule for informing reimbursement decisions for common drugs, we can say that for evaluating DRDs, such a rule does not exist yet. In fact, as mentioned earlier, the evaluation criteria to include are numerous and change from one context to another. But even if

we assume that the list of criteria has been well defined, the question of how these criteria have been weighted still remains unanswered. This will lead to an unfavorable situation for both the decision making process as well as the decision maker. For the latter, as the interrelation between the different criteria is not well defined, he/she will be under a high cognitive pressure judging the overall performance (How good is the drug for reimbursement?) of the drug especially when the performances on each of the criteria are not proportional. As a consequence of this attitude, the decision making process becomes less transparent as it relies majorly on the decision maker personal judgment who would be unable to explain the reason behind his/her decisions by tangible proofs. Let us for instance put the emphasis on the effectiveness of the drug. The level of uncertainty about the effectiveness of the majority of DRDs is not low. Despite the fact of having doubts about their effectiveness, some DRDs have been funded while others not. At least two reasons could explain this behavior. Either the decision maker is fixing an implicit threshold to determine the accepted level of uncertainty or merely the decision was more influenced by how the drug was evaluated on other criteria or most likely both together. This example illustrates not only the complexity of reimbursement like decisions of DRDs but also how blurred the rules underpinning such decisions are.

DRDs reimbursement decisions are of a great seriousness because they engender continuous and considerable budgetary engagement if the drug has

been granted funding or a great moral responsibility as well as potential social pressures in case of funding refusal. For this reason, we believe that resource allocation decisions for DRDs should be performed through a transparent and efficienct process that guarantees accountability, credibility and comparability of decisions.

1.2   Research Questions and Obejectives

This work tackles the following research questions :

1. What are the challenges in the assessment of drugs for rare diseases for reiumbursement and beyond decisions.?

2. How to improve the evaluation of drugs for rare diseases through multi-criteria decision making paradigm?

3. How to assist the decision making process for the evaluation of drugs for rare diseases?

The objectives of this work are :

1. Provide a thorough understanding of the drugs for rare diseases, the economical and sociatal challenges in their evaluation.

2. Achieve a better understanding of the perception of value for rare diseases.

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3. Build a decision making tool that will enhance the transparency and credibility of the evaluation of drugs for rare diseases.

1.3   Thesis Methodology

We intend to present a decision aid process for the assessment of drugs for rare diseases. The process is based on an MCDA method called UTADIS-GMS. In MCDA literature, UTADIS-GMS is classified under the class of preference disaggregation methods. Rather than choosing a decision model to adopt, these methods try to observe how the decision maker informed previous decisions and then infers the appropriate model compatible with the previous decisions. Thismodel will be used in turn to infer future decisions. This method presents many advantages. It uses a model of additive value function to represent the preferences of the decision maker which are easily interpreted. Also, from the decision maker's perspective, the method offers the possibility to test his/her actions before making the final decision. For the decision making process, the method is a robust and explicit procedure that enhances the transparency and accountability of the decision making.

The decision aid process begins by establishing a consistent family of criteria of evaluation and a list of drugs to evaluate. The evaluation consists of sorting the drugs into two groups (To receive funding: yes or no). Then, the decision maker is asked to select a set of reference drugs. On which he/she

is asked to give his/her preferences in terms of sorting into specified groups. Based on the decision maker's preference, the method will build appropriate additive value model(s). The latter will serve to evaluate new drug. The model was applied through a case study. In which, we first identify a list of 8 criteria of evaluation and define their measurement scale. Then 8 drugs were selected to form the set of reference drugs and evaluated on the different criteria. They are DRDs that were evaluated by the province of Ontario for reimbursement purposes (5 drugs were evaluated as eligible for reimbursement while 3 drugs not). We then tested the model with three new drugs. According to the results, only one drug was selected for reimbursement.

1.4 Contribution and Organization of the Thesis

This work presents three main contributions. Firstly, a deep exposition of the challenges surrounding the evaluation of DRDs. Secondly a better understanding of the perception of value for the drugs for rare diseases. Thirdly, building a decision making tool that will enhance the transparency and credibility of the evaluation of drugs for rare diseases.

We will expose the problem of reimbursement of drugs for rare diseases in Chapter 2. Chapter 3 will be reserved to talk about the MCDA methods, their previous application in evaluating drugs for rare diseases and the

UTADIS-GMS method. Chapter 4 will propose our model for the assessment of drugs for rare diseases based on an application of UTADIS-GMS for the assessment of drugs for rare diseases. Chapter 5 discusses the results and analysis. Chapter 6 constitutes a conclusion.

Chapter 2

Drugs for Rare Diseases

In this chapter we define drugs for rare diseases and explore their social and economical context through related literature. We start by defining the concept of DRDs in section 2.1. Then we present some regulatory aspects in section 2.2. In section 2.3, we discuss the main challenges in their assessment.

2.1 Definition of Drugs for Rare Diseases

A disease is "an impairment of the normal state of the living human, animal or plant body or one of its parts that interrupts or modifies the performance of the vital functions, is typically manifested by distinguishing signs and symptoms, and is a response to environmental factors (as malnutrition, industrial hazards, or climate), to specific ineffective agents (as worms, bacteria, or viruses), to inherent defects of the organism (as genetic anomalies),

or to combinations of these factors (Dictionary and Thesaurus, 2015)

Rare diseases are defined as diseases affecting a very small number of individuals in the population. In disease epidemiology, the prevalence rate of a disease is used to measure this number. Simply, the prevalence rate of a disease is the number of people affected by the disease over the whole number of the population during a fixed period of time (prevalence period) (Waning et al., 2001). However, there is no universal definition of how small this number is. In the United States (US) for example a disease is assigned the attribute rare if it is affecting no more than 200,000 individuals of the population at the same time. Japan employs a cut off number of 50,000 (Aronson, 2006). In terms of prevalence, we employ a rate of 7 cases per 10,000 population in US, 2.5 cases per 10,000 population in Japan (Lang and Wood, 1999), 5 cases per 10,000 population in the United Kingdom (UK) and Europe (NICE Citizens Council, 2004)(European Parliament and Council Regulation, 2000). The World Health Orgnaization (WHO) suggests a rate of 6.5-10:10,000 or less (Aronson, 2006). In Canada, such a prevalence threshold to classify rare diseases does not exist yet. In Ontario, however, a working prevalence rate of 1:100,000 is currently adopted (Ontario Citizen Council, 2010).

Rare diseases emanates in majority of cases from genetic disorders. 85% of rare diseases are classified as serious or life threatening (Pryde and Groft, 2014). Around 50% of them affect children (Pryde and Groft, 2014). Among them, 30% die before the age of 5 (EURODIS, 2009). Rare diseases are rare,

however they are numerous. We estimate around 7,000 different rare diseases around the world (Groft and Paz, 2010). This number is in perpetual increase as approximately 250 new diseases are described every year in medical research literature (Wastfelt et al., 2006). Rare diseases are affecting a small, perhaps neglected in number, portion of the population. However, all together, they are estimated to affect around 10% of the population of the United States as well as Europe. In terms of population affected, we count an estimated number of 30 million individuals affected by a rare disease in each of the USA and in the EU .

A drug for rare disease DRD is a medicinal product developed to treat, diagnose or prevent a specific rare disease (Franco, 2013). In literature, DRDs may be referred as orphan drugs (Wilson, 2013). According to Pryde and Groft, *"An orphan drug or orphan medicine is a formal regulatory term used to describe a drug product that has been granted orphan status by a regulatory agency. Orphan designation is reserved for medicines that will treat diseases with prevalence below the threshold set for rare diseases, and may have additional factors such as the lack of availability of alternative treatments."* (Pryde and Groft, 2014). The development of drugs for rare diseases has been very challenging. The next section will shed light on the history and development for DRD.

2.2 Development of Drugs for Rare Diseases: A Regulation Change Was a Must

In this section we present some regulatory aspects for DRDs. We raise the issue of their availability, then we introduce the American Drug Act put in place in the USA and similar regulations established in other countries to partly address this issue.

2.2.1 The Availability of DRDs

Development and production of drugs is a very lengthy and costly process (DiMasi et al., 1991). On one hand, it is a time consuming process. It starts by several years of research and development to come up with promising drug candidate substance(s). The different drug development steps consist of a series of laboratory analyses and animal experiment followed by clinical trials on patients to provide evidence about the safety and the efficacy of the treatment (Wilson, 2013). On the other hand, this process is very expensive. A single drug could reach up to 1.8 billion dollars (Paul et al., 2010) in developing expenses that would include failure tests done before reaching the desired results (DiMasi and Grabowski, 2012). For DRDs, the number of potential patients to recoup these costs from is very low. Economically speaking, for pharmaceutical companies, the market of DRDs is expected to be not profitable. Hence, developing DRDs was not a priority.

As a result, very few drugs to treat rare diseases were available on the

market. To overcome the problem of availability of DRDs, governments as health care givers started adjusting their regulations to encourage the research and development of DRDs. The United States took the initiative and introduced in 1983 the Orphan Drug Act (US Congress, 1983) to regulate the market of orphan drugs. It included a package of incentives to pharmaceuticals to enhance the availability of DRDs. The European Union as well as other countries by their turns introduced new regulations for DRDs.

2.2.2 The Orphan Drug Act

In 1983, the United States of America introduced the Orphan Drug Act US Congress (1983). This new regulation has for purpose to encourage pharmaceutical companies to produce drugs for rare diseases. After 30 years of approbation and entry into force of this act, the results are satisfactory. The following paragraphs will shed light on the development of the Orhan Drug Act and the subsequent consequences.

In the late seventies and early eighties of the last century, there was a movement of public awareness led by patient advocacy groups like the National Organization for Rare Disorders NORD (Wong-Rieger, 2013) about the fact that there are many rare diseases present among American citizens with no adequate drugs developed for yet because pharmaceutical industry was not focusing its efforts on (Wilson, 2013). In fact, it was a consensus that under the existing market conditions pharmaceutical companies were not motivated by developing such products. So, there was a reason to believe

that promising orphan drugs will not be developed until change will be made in the applicable laws to encourage and facilitate the development of drugs for rare diseases which has been perceived as a public interest.

On January 4th 1983, US President Ronald Reagan signed the Orphan Drug Act into law. The new legislation organized the sector of rare diseases and orphan drugs by defining the admissibility criteria for a drug to be labeled as "Orphan". Within the Federal Drug Administration (FDA) , the Office of Orphan Products Development (OOPD) is the authority responsible for granting such designation. A product sponsor could ask for this designation at any point of time through its development process. This designation is not a proof of effectiveness or safety and it does not imply a market approval for the product. However, it gives a privilege access to a bunch of incentives and financial benefits to the product during its development phase as well as its marketing phase eventually if approved. These benefits consist of 50% tax credit for clinical developments costs, exemption from application user fees, subsidies for conducting clinical trials and market exclusivity for 7 years. (Pryde and Groft, 2014).

After 30 years in effect, it seems that the Orphan Drug Act successfully achieved its mission. Before the act was signed, only 10 DRDs received marketing approval Pryde and Groft (2014). While, today, we register around 480 DRDs existing in the market and more than 3200 products designated as orphan Pryde and Groft (2014).

2.2.3 Similar Regulations

Similarly, the European Union introduced the regulation No 141/2000 on orphan medicinal products (European Parliament and Council Regulation, 2000). The purpose of the regulation is to lay down a community procedure for the designation of medicinal products as orphan medicinal products and to provide incentives for the research, development and placing on the market of designated orphan medicinal products. The regulation defines the criteria of orphan designation and designs the Committee for Orphan Medicinal Products (COMP) to be responsible for granting the status of "orphan" for medicinal products under request of its sponsor (Pryde and Groft, 2014). The European regulation signaled that incentives for research and development have been seen necessary to promote drugs for rare diseases. As a consequence, this text of law comes with a package of incentives for DRDs including a 10 year market exclusivity period, grants for conducting clinical trials and a protocol assistance consisting of providing scientific advice during the development phase of the product (Simoens, 2011).

The results are satisfactory. In 2014, 1331 designations of orphan medicinal products have been approved and 96 were authorized in the market that may cover more than one orphan designation European Parliament and Council Regulation (2000).

Countries like Japan, Australia, Singapore have also adopted similar regulations (Wilson, 2013). For Canada, drugs for rare diseases are accessed through the standard process of drugs approval and the emergency drug

release program (Wong-Rieger, 2013). However, being one of the rare developed countries without a special framework for rare diseases, the Canadian government announced in 2012 the intention to create a specific regulatory framework for drugs for rare diseases as well as establishing a Canadian window on ORPHANET, the online universal database on rare diseases Government of Canada (2012). Ontario though has put in place a special framework for the assessment of drugs for rare disease completely different from common drug evaluation Winquist et al. (2012). Since 2014, the framework has also been applied in the province of New Brunswick.

The American Orphan Drug Act with similar legislation established around the world could be considered as a huge step forward in treating patients with rare diseases. These regulations reflect the degree of public consciousness to provide cures for rare diseases. there is no doubt that these regulations participated immensely in making available drugs to cure or treat rare diseases or disorders. However, let us ask this question: Is a drug available on the market with efficacy and safety proved means that the drug is accessible for patients? The next section tries to provide some elements of response to this question.

2.3   Challenges in the Assessment of DRDs

Certainly the establishment of regulations to promote the development and production of drugs for rare diseases has shown very positive results in terms

of their availability. However, even though availability of the drug is a necessary condition toward its accessibility to patients, it is not yet a sufficient one. In fact, drugs for rare diseases are very expensive for patient pockets. Without a funding or reimbursement plans by public authorities or private insurers, it is practically impossible for patients to afford these drugs. However, for public authorities (or private insurers), reimbursement decisions for DRDs are very challenging. On one hand, the drug is very expensive and surrounded with a high level of uncertainty regarding its medical effectiveness. On the other hand, the drug exists most of the time without an alternative treatment to it and patients find it unfair not to receive it.

The economical and societal challenges surrounding the assessment of drugs for rare diseases are discussed in the following paragraphs.

2.3.1 Economical Challenges in the Assessment of DRDs

Drummond, Stoddart and Torrance define an economic evaluation as *"the comparative analysis of alternative courses of action in terms of both their costs and consequences"* Drummond et al. (1997). The motivation behind economic evaluation is to rationalize the allocation of resources. Rationalization is often reached by maximizing the benefit earned per unit of cost spent. In fact, economic evaluations of healthcare programs are based on the opportunity cost principle which implies that resources are to be allocated to the most cost effective programs as a way to maximize health benefit. The program cost is expressed in monetary terms while health benefit is very of-

ten measured in units of QALY (Quality Adjusted Life Years) corresponding to the expected number of years to live in perfect health. Then, the cost effectiveness of a program will be calculated as the number of QALYs divided by the total cost. However, to really reflect the opportunity cost idea, the cost effectiveness is usually interpreted relatively with regard to other programs seen as alternatives. Therefore, we refer instead to the incremental cost effectiveness ratio (ICER). ICER is interpreted as the extra unit of benefit generated by the extra dollar spent. Whether directly or indirectly, health care authorities tend to fix a cost effectiveness threshold. It reflects the maximum willingness to pay for health care. However, DRDs fail to pass this threshold (Drummond et al., 2007). This disadvantage is due to the exorbitant cost of DRDs in opposition to a relatively weak evidence about effectiveness. For instance, while the threshold is at an interval of £20,000-30,000 in the United Kingdom, Enzyme replacement therapy for Gaucher's disease exceeds a ratio of £200,000 (Connock et al., 2006). In the following, we will try to shed light on the two components of cost effectiveness ratio, namely the cost and the effectiveness to show the issues associated with each.

Why DRDs are very expensive?

Orphan drugs are amongst the most expensive drugs in the world. An article on Forbes magazine (Herper, 2010), cited 9 drugs with annual cost of more than $200,000. The high cost of orphan drugs could be explained by three factors. The first factor is the cost structure of the product itself which is

characterized by a considerable research and development cost. The second factor is the monopolistic position pharmaceutical companies enjoy in the orphan drug market. The third factor is the weakness of the regulation that permits DRD sponsors to take advantage of the incentives and encouragements.

Let us begin by understanding the cost structure of a drug. In fact, drug development process is lengthy, spreading over many years (DiMasi et al., 1991). This process is also very expensive. Developing a single approved drug could reach up to 1.8 billion dollars (2008 US dollar) (Paul et al., 2010). Orphan Drugs like regular ones are characterized by a high fixed cost of research and development (Simoens, 2011). Furthermore, the number of potential patients to recoup these costs from is very low. In consequence, pharmaceutical companies find themselves obligated to apply high prices for orphan drugs to recapture the expensive cost of research and development (Drummond et al., 2007). In fact, a European study analyzed orphan drug prices in 25 countries and found that prices for drugs for diseases with low prevalence are higher than "common" drugs. (Alcimed, 2005).

Besides the cost structure of drugs, the market of orphan drugs is not in an accepted equilibrium. We talk about a market where few producers (monopolistic situation) are struggling (highly expensive cost of research and development efforts) innovating products to sell them on a non-well regulated market yet to a relatively very small number of buyers. In this situation, the

market is not profitable for suppliers to enter it. That is, producers register a negative producer surplus (McCabe, Edlin and Round, 2010) (which is simply the difference between total revenue and total expenditure). In order to motivate any producer to enter a market, the increase of its surplus is obviously inevitable. This goal could be achieved by one of these three measures: whether by increasing the product return to becomes profitable enough (augment the price which is already high), or by enlarging a generous demand to prompt supply consequently (demand is always small since it is rare disease) or by the mediation of a third authority, the government, that judges it mandatory to spend the necessary resources in different forms of subsidies to induce the offer (McCabe, Edlin and Round, 2010). In this way, the Orphan Drug Act has been introduced in the United States in 1983. It provides federal funding of grants and contracts to perform clinical trials of orphan products, a tax credit of 50 percent of clinical testing costs and market exclusivity during seven years from the date of marketing approval. The governmental encouragements played indeed a positive role in the invention of new drugs for rare diseases and disorders. However, they did not demonstrate a similar effect on decreasing the cost of these products. Pharmaceutical companies enjoy a monopolistic position on the market. This monopolistic power does not emanate only from the originality of the product (as in most cases there is no other substitute health technology) but also from the market regulation such as the marketing exclusivity policy.

In fact, the moral of inciting these regulations was to provide a fair access to

health care to all (Cote and Keating, 2012). Pharmaceuticals however took advantage of these regulations by exploiting these incentives to apply high prices or continue to do so(Simoens, 2011). For instance, the EU regulation offers a 10 year market exclusivity with a review check at the 5th year to assess the policy. If the drug has been assessed as sufficiently profitable during the first 5 years, the privilege of market exclusivity may be withdrawn after the 6th year. It appears that this policy predicted the case where excessive profits could be generated by taking advantage of the barriers to enter placed during 10 years. However, in practice, no orphan medicinal labeled product had been penalized by withdrawing the market exclusivity status despite that proofs showing registration of excessive profits are available (Blankart et al., 2011). As an example of such practice, Blankart et al. mentioned the case of Imatinib sponsored by Novartis under the name of Gleevac in USA and Canada and Glivac in Europe (Blankart et al., 2011). As of 2014, Gleevac has been approved 8 different orphan drug designations by the FDA (FDA.org). In total, the company's net sale on Gleevac registered a total of US $ 4.7 million in the world and 2 million in USA (Novartis, 2014).

This monopolistic power allows pharmaceutical companies to apply excessive prices. On the other side, health care payers faced to the lack of knowledge of the cost structure of these products and to the immense pressure from rare disease lobbies to fund orphan drugs find themselves in a weak negotiation position (Rinaldi, 2005). Therefore, they are succumbed to pharmaceutical companies' rules.

What is wrong with the effectiveness of DRDs?

Rare diseases are still not very well understood. Our lack of knowledge resides in part in the lack of the medical evidence on the effectiveness eventual treatments for rare diseases are aiming to provide. In fact, there often exists a limited and weak clinical data at the launch time of orphan drugs on the market (Simoens, 2011). This lack of data led to the difficulty of assessing with certainty the benefit orphan drugs are supposed to provide.

To get the authorization to access the market, a medical treatment has to prove its safety, quality and efficacy(Government of Ontario, 2015). Efficacy is the measure of the performance of the treatment, that is the desired clinical outcomes (Compher, 2010), under ideal and controlled circumstances while effectiveness is the measure of the performance of the treatment under real world circumstances (Singal et al., 2014). Even though, in practice the distinction between measuring the effectiveness and the efficacy is not dichotomous. The Effectiveness in this document is employed to refer merely to the ability of the treatment to do what it intends to do in terms of medical benefit.

Medical evidence is provided by different sources. Those sources are hierarchically ranked by their degree of strength of the evidence. Randomized controlled trials (RCTs) are seen as the gold standard for the measure of medical effectiveness and classified amongst the best sources in the ranking.

RCTs, as indicated by their name, are clinical trials consisting of subdividing a group into two. One will receive the treatment, the other not. The decision of whom to receive the treatment or not is made randomly. Nevertheless, the opportunity of performing a RCT is not easily available in the case of rare diseases. Merely, a rare disease has a very low prevalence which makes it very hard to gather a number of patients enormous enough to generate statistically powerful results about the medical effectiveness of the corresponding treatment. In these cases, the reliance has been on surrogate methods (observational studies, registries, surrogate endpoints) yielding weaker evidence than RCTs (Connock et al., 2006). In the impossibility of performing controlled trials, authorities faced to the ethical duty to accept the reimbursement of a drug for a rare disease, are compelled to accept other sources of evidence. For example, it happened that the Federal Drug Agency approved a drug based on a study of only 16 patients (Hughes et al., 2005). Consequently, the quality and the certainty of the evidence remain in question. For instance, a systematic review to assess the safety and the efficacy of enzyme replacement therapy for Fabry disease (a treatment for a rare disease) (Alegra et al., 2012) reported that the response to the treatment is variable and thus not concluding across patient subgroups and the uncertainty around its effectiveness is still remaining.

The high cost of orphan drugs coupled with the lack of medical evidence regarding their long term effectiveness will lead to a disadvantageous incre-

mental cost effectiveness ratio (ICER). For instance, while the threshold is at an interval of 20,000-30,000 in the United Kingdom, enzyme replacement therapy for Gaucher's disease exceeds a ratio of 200,000 (Connock et al., 2006). Consequently, regular economical appraisal are limited in the appraisal of drugs for rare diseases.

Absence of alternative treatment

Cost effectiveness analysis could be seen as a measure of the efficiency of the public money spending. For instance, if two technologies are available as alternatives to treat the same disease or disorder, a cost effectiveness analysis would favor the technology that brings the maximum benefit with the minimum cost. In many cases, we find that DRDs are the only technology available. In this sense, a cost effectiveness analysis would compare funding the drug with the alternative of doing nothing. Consequently, we can not talk about a measure of efficiency anymore as the comparator is the passive scenario of keeping the patient to face his/her own destiny. Therefore, Hyry et al. (2014) argue that cost effectiveness can not be deployed when the choice is between treatment and no treatment.

2.3.2 Societal Challenges in The Appraisal of DRDs

Beside the economical challenges, drugs for rare diseases pose some societal challenges. For resource allocation decisions, health care payers could not neglect such factors. In the following we shall address the societal issues

surrounding the appraisal of drugs for rare diseases.

Drummond et al. (2007) argued that one of the challenges with DRDs is the inability of current economic evaluation tools used, namely the incremental cost effectiveness ratio (ICER), to reflect the societal preferences regarding the value attached to the health benefit these drugs will provide as output. In fact, ICER is supposed to reflect the society's willingness to pay for health technologies in general and drugs more specifically. We can see in Figure 2.1 that the group A of health technologies have simultaneously a relatively accepted ICER and a proportionate societal value. Group B in the figure though shows examples of health technologies that beside their low ICER, they are not assigned funding because merely society undervalue their health benefit as it is the case for man impotence treatments. DRDs are belonging to group C of health technologies. This group is characterized by a relatively high societal value although a very disadvantageous cost effectiveness level (High ICER). This statement will result in challenges in economic valuations of DRDs as we mentioned in section 2.3.1 but also suggests that society is considering values other than maximizing the health benefit. In fact, in a study of the impact of cost effectiveness analysis in reimbursement decision in Australia, George et al. (2001) found that the Pharmaceutical Benefits Advisory Committee, the agency responsible for assessing health technologies in Australia, often takes other societal considerations in assessing health technologies in parallel with cost effectiveness criterion such as the level of availability of alternative treatment, the perceived need in the

community. Without pretending exhaustivity, we shall present some of the societal considerations when allocating resources for DRDs.
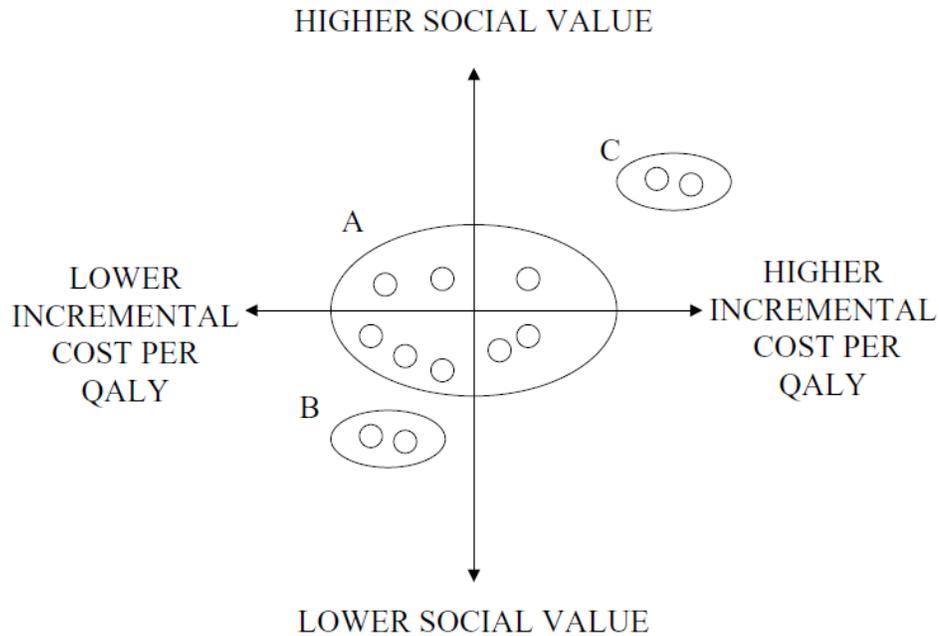
Figure 2.1: The relationship between social value and incremental cost per quality adjusted life years (QALY)
(Drummond, 2008)

Equity and fairness considerations in resource allocation for DRDs

Equity and fairness of resource allocation has been evoked for the case of DRDs by many scholars (McCabe et al., 2005; Simoens, 2011; Drummond, 2008; Hughes et al., 2005). Considering equity principles in the allocation of resources in health care aims to reduce the disparities between social groups by trying to treat similar cases similarly or the different cases differently

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(Drummond and Towse, 2014).

Actually, The Orphan Drug Act and similar regulations expressly or implicitly emanates from the principle of fairness of access for health care to all. In fact, the Orphan Drug Act was motivated by the fact that *"...orphan drugs will not be developed unless changes are made in the applicable federal laws to reduce the costs... and to provide financial incentives to develop such drugs "* which *"...is in the public interest to provide such changes and incentives for the development of orphan drugs"* (US Congress, 1983). Similarly, the European legislation stated that *'patients suffering from rare conditions should be entitled to the same quality of treatment as other patients'*. These two statements refers directly to the equity principles and indirectly recognize that such principles should be respected and consolidated in the case of rare diseases.

Moreover, empirically speaking, a study surveyed 1547 Norwegian adults to determine whether a general societal preference for prioritizing treatment of rare diseases over common ones exists. The study concluded that even though respondents did not express any intention to value rarity in itself, they are yet for a fair distribution of resources that does not neglect patients affected by rare diseases (Desser et al., 2010).

For resource allocation decision making, cost effectiveness, a utilitarian rooted approach, is with no doubt a valid measurement if we aim to maximize the health outcome for the whole society. From this perspective, some would

say that this is an equitable criterion of judgment in the way that it makes no discrimination between people on any basis. However, voices have been raised calling for the necessity to incorporate considerations for the appraisal of DRDs. Drummond and colleagues (Drummond, 2008) claimed that using the method of Person Trade Off (PTO) to elicit preferences for health status (Nord, 1995) would be a promising way to do so. In the same vein , Hughes et al. (2005) argued that an equity weighted QALYs would be interesting as well to fill the societal gap in the appraisal of DRDs. These ways are theoretically promising especially because they come also to cover the weaknesses of QALYs as a measure of the value of health outcomes. However, we shall note that they can not be seen as a specific remedy to the problem of assessing DRDs. Also, their applicability is far from being an easy task.

Instead of the utilitarian approach to assess DRDs, other points of view emerge. Generally, they consider rare diseases as a special case and so their assessment should be. We shall present some approaches that could legitimize assigning resources for DRDs. Firstly, patients with rare diseases could be seen as a burden for the society and hence their funding could be vindicated from a social solidarity perspective. In fact, society should show support to vulnerable groups of people and particularly patients with rare diseases in this case as they are facing life threatening conditions for which they would have to incur the high financial burden of the treatment themselves (Simoens, 2011). Secondly, we can approach evaluating DRDs from a human right perspective. *'Everyone has the right to a standard of living adequate*

for the health and well-being of himself and his family, including food, cloth-
ing, housing and medical care and necessary social services, and the right to
security in the event of unemployment, sickness, disability, widowhood, old
age or other lack of livelihood in circumstances beyond his control' (United
Nations, 1948). From this perspective, patients with rare diseases should not
be deprived from available treatments and therefore should not be disquali-
fied from any reimbursement plans under the pretext of cost. Thirdly, The
rule of rescue is also another perspective to consider eventually when dealing
with the dilemma of funding DRDs. The term rule of rescue was coined to
describe the imperative people feel to rescue identifiable individuals facing
avoidable death (Jonsen, 1986). The motivation that pushed society to allo-
cate massive amounts of money on search missions for lost planes or boats
when little chance of finding those who are missing would be the same that
will push them to allocate resources to treat patients with rare diseases that
cause a threat for their lives. Whether seen as a duty or sympathy the rule of
rescue is another approach to deal with these patients who most frequently
are facing life threatning diseases. (McKie and Richardson, 2003).

Beside these positions, a range of equity principles could play in favor of
allocating resources to DRDs. However, no matter what the position is , it
will frequently come in contradiction with the well known and broadly used
utilitarian approach. Hence, adopting a different approach will rise a number
of questions regarding the credibility of the health care system as from yet
an equity perspective rare diseases are not the sole diseases that need such

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special considerations (McCabe et al., 2007).

Impact of rare diseases on patients and caregivers

In a study reporting the impact of rare diseases, Shire, a bio pharmaceutical company interested in diseases, published a research that shed light on the impact of rare diseases on patients and caregivers (Shire, 2013). Physicians in both USA and UK reported that diagnostic of a patient affected by a rare disease is not straightforward and there is not only a lack of information about these diseases but also, it is difficult to coordinate with other physicians in this regard as there is not enough opportunities of networking between physicians who treat rare diseases. As a consequence, both the quality and the time of the diagnosis and the treatment will be negatively impacted. For instance, according to patients included in the survey, it takes on average 7.6 years in the USA and 5.6 years in th UK for a patient with a rare disease to receive a proper diagnosis. Before reaching the right diagnosis, patients and caregivers reported that typically 8 physicians have been visited and encountered 2 to 3 misdiagnoses. Of course, in parallel with the medical burden, this delay in diagnosis and the lack of information about rare diseases is not without other financial, mental and emotional negative consequences on both patients and caregivers. On the economical and financial side, the survey revealed that respondents have seen some financial problems especially in the USA. This conclusion was based on a certain number of indices such that credit scoring, borrowing money from family or friends to pay for expenses...

. Beyond the financial side, being affected by a rare disease is also a source of mental and emotional problems for both patients and caregivers as well. Patients in both the USA and the UK have reported that disease causes negative medical impacts too such as depression, anxiety, stress, social isolation and signs of worries based on future outlook of disease as well as on lack of information available about the disease. Similarly, caregivers' emotional and mental situation is not better as they showed similar negative impacts.

Rare diseases are certainly deteriorating patients quality of life. But, there is no doubt that in the actual situation where there is not enough information regarding these diseases and the low level of access for the treatments, impact on caregivers is not marginal and increasing. In the USA alone, we count approximately 30 millions patients affected with a rare disease. If we count the caregivers too, one conclusion could be reported: The whole impact of not reimbursing DRDs on society is not marginal.

2.3.3 The Need for a New Assessment Framework for DRDs

The economical challenges coupled with the societal and political pressures gather scholars and practitioners interested in drugs for rare diseases around a consensus that cost effectiveness analysis is very limited to address the specifications of these drugs and hence are unable to gauge their value. It

has been shown that MCDA will be a promising solution to overcome the challenges faced during the evaluation of DRDs. In fact, many notable works have raised this point. In 2012 Shire, a biopharmaceutical company, organized a round table discussion on the topic of 'The need for a holistic health technology assessment of orphan drugs: why and how?'. The final report of the round table illustrates the challenges of the actual system and argued that a MCDA framework is a pertinent solution because it provides a transparent and systematic method of evaluation that reflects stakeholder preferences on factors that go beyond simple cost effectiveness (Shire, 2012). Other authors have also supported the application of multi criteria decision analysis to health technologies for rare diseases. Simoens (2014) presented an overview of the challenges in the appraisal of orphan drugs, (already mentioned in 2.3.1) and mentioned that adopting a MCDA framework for the evaluation of DRDs seems a natural procedure as such an evaluation is indeed multi-faceted and so their evaluation should be. In addition, Hughes-Wilson et al. (2012) argument that payers are in need for a transparent reimbursement system able to lay out clearly high unmet medical needs and capable to take into consideration all the specificities of DRDs.

In the following Chapter we will cover paradigm of Multi Criteria Decision aid and more specifically, we will introduce the UTADIS GMS method and will also cover the advantages of the application of UTADIS GMS for both the process of evaluating DRDs and for a better understanding of the value

of these drugs.

Chapter 3

MCDA and UTADIS-GMS Method

In this chapter we will start by presenting the framework of Multi Criteria Decision Aid (MCDA) more specifically multi-criteria sorting problems. Then, we will review the paradigm of preference disaggregation in MCDA before focusing on the UTADIS-GMS method, its foundations, origins. Several MCDA previous works on the assessment of DRDs will also be presented along with their strengths and limitations. Some areas of improvement will be identified and used to set the contribution and added value of the present work.

3.1 Multi Criteria Decision Aid and Sorting Multi-Criteria Problems

In discrete multicriteria decision problem we consider A, a set of alternatives, G, a set of criteria and E, a set of evaluations for each alternative under each criterion. The criteria express the different and often conflicting objectives of the decision-maker. Roy has identified four main types of multicriteria decision problems (Roy, 1976):

1. **The choice problem:** The goal is to select a single best option or reduce the group of options to a subset of equivalent or incomparable 'good' options.

2. **The sorting problem:** Options are sorted into predefined groups, called categories. The aim is to then regroup the options with similar behaviours or characteristics for descriptive, organizational or predictive reasons.

3. **The ranking problem:** Options are ordered from best to worst by means of scores or pairwise comparisons, etc. The order can be partial if incomparable options are considered, or complete (see AppendixA for more information on preference relations and preference structures).

4. **The description problem:** The goal is to describe options and their consequences. This is usually done in the first step to understand the characteristics of the decision problem.

In what follows, we will be focusing on sorting problems. As mentioned above, a multi criteria sorting problem is present when the decision maker tries to assign alternatives into predefined ordered categories reflecting their overall judgment by the decision maker. Alternatives represent the different objects of the ranking. Sometimes we refer to them as actions, options, programs...
. Criteria represent all the pertinent elements of comparison between the different alternatives. Depending on the context, we may refer to criterion by point of view, attribute (Roy, 2005).

All that being said, let us present some notation :

- $A = \{a_1, a_2, ..., a_i, ..., a_m\}$ with $i \in I = \{1, 2, 3, \cdots, i, \cdots, m\}$ the set of alternatives.

- $G = \{g_1, g_2, ..., g_j, ..., g_n\}$ with $j \in J = \{1, 2, 3, \cdots, j, \cdots, n\}$ is the set or family of criteria.

- $C = \{C_1, C_2, ..., C_h, ..., C_p\}$ with $h \in H = \{1, 2, 3, \cdots, h, \cdots, p\}$ p predefined and ordered classes where $C_{h+1} >> C_h$ ($>>$ is a complete preorder on the set of classes).

Following this nomenclature, we have $g_j(a)$ the evaluation of alternative a on criterion j. We assume that the greater the value of $g_j(a)$ the better the performance of a on criterion i. Hence, $\forall a, a' \in A$, if $g_j(a) \geq g_j(a')$, then a is at least as good as a' with reference to i and we note $a \succsim_j a'$. Therefore, based on the different criterion evaluations, we can set the overall comparison between a and a' :

- If $\forall j \in J \, a \succsim_j a'$ and $\exists j \in J \, : a \succ_j a'$, we say that a **dominates** a'

- If $\forall j \in J \, a' \succsim_j a$ and $\exists j \in J \, : a' \succ_j a$, we say that a **is dominated by** a'

- If $\forall j \in J \, : a \succsim_j a'$ and $a' \succsim_j a$, we say that a and a' are **similar**.

- If no dominance or indifference is possible, we say that a and a' are **incomparable**.

Decision making is pretty straightforward in case of absolute dominance or indifference. The set of alternatives is explicitly ordered and the decision maker is aware of the overall performance of the alternative. However, in incompatibility situations, the decision making is much more complicated. Unfortunately, this case is the most frequent one in real life problems where one alternative dominates another on a number of criteria but is dominated on other ones (Belton and Stewart, 2002; Vincke, 1992)

MCDA models come to propose a way of how to aggregate the local evaluations on the different criteria to come up with an overall evaluation of the different alternatives and then be a solid basis for judgment between the different actions. Let $M = (A, G, E)$ be the MCDA model where E being

the evaluation matrix as shown below.

$$
E =
\begin{array}{c}
\\
a_1 \\
a_2 \\
\vdots \\
a_m
\end{array}
\begin{array}{cccccc}
1 & 2 & \cdots & j & \cdots & n \\
\left(\begin{array}{cccccc}
g_1(a_1) & g_2(a_1) & \cdots & g_j(a_1) & \cdots & g_n(a_1) \\
g_1(a_2) & g_2(a_2) & \cdots & g_j(a_2) & \cdots & g_n(a_2) \\
\vdots & \vdots & \ddots & \ddots & \vdots & \vdots \\
g_1(a_m) & g_2(a_m) & \cdots & g_j(a_m) & \cdots & g_n(a_m)
\end{array}\right)
\end{array}
$$

Different MCDA aggregation models have been proposed in the literature. We can differentiate two big families of models. The first, the outranking methods, sometimes referred to as the European school ones, consists mainly in performing pairwise comparison of the different alternatives. ELECTRE (Roy, 1968; Figueira et al., 2010), PROMETHEE (Brans and Mareschal, 2005; Brans, 1982) families of methods represent the famous methods under this class. The second school of thought, also referred to as the American school consists of elaborating an aggregating score for each alternative based on local scores acheived on each criterion. AHP (Saaty, 1986, 2005), MAC-BETH (Bana e Costa et al., 2005; Bana e Costa and Vansnick, 1997), MAUT (Dyer, 2005; Keeney and Raiffa, 1976) are among the major methods considered in this category. In particular, Multi Attribute Utility Theory (MAUT) assigns a value on each criterion to represent the marginal utility of alternatives on this criterion. The value assigned to express the overall marginal utility is calculated as the aggregation of the different marginal utilities.

Let U be the overall evaluation of a.

$$U = U(g(a)) = U(g_1(a), g_2(a), ..., g_n(a)) \qquad (3.1)$$

The aggregation may take the additive form. Additive models are easy to perform and very straightforward to apply and to explain. This makes these models widely used in many decision making contexts. Despite their widespread use, these models are lacking of rigorosity especially concerning the empirical validity of their major assumptions. In fact, these models are primarily based on Von Newman and Morgenstern expected utility theory EUT (Von Neumann and Morgenstern, 1947). It states that an object is preferred to another if its expected utility is greater. EUT is based mainly on the following assumptions: completeness, transitivity, independence and continuity. However, empirical studies have shown some violations of these assumptions. For instance, we cite the paradox of Allais (Allais, 1953) and the paradox of Ellsberg (Ellsberg, 1961) concerning the independence axiom and the paradox of Luce (Luce, 1956) in what concerns the transitivity axiom. Moreover, additive models present a technical issue consisting of determining the weights assigned to each criterion. Weights assignment is done weather randomly by decision analysts or provided as is by decision maker as an approximation of the importance of the criteria of evaluation (Greco, Mousseau and Słowiński, 2010). It is obvious that different criteria weighting systems would lead to different decisions. Hence, the task of weighting is of a crucial

importance that yet remains one of the big challenges of the MAUT methods.

UTADIS-GMS is an MCDA method that brings a solution to the weighting problem within the MAUT models for sorting problems. It tries to generate a set of additive utility functions to represent the preference of the decision maker. The method could be categorized under the preference disaggregation methods. In fact, the preference disaggregation paradigm rethinks the decision making process to bypass the problem parameterizing in regular aggregation MCDA methods (weights, thresholds,...)(Jacquet-Lagrèze and Siskos, 2001).

In the following, we introduce the preference disaggregation principle and we expose the UTADIS-GMS method and its advantages.

3.2   The UTADIS-GMS Method

UTADIS-GMS is an MCDA method based on the preference disaggregation philosophy. It utilizes the paradigm of ordinal regression to infer decision making from a given information provided by the decision maker concerning his/her preferences. From this perspective, the method could be seen as a generalization of the UTA method (Siskos et al., 2005; Jacquet-Lagreze and Siskos, 1982). In the following we will first start by evoking the framework of preference disaggregagtion paradigm. Then, we will introduce the UTADIS-

GMS method, its foundations and computational procedures and advantages.

3.2.1 Preference Disaggregation Procedure

Preference disaggregation paradigm aims to assess a decision model(s) from a preference structure provided by the decision maker (Jacquet-Lagrèze and Siskos, 2001). In the aggregation paradigm, the preference aggregation model is known a priori while the global preference is unknown. While in preference disaggregation paradigm, we refer to given global preferences to assess the preference model. In this sense, it appears that the information (tradeoff weights, discrimination threshold, aspiration levels,...) needed to build the global aggregation models is *indirectly* elicited in contrast with the preference aggregation models where the decision maker *directly* determines these pieces of information (Greco et al., 2008).

The general philosophy of the preference disaggregation models considers that the decision maker is more comfortable making the decision rather than explaining how this decision has been made (Greco et al., 2008). Hence, the determination of the preference aggregation model parameters results in a random assignment from the decision analyst or a simple guess from the decision maker as an approximation of these parameters. To avoid this cognitive burden, preference disaggregation philosophy, as shown in Figure.3.1, tries to infer the aggregation model(s) in accordance with previous preference structures rather than narrowing the process of decision making to only one model.
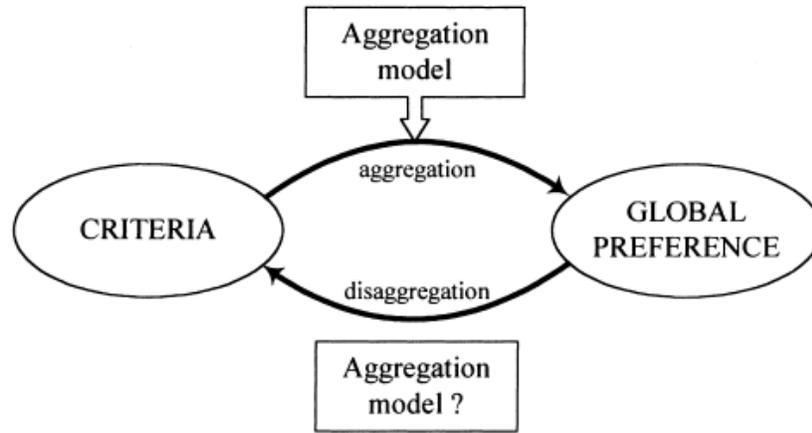
Figure 3.1: The aggregation and disaggregation paradigms in MCDA

To infer the preference model, we rely on the DM's preference information. That is, we try to find a set of actions on which the decision maker is able to perform a robust preference structure (i.e true and independent from any chosen preference aggregation model) (Jacquet-Lagrèze and Siskos, 2001). We refer to this set of actions as a reference set noted A^*.

The development of disaggregation methods began in 1978, with the UTA method (Jacquet-Lagrèze and Siskos, 1978) in cahiers du LAMSADE. Since, we have been seeing emerging a number of methods and applications emanating from the principle of preference disaggregation. Without claiming exhaustivity, we can cite under the umbrella of the *disaggregation-aggregation* approach the following methods: Measuring Attractiveness by a Categorical Based Evaluation Technique MACBETH(Bana e Costa et al., 2005;

Bana e Costa and Vansnick, 1997), Dominance based Rough Set approach DRSA(Greco et al., 2005, 1998) and UTA-like methods which UTADIS-GMS is one of them. The next section will shed light on the UTADIS-GMS method.

3.2.2   UTADIS-GMS Method

UTADIS-GMS is a multi-criteria method adopting the preference disaggregation principle. It was first introduced by Greco, Mousseau and Slowinsky in 2009 (Greco, Mousseau and Słowiński, 2010) for the purpose of sorting a finite set of alternatives evaluated on multiple criteria.

UTADIS-GMS method consists of eliciting the preference information of the decision maker on a set of reference alternatives (Figueira et al., 2009; Greco et al., 2008) and tries to exploit it to infer the decision in terms of class assignments. The preference information provided is composed of a sorting into a set of predefined categories. Then, this information will serve to build a set of additive value functions *compatible* with the provided preference information. The paradigm of ordinal regression is underpinning the transfer of knowledge from the preference information into an additive value model (Greco, Słowiński, Figueira and Mousseau, 2010). The output of the method will be in terms of *necessary* and *possible* preference relations(Greco et al., 2008). A necessary preference relation between a and a' indicates the certitude of the existence as well as the nature of a preference relation between the two alternatives. While a possible preference relation, as its name mentions, indicates possibility of the existence and the uncertainty of the nature

of the preference relation between the two alternatives in question.

3.2.3 UTADIS-GMS Computational Procedures

Briefly, let us remind the following notations :

- $A = \{a_1, a_2, ...a_i, ..., a_m\}$ the set of m finite alternatives.

- $A^R \subseteq A$ the set of reference alternatives.

- $G = \{g_1, g_2, ..., g_j, ..., g_n\}$ with $j \in J = \{1, 2, 3, \cdots, j, \cdots, n\}$ is the set or family of criteria.

- $C_1, C_2, ..., C_p$ p pre-defined and ordered classes, where $C_{h+1} >> C_h$ ($>>$ is a complete order on the set of classes), $h = 1, .., p-1$.

- $X_j = x_j \in \mathbb{R}$ a set of all different evaluations on g_j, $\quad j \in G$.

- $x_j^0, x_j^1, ..., x_j^{m_j}$ ordered values of $X_j, x_j^k < x_j^{k+1}, k = 0, 1, ..., m_j - 1, m_j \leqslant m$.

- U is an additive value function used to represent the DM's preferences: $U(a) = \sum_{j=1}^{n} u_j(g_j(a))$ where u_j are the marginal value functions defined by $u_j(x_j^k)$ such that:
$u_j(x_j^k) \leq u_j(x_j^{k+1}), k = 0, 1, ..., m_j - 1, j \in G$.

- For normalization purpose, we shall set $U \in [0, 1]$ $\quad \forall a \in A$:
$u_j(x_j^0) = 0, \forall j \in G$ and $\sum_{j=1}^{n} u_j(x_j^{m_j}) = 1$.

The preference information provided by the decision maker

To infer the additive value decision model, the preference information provided by the decision maker (DM) is in the form of an assignment of all alternatives from the reference set to a possible class (es). That is $\forall a^* \in A^*$, the DM defines a desired assignment $a^* \rightarrow [C_{L^{DM}(a^*)}, C_{R^{DM}(a^*)}]$. It is an interval of contiguous classes $C_{L^{DM}}(a^*), C_{L^{DM}}(a^*) + 1, ..., C_{R^{DM}}(a^*)$. L^{DM} represents respectively the order of the class that the decision maker considers as the minimum class to assign the alternative a^* to. Similarly R^{DM} is the order of the maximum class.

Setting the set of linear constraints

Once the preference information is before hand, we shall utilize it in order to build up our additive value model. In fact, a value function is compatible if $\forall a^*, b^* \in A^*, L^{DM}(a^*) > R^{DM}(a^*) \Rightarrow U(a^*) > U(b^*)$. In order to preserve this preference relation, a compatible function U should obey to the following constraint:

$$Max\ \epsilon \qquad s.t. \begin{cases} U(a) \geq U(b) + \epsilon \iff L^{DM}(a) \geq R^{DM}(b) \quad \forall a,b \in A^* \\[2mm] u_j(x_j^{*k}) - u_j(x_j^{*k-1}) \geq 0, \quad j = 1,...,n; k = 2,...,m^*(A^*) \\[2mm] u_j(x_j^{*1}) \geq 0, \ u_j(x_j^{m(A^*)}) \geq u_j(x_j^{m_j}), \quad j = 1,...,n \\[2mm] u_j(x_j^0) = 0, \quad j = 1,...,n. \\[2mm] \sum_{j=1}^n u_j(x_j\ m_j) = 1. \end{cases}$$

Let ϵ^* be the solution for this problem. If $\epsilon^* \leq 0$, then $\mathscr{U}_{A^*} = \emptyset$. In this case, the preference information provided is not able to provide any decision model. In this case, we recommend to the decision maker to revise his/her preference information. When $\epsilon^* > 0$, we are sure that $\mathscr{U}_{A^*}$ contains at least one additive value function U that restores the decision maker preference information given. In this case, we can generalize the use of U to the rest of the alternatives on A by saying $\forall a, b \in A$:

- if $U(a) \geq U(b)$ then $L^{DM}(a) \geq R^{DM}(b)$

- if $U(a) < U(b)$ then $L^{DM}(b) \geq R^{DM}(a)$

However, $\mathscr{U}_{A^*}$ may contain more than one value function U. In this case, we may have a function that sorts a, b differently than another function. To deal with this issue, we introduce the following preference relations:

- **A necessary preference relation** $\succsim^N$**:** if $U(a) \geq U(b)$, $\forall\, U \in \mathscr{U}_{A^*}$

- **A possible preference relation $\succsim^P$:** if $\exists$ at least one value function $U \in \mathscr{U}_{A^*}$ such that $U(a) \geq U(b)$

Therefore using the UTADIS-GMS, $\forall a, b \in A$, we will end up with the following preference relations $(a \succsim^N b$ or $b \succsim^P a)$.

Similarly, using the necessary and possible preference relations, we can define the following relations :

- **Minimum possible class :**

$$L_P^U(a) = Max\bigg\{\{1\} \cup \big\{L^{DM}(a^*) : a \succsim^P a^* \, , a^* \in A^*\big\}\bigg\}$$

.

- **Minimum necessary class :**

$$L_N^U(a) = Max\bigg\{\{1\} \cup \big\{L^{DM}(a^*) : a \succsim^N a^* \, , a^* \in A^*\big\}\bigg\}$$

.

- **Maximum possible class :**

$$R_P^U(a) = Min\bigg\{\{p\} \cup \big\{R^{DM}(a^*) : a \succsim^P a^* \, , a^* \in A^*\big\}\bigg\}$$

.

- **Maximum necessary class :**

$$R_P^U(a) = Min\left\{ \{p\} \cup \left\{ R^{DM}(a^*) : a \succsim^N a^* \, , a^* \in A^* \right\} \right\}$$

.

3.2.4 Previous application of the Method

UTADIS-GMS is a variant of the UTA family of models. UTA methods refer to the philosophy of assessing a set of value or utility functions,assuming the axiomatic basis of Multi Attribute Utility Theory and adopting the preference disaggregation principle. UTA methodology uses linear programming techniques in order to optimally infer additive value/utility functions, so that these functions areas consistent as possible with the global decision-makers preferences (inferenceprinciple). Siskos et al. (2005). UTA and UTA like methods have shown their validity and efficiency in addressing real world decision making problems in a variety of fields like finance, marketing or human resource management Siskos et al. (2005).

3.2.5 Advantages of the Method

UTADIS-GMS as a preference disaggregation approach presents the following advantages for decision making :

- The notion of necessary preference relation seems respecting the robustness concerns (Roy, 1998): The necessary ranking is static and

independent of any additive value function used. This will guarantee stable elements of decision making regardless of the model to use (Greco, Mousseau and Słowiński, 2010).

- The interactivity of the method with the decision maker: The master piece of the method consists of the preference information provided by the decision maker on the set of reference actions. A simple observation of the mechanism of the method allows us to note that the decision maker is able at any time during the process of decision making to interact by enriching (or impoverishing) the preference information provided by whether extending (restricting) the set of reference actions(Figueira et al., 2009).

- The method is based on the ordinal regression paradigm evoked in UTA method, however it extends UTA method. In fact, it scans the set of all additive value functions while UTA considers only piecewise functions. (Greco et al., 2008).

3.3   Previous MCDA Works To Assess DRDs

It has been shown that MCDA will be a promising solution to overcome the challenges faced during the evaluation of DRDs. In fact, many notable works have raised this point. In 2012, Shire, a biopharmaceutical company, organized a round table discussion on the topic of 'The need for a holistic health

technology assessment of orphan drugs: why and how ?'. The final report of the round table illustrates the challenges of the actual system and argued that a MCDA framework is a pertinent solution because it provides a transparent and systematic method of evaluation that reflects stakeholder preferences on factors that go beyond simple cost effectiveness (Shire, 2012). Other authors have also supported the application of multi criteria decision analysis to health technologies for rare diseases. Simoens presented an overview of the challenges in the appraisal of orphan drugs,(already mentioned in 2.3.1) and mentioned that adopting a MCDA framework for the evaluation of DRDs seems a natural procedure as such an evaluation is indeed multifaceted and so their evaluation should be (Simoens, 2014). In addition,Hughes-Wilson et al. argument that payers are in need for a transparent reimbursement system able to lay out clearly high unmet medical needs and capable to take into consideration all the specificities of DRDs (Hughes-Wilson et al., 2012).

MCDA models have been proposed to assess the value of DRDs. For instance, in an article entitled 'A pilot Study of Multi Criteria Decision Analysis for valuing orphan medicines', Sussex et al. proposed to establish and apply a framework of weighted attributes to value DRDs with the aim to provide an explicit understanding of trade offs for decisions on their ability for funding (Sussex et al., 2013). Criteria of evaluation were selected from a literature review of health technology assessment for DRDs and interviews with clinical experts, economists and representatives from rare disease patient groups.

A number of eight attributes were kept while each was evaluated on a 7 point numerical scale. Then, an additive model was used for aggregation. Two different weighting schemes were presented. The first was according to a panel of experts while the second included patient group representatives. The study showed that the two groups don't share the same system of preferences because they weighted evaluation criteria differenty. The work of Sussex et al. showed the applicability of MCDA method to assess the drugs for rare diseases and was a trigger for other research investigations onto that question. In fact, the work was original in presenting a new method (not a classical cost effectiveness) to evaluate DRDs. Indeed it answered some relevant questions. The first question was in fact whether or not the application of MCDA methods for assessing DRDs is possible or not. The answer to that question was a of course Yes. Another question was how to select the criteria of evaluation. The work selected it through both literature review and experts point of view.

A number of other attempts followed using MCDA models to better evalute the DRDs. Schey and Connolly (2014) also conducted a study in which they applied an MCDA model to assess DRDs. They assessed the performance of 6 different drugs based on an aggregate model including 9 criteria. The criteria were evaluated on a 3 point numerical scale. Here their main work consisted merely on putting on application the evaluation of DRDs through MCDA using a set of attributes already existing in the literature. Also they investigate the relationship between the performance

of drugs (based on the MCDA aggreagate score) and the associated annual cost. This latter was found exisiting and positive. More interestingly, they assessed the model with different criteria weighting systems. However, they did not mention why they did so. Our guess is that the process of weighting criteria is crutial as it influences the output of the evaluation MCDA model. However, questions of how to weight the criteria of evaluation and why has not been covered in their research.

Similar studies have followed . For instance,(Fedyaeva et al., 2014; Trip et al., 2014). They were in the same vein. That is, they were provided solid proofs that the application of MCDA methods is indeed possible and plausible.

Also, in practice, since 2013, NICE the British agency responsible for evaluating health technologies has been adopting a mutli criteria framework for the assessment of DRDs. The model includes the following criteria: nature of the condition, impact of the new technology, cost to the National Health Service and Personal Social Services, value for money, impact of the health technology beyond direct health benefits and the impact of the technology on the delivery of the specialized service.

3.4 MCDA: The Empty Space in The Assessment of DRDs

It is true that so far there has been an agreement on the inability of the actual assessment system of DRDs for reimbursement decisions and beyond. It is true that a MCDA paradigm is seen as a promising solution to address the different challenges posed by DRDs. We shall note however that the use of MCDA in the assessment of DRDs is yet to be developed as some issues are yet to be investigated. In the following, we raise some of them.

3.4.1 The choice of the MCDA model

The research in this area dates back to the sixtees of the last century and ever since there has been a wide range of MCDA models. The application of MCDA for the assessment of DRDs is yet relying exclusively on the classical additive aggregation models. These models are widely used in application areas, however it represents a certain number of limits as mentioned earlier in this Chapter (Section 3.1). Other models could be undertaken for the purpose of evalutation of DRDs. For instance, Analytic Hierarchy Process models, or the Outranking models. To our knowledge, so far a serious application of MCDA for DRDs outside the framework of additive utility models does not exist.

Even if the community of health economics decided for a reason or an-

other to stick with the utility based models, which could by the way represent a numerous advantages such as the possiblity of inter program comparison, we shall not mention that there are some questions that need to be answered to improve the quality of the decision of evaluating DRDs. Here we present some of those issues:

Firstly, the issue of choosing evaluation criteria. While there has been a consensus on using QALYs as a measure of value in cost effectiveness analysis despite the availability of other measurement systems, in MCDA, it is not yet the case. Indeed, the value of the drug is supposed to be reflected by the different criteria of evaluation. Webuild a consistent and exhaustive family of criteria of evaluation. Each criterion provides a clear idea about one aspect different from others reflected by other criteria. All criteria together form jointly an exhaustive system of valuation. However, the absence of a consensus about the criteria of evaluation will lead to incomparability and unaccountability problems as each evaluation system may result in a different evaluation. Hence, we may lose the power of comparability between different systems of evaluation. To our knowledge, such a consensus on the list of evaluation criteria to retain is not reached yet. A possible explanation could result on the specificities of each country or agency compared to others.

Secondly, the issue of deciding on the importance of the criteria in an evaluation system. Here, the risk is to lose the credibility and transparency

of the evaluation system. In fact, weighting criteria reflects the degree of importance assigned to one criterion compared to others. All things being equal, the more weight for that criterion, the more its power to influence the decision. We can say therefore that the weighting system is also, in addition with the selection of criteria, a direct way to valuate DRDs. The problem of weighting criteria could be seen from two angles: On whom lies the responsibility of weighting the criteria? And how?

For the first question, the system of DRDs reimbursement involves different stakeholders. Patients and care givers (usually lobbied in form of patient advocacy groups), governments and payers (usually represented by evaluation and reimbursement agencies), pharmaceutical and biotechnological companies (as sponsors of the drug) and general society opinion. Each stakeholder has his/her own position that is not most likely in accordance with other stakeholder's position. As for patient and carers, since they are the direct and foremost beneficiaries of the drug, their evaluation will favor the medical benefit of the drug, the rarity of the disease and neglect or at least value less the cost related to it or the lack of effectiveness evidence and omit therefore the risks associated with it. As for the sponsor, because it is the manufacturer of the product, it will favor the innovative side of the drug an eventual improve in quality of life the most and would value less other aspects such as related risks. Opinion from general public are indeed important as we should bear in mind that it is public money that we are trying to rationalize its spending. However, we may risk having a typical

general person without a precise knowledge about the specificities of DRDs to ask his/her preferences. For instance, in (Sussex et al., 2013), a group of experts and another of patient representatives were asked to weight a selected list of evaluation criteria. The patient representative group valued greater the quality of daily lives of patients and their carers than the group of experts did. The value of the drug is likely perceived differently for each of those mentioned positions. Therefore, the criteria weighting system will be different from a perspective to another.

The second question is how the stakeholder defines clearly his/her or her preferences in terms of weights. MCDA models applied so far in the appraisal of DRDs are mostly additive value methods. They ask the stakeholder to express his/her opinion on the importance of criteria in terms of scoring coefficients or percentages. However, in front of an already made decision model, the stakeholder usually finds cognitively very hard to translate his/her perception of the importance of criteria in terms of weights. He/She finds it easier to perform decisions rather than explaining them orally or following a logical sense. This consitutes another obstacle through a clear valuation of DRDs.

3.5 The Added Value of The Present Work

This work proposes a decison making tool that assists in the process of DRDs assessment for reimbursement purposes. It focuses on the issue of criteria

weighting because it represents a great risk of loosing the credibility of the evaluation system as different weighting systems will likely result in different decisions as output. This work also aims to value DRDs for reimbursement decisions. It is the reason why it sticks with valuing DRDs from a payer position considering it the natural choice for the study purpose. We also assume that the decision makers have the sufficient knowledge about the drug, budgetary limits, the political pressure and the societal impact of an eventual decision on all the other stakeholders.

This work fills some blanks in the empty space of applying MCDA in the assessment of DRDs. Eventhough, the present work will not directly tackle the choice of criteria, it will go deep with the issue of weighting them. As we noted that the process of identfying the weighting system is closely related to the process of valuation of DRDs, the present work gives answer to the two questions of on whom lies the responsibility of valuing DRDs (implicitly who weight the criteria? and how?). Indeed, for the first question, we had to select from a pool of 4 answers : patients and caregivers, pharmaceutical and biotechnological companies, the general public opinion or the government bodies and payers. The present work chose to stick with the latter, government bodies and payers (the decision maker). Valuing DRDs from this perspective is considered a natural choice. As the decision maker had a larger perspective to look at the problem that includes all the others. She has before hand the sufficient knowledge and understanding about the drug,

the budgetary limits and a deep understanding of the political pressures and societal impacts of an eventual decision on all the other stakeholers. As for the second question of how the decision maker defines clearly his or her preferences in terms of weights. This work condiders that MCDA models applied so far in the appraisal of DRDs are mostly additive value methods. They ask the stakeholder to express his/her opinion on the importance of criteria in terms of scoring coefficients or percentages. However, in front of an already made decision model, the stakeholder usually finds cognitively very hard to translate his/her perception of the importance of criteria in terms of weight. He/She finds it easier to perform decisions rather than explaining them orally or following a logical sense. It is this philosophy that had been adopted for this work. in other words, instead of exlaining decisions, we let the decision maker make them and then, we go back to understand them.

This work takes into consideration the limits identified previously in the application of multicriteria decision making techniques for the evaluation of drugs for rare diseases. It aims at providing a practical and reliable tool for decision makers when faced to make complex decisions about funding or not such drugs. Also, implicitly, this work helps in understanding the value accorded to the benefits of drugs for rare diseases.

First, let us talk about the practicality and relibality of the application of this work for the decision making process. In fact, the UTADIS GMS method is more a declarative method rather than a procedural one. That is, the decision maker is asked what actions to do rather than how to do

it. It is the method's responsibility to describe how the decision has been made, all in a mathematically rigorous way. This is a very big advantage. On one hand, for the decision maker, such a method will free her/him from all the cognitive burden associated with the process of decisison making (for instance: how to determine the importance of criteria.) and also it provides him/her with the opportunity to test the model mutlitple times by increasing each time the set of reference actions (alternatives). On the other hand, for the decision process, the method will guarantee a high level of reliability. Also, we shall note that the method builds up a utility model and implicilty identifies its parameters. That being said, the decision making process is easily traceble. In other words, the method not only provides us with the output of the decision problem but also it gives an explanation for it.

Second, this work helps understanding the values decision makers associated with the benefit of the drugs for rare diseases beyond their economic one. In fact, as the method identifies the parameters of the model namely the wheights of criteria, these latter are representative of the importance of each criterion of evaluation. Therefore, it is a numerical representation of the different facets of value. The higher the weight, the higher the perception of decision maker of that aspect of value.

To sum up, this chaper emphasised the benefits of applying MCDA techniques to cover the issue of evaluating DRDs. It presented some the actual MCDA attempts to cover this issue and then identified the limits and the possible imporvements. Some of the possible improvements had been adapted

by the present work namely the issue of weighting the criteria. By working on this issue, the work will provide two main axis of improvement namely provide a practical and reliable decision making framework for the evaluation of drugs for rare diseases and also help understanding the facets of value drugs for rare diseases may present in addition to their value for money. In the following chapter, we present an application of the UTADIS GMS method for the evaluation of drugs for rare diseases.

Chapter 4

Assessment of DRDs

In this chapter we will present our model for the evaluation of DRDs. The operation consists of evaluating a set of DRDs using UTADIS-GMS. The output will be in terms of two sorted sets of DRDs. The first set is the set of funded drugs. Consequently, the second set will be the set of unfunded drugs. In Section 4.2 we will define the family of evaluation criteria, in Section 4.3, we will describe the set of reference drugs used to infer the preferences of the decision maker. Section 4.4 summarizes the evaluations and presents the evaluation matrix and Section 4.5 presents the decision maker preferences while Section 4.6 presents the drugs to evaluate by the model.

4.1 The Decision Aid Making Process

Here, we explain in detail how the decision aid making process for evaluating drugs for rare diseases is performed through the UTADIS-GMS method. Figure 4.1 illustrates the different steps the decision maker goes through.

As shown in Figure 4.1, the process comprises 4 different steps. First, is setting the MCDA sorting problem framework. Second is collecting data as input for the UTADIS-GMS method. Third is checking the consistency of the results. Fourth is the interpretation of the output result.

In the first step, all the work consists of setting the stage for the decision aid proces. In fact, here we collect the information required to set up the decision model. Namely, establishing the list of criteria and their measurment scale. Also, identifying the list of alternatives (the drugs for rare diseases).

The second step consists of eliciting the information from the decision maker. It consists firstly of elaborating the evaluation matrix. This latter contains the evaluation of all alternatives on regard of each corresponding criteria. Secondly, comes setting the reference set of alternatives. Then, the assignment of those altenatives into their possible classes. Since, in this case, we only identified two classes, all the reference drugs are assigned to either ones (or possibly both in case the decision maker is unable to arbitrate).

The third step checks if the decision maker's preferences coupled with the evaluation matrix makes sense or not. In other words, we check the existence of at least one additive value function that represents the coherence

of the decision maker preference with the evaluation matrix. Since, the evaluation matrix is a given piece of information, in case of inconsistency, the decision maker is asked to review his or her preferences on the reference set of alternatives.

Once the problem is consistent, the model moves to assess the rest of the alternatives (those not included in the reference set). The major output of the method is a sorting of the alternatives (drugs). The model provides us also with other results that could be relevant for the decision maker. More details are discussed in 5.1.4. The result of the method are then interpreted by the decision maker. The purpose is to assess if the information provided by the model is sufficient and coherent to perform decision upon. If the decision maker is not satisfied with the results, he/she can go back and reevaluate her preferences or enlarging the set of reference alternatives.

4.2 Building The Family of Evaluation Criteria

Adopting a decision maker perspective will not guarantee a sound decision making process unless a clear understanding of the presumed value of the candidate drug is well defined. Cost effectiveness is a decision rule that represents the value for money in a unidimensional measurement. For DRDs, such a rule does not apply as most DRDs are very expensive and do not show a reciprocal level of effectiveness. Reimbursement of DRDs is yet a matter
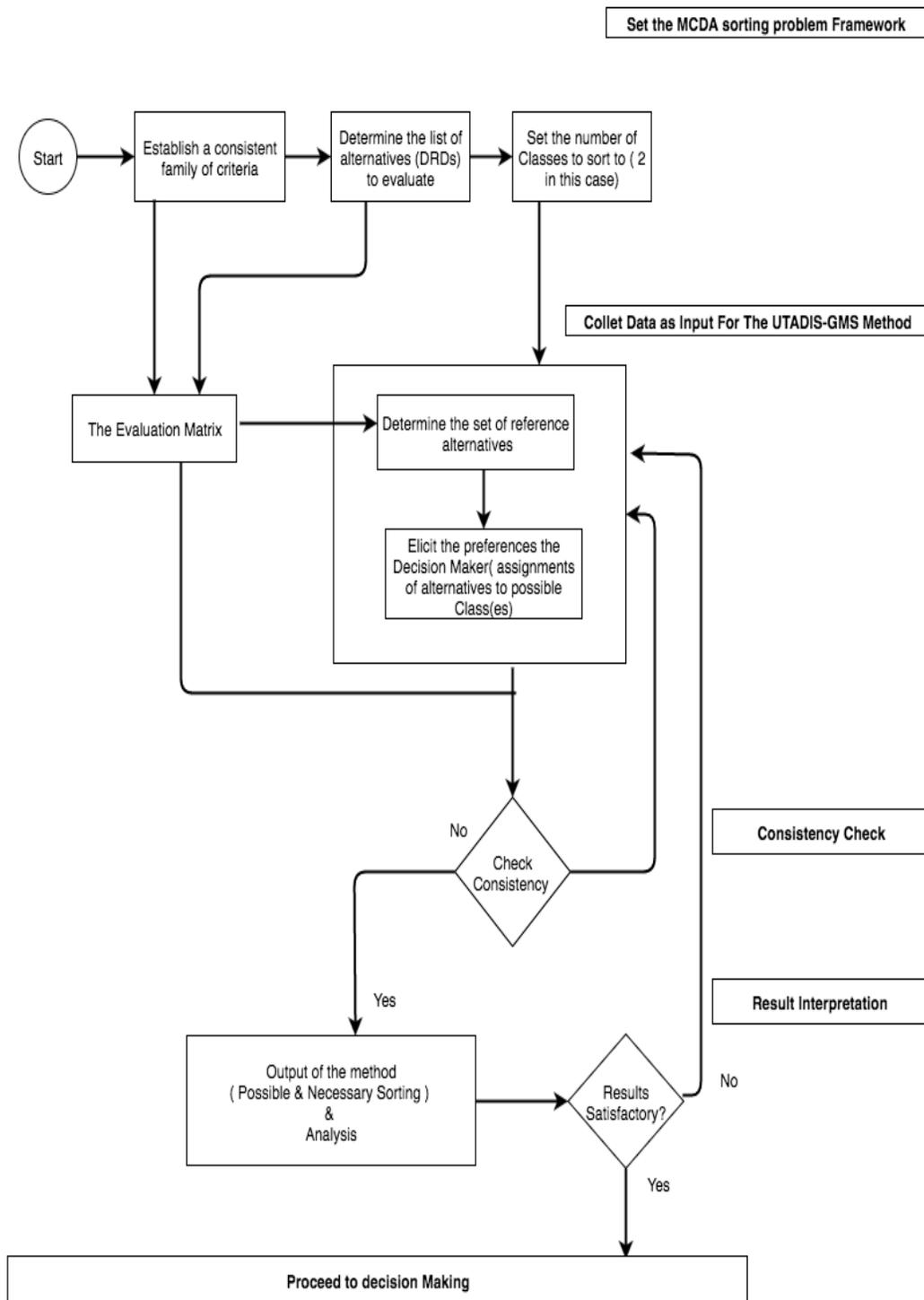
Figure 4.1: The Decision Aid Making Process for DRDs using UTADIS-GMS method

of resource allocation. However, their funding will be very hard if any cost minimization aspect is to be considered exclusively. Instead, reimbursement is to be granted to drugs that show the highest value but not value for money exclusively. In other words, a candidate drug will be seen assigned funding as long as it shows proofs of acceptable value with no regard to cost. However, it will be denied funding if it has been found that the cost of the product doesn't reflect its value. So, now it turns out to be a matter of value as mentioned by (McCabe, Stafinski and Menon, 2010). A value system is the responsible mechanism of defining what is good and what is bad or what is desirable and what is less desirable. For evaluating DRDs, we retain the value system in accordance to the following items inspired from literature (Hughes-Wilson et al., 2012) :

- Technology innovation and originality: This illustrates the degree of technology being used during the development phase and the effort undertook during the research phase. In parallel, the drug is valued relatively with other substances existing on the market, if there is any.

- The characteristics of the disease: The candidate drug is valued according to the disease it intends to treat. The severity of the disease and its life threating degree will be accounted among other factors to increase the value of the treatment.

- Effectiveness: This illustrates the extent to which the candidate treatment is able to influence the natural history of the disease. That is the

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impact of the drug on both degrees of morbidity and mortality.

Hughes-Wilson et al. (2012) exposed these different elements of value in terms of a number of criteria. The work of (Hughes-Wilson et al., 2012) recognizes the specificities of DRDs and their extremely high cost. But they have also reported some behaviors in the actual systems of rare diseases that would benefit the pharmaceutical companies and indirectly will likely inflate their cost and therefore reflect an erroneous value. As cited by the authors these behaviors are: Multiple indications for the same drug (or substance), marketing a drug under a rare label and then under a common status and vice versa, gaining orphan marketing authorization of an existing therapy, the existence of other treatments for the same condition. As a correction for these behaviors and to pursue the purpose of developing a system that is not only adapted to the specificities of DRDs but also one that provides clear and transparent guidance in the decision making process. The authors have retained the following criteria that we will adopt in our turns in the present work:

- **Rarity of the disease:** Rarity in itself is not sufficient enough to explain DRDs value. However, the rarer the disease, the more complex its evaluation will be. In fact, a positive correlation between the rarity of the disease and the cost behind its research and development had been shown (Simoens, 2011). Also, rarity impacts negatively by increasing the complexity of performing clinical trials when smaller number of pa-

tients is present that are usually geographically widely spread. Rarity as well has a direct impact on the drug price as the rarer the targeted population, the higher would be the cut ratio of the total cost.

- **Level of research undertaken**: The level of research undertaken before getting the product to the market varies from a product to another. A company that has invested time and money in intensive research and development phase would be favored in this regard.

- **Level of uncertainty**: Uncertainty is generally surrounding the medical effectiveness of the DRDs. Coupled with their extremely high prices, reimbursement agencies would be extremely careful about funding these drugs as the associated risk is very high. Proofs of medical evidence that supports the effectiveness of the drug are hard to find due to the nature of the disease and in the lucky scenario, finding them will generate extra cost. These elements include clinical trials (randomized or not), the use or not of an active comparator, the size of the patient population studied and the level of statistical significance in the treatment effect.

- **Follow up measures**: Yet, this item could be sometimes a determinant of the high cost of drug. As even after receiving a market authorization, a drug could be required for follow up measures especially if it is surrounded with high uncertainty level. These measures could vary in size, duration, complexity, objective, and of course cost.

- **Disease severity**: The more severe is the disease the more harmful the impact on society will be especially on patients and their carers. This societal burden is illustrated by parameters such as hospitalizations, symptomatic care, disability, work absenteeism just to name a few.

- **Available alternatives as opposed to unmet medical need**: A treatment is more valued societally, ethically and morally with the absence of any other alternative. However, being the first treatment in the market would likely generate in contrast other inherent costs related to majorly to disease awareness campaigns.

- **Level of impact on condition/ disease modification**: A drug is supposed to modify the course of progression of a disease. In best case scenario, the drug use will result in a complete cure. The impact of a drug on a condition manifests also in other forms varying considerable changes on mortality to moderate impact on morbidity. Obviously, the better is the modification the more valuable the drug will be.

- **Use in unique indication or not**: Drugs which receive several indications would increase their odds of yielding higher revenue. In addition, for single indication drugs to continue surviving on the market, a direct or indirect form of governmental incentive or subsidy is often required as the case for DRDs.

We shall mention though that one criterion from the study of (Hughes-Wilson et al., 2012), namely manufacturing complexity, has been omitted in

the following one due to the difficulty encountered to find the appropriate measurement of the different drugs on that criterion.

4.2.1 Building the Scale of Measure for the Different Criteria

All the criteria are evaluated on a 3 point ordinal scale. On an ascending order, they are: lower, medium & higher as described in Table 4.1. The different measurement systems for each criterion are also explained as follows.

- **Rarity:** is measured on a three point ordinal scale as indicated in Table 4.2. the differentiation is based on the prevalence ratio of the disease. The lower the ratio is, the higher the ranking will be. We adopt the threshold ratio of $1 : 2,000$ to classify a disease as a rare disease. Hence, if the ratio is in the range of $[1 : 2000; 1 : 20.000]$ it will be assigned the attribute lower. Medium and Higher attributes will be assigned to ratios of $[1 : 20.000; 1 : 200,000]$ and $1 : 200,000$ and less respectively.

- **Level of research undertaken:** As showed in Table 4.3, this level is measured on a 3 point ordinal scale to reflect the degree of research cost undertaken by the company. The criterion is intended to reflect drug sponsor research effort to understand the disease and the related

Table 4.1: **Criteria for evaluation of drugs for rare diseases and corresponding measurement**

Criteria	Price Differential		
	Lower	Medium	Higher
Rarity	1:2,000 - 1:20,000	1:20,000 - 1:200,000	Less than 1:200,000
Level of research undertaken	Literature review	Building on previous existing knowledge	Blue-sky: starting research & development program in an unknown area
Level of uncertainty of effectiveness	Immature, but promising data	Appropriate surrogate end-points	Robust clinical end-points
Follow Up Measures (Additional benefits and associated costs)	Moderate to none	Designed to answer specific, defined, delineated question	Safety and efficacy studies + size and duration of study
Disease Severity	Morbidity	Mortality / severe invalidity in adulthood	Mortality / severe invalidity as infant
Available Alternatives (Unmet medical need)	Alternatives with similar characteristics	Alternatives but offering strong innovation to the disease treatment	No alternative
Level of impact on condition/disease modification	Low	Medium	Strong
Use in Unique Condition	Existing orphan or non-orphan indications for the same molecule	Potential for multiple indications	Unique indication no other use possible

Table 4.2: Rarity (by prevalence rate)

Lower	Medium	Higher
$[1:2,000:1:20,000]$	$[1:20,000:1:200,000]$	$\geq 1:200,00$

drug. Measuring the research effort is somewhat complex. Therefore, we shall direct our focus to the number and quality of clinical trials the drug sponsor had performed with the purpose to understand the health outcomes of the drug. We shall attribute "Lower" to any research effort limited to basic literature review in order to get the market authorization without registering any relevant clinical trial in relation to the drug and the disease in question. This could be the case of an already existing drug on the market that wishes to benefit from any advantages from being labeled as a DRD. The attribute "Medium" is assigned to DRDs where only one clinical trial had been performed. The attribute "Higher" will be assigned to extensive research where we registered the presence of at least two documented clinical trials to assign such attribute.

Table 4.3: Level of research undertaken (by number of clinical trials)

Lower	Medium	Higher
Literature Review (No clinical trial)	Only 1 clinical trial registred	At least 2 clinical trials

- **Level of uncertainty of effectiveness:** Assessing the value of the effectiveness of DRDs is a big challenge. Table 4.4 describes the mea-

surement of this item. We shall refer to a three point ordinal scale to measure it. In this study, we refer to two parameters for measuring the level of effectiveness: Primarily, the quality of clinical trials and secondarily, literature review. For clinical trials, first distinguishing element to take into account, is the nature of study. A RCT with a large enough number of enrolled patients is naturally better evaluator of the quality of effectiveness than other clinical trials such as observational ones. The second distinguishing element to pay attention to is the clinical endpoints measured. Primarily endpoints are those for which the study is powered and subjects are randomized. However, for some cases, mainly in DRDs, measuring primarily endpoints is not feasible. Hence, reference to surrogate endpoints is seen as an alternative to measure the effectiveness of the drug. However, such measurement will deteriorate the quality of effectiveness. Other parameters could impact the level of effectiveness such as the size of the population, the level of statistical significance of the treatment effect (Hughes-Wilson et al., 2012). For this reason, we shall refer, on the second plan, to literature review for the assessment of the level of uncertainty of effectiveness. All that being said, we assign the attribute "Higher" for DRDs that reported RCT that measured clearly robust primary clinical trials. The attribute "Medium " will be assigned to DRDS that reported RCT but measured only appropriate surrogate end-points or for lack of data, we shall refer to scholar positions that support the quality of effectiveness.

The attribute "Lower" will be assigned to DRDs that did not report any RCT or for which literature review support weak level of effectiveness.

Table 4.4: Level of uncertainty of effectiveness (by Quality of clinical trials, outcome measurement and/or Literature review)

Lower	Medium	Higher
•No RCT •RCT with low statistical evidence about effectiveness level •Literature review (Not enough data supporting effectiveness level)	•RCT (Surrogate end points) •Literature Review (acceptable but not strong evidence of effectiveness)	•RCT (Primarily end points) •Literature review (Solid evidence supporting strong effectiveness)

- **Follow up measures:** is measured on a three point ordinal scale as described in Table 4.5. The attribute "Higher" will be assigned to DRDs that show proof of elaborated clinical trials after being authorized on the market. The attribute "Lower" is assigned for drugs that did not show any proof of that kind. However, we could face the case where a tiny effort is performed and this will be assigned the attribute "Medium". It is the case for instance of drugs sponsor who did not performed clinical trials for effectiveness or safety purposes after market authorization but nevertheless showed proof of further research or follow up of any other kind.

Table 4.5: Follow up measures

Lower	Medium	Higher
No proof of further research undertaken after market authorization	Proof of research undertaken outside the framework of clinical trials.	At least one clinical trial performed for efficacy/safety measurement.

- **Disease severity:** is also measured on a 3 point ordinal scale as shown in Table 4.6. The attribute "Lower" is assigned to diseases that effect negatively the morbidity with no evidence of impact of mortality . The attribute "Medium" is assigned to diseases that impact negatively morbidity but also becomes life threatening in adulthood. The attribute "Higher" is assigned to diseases that impact negatively morbidity but also becomes life threatening since infant-hood.

Table 4.6: Disease severity

Lower	Medium	Higher
•Morbidity/Quality of Life	•Morbidity/Quality of Life •Life threat during adulthood.	•Morbidity/Quality of Life •Life threat during infant hood.

- **Available alternatives/unmet medical need:** is measured on a three point ordinal scale from lower to higher as shown in Table 4.7.

The attribute "Lower" is assigned to DRDs for which other alternatives with at least similar characteristics (effectiveness, innovation) exists. The attribute "Medium" is assigned to DRDs for which other alternatives with lower characteristics exists. The attribute "Higher" is assigned to DRDs that do not have any substitute alternative.

Table 4.7: Available alternatives(unmet medical need)

Lower	Medium	Higher
Alternative with similar or higher (technological/effectiveness) characteristics	Alternative with lower characteristics	No available alternative.

- **Level of impact on condition/ disease modification:** is also measured on a three point ordinal scale as shown in Table 4.8. The attribute "Higher" is assigned to DRDs that completely cure or definitely stops the disease prognosis. The attribute "Medium" is assigned to DRDs that show a strong positive impact on the patient quality of life, morbidity and mortality, able to stabilize the disease without the ability to stopping its prognosis though. The attribute "Lower" is assigned to DRDs that show poor impact on mortality, quality of life and are unable even to stabilize the disease progression. The elements of classification are mainly based on data found on literature and scholar positions.

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Table 4.8: Level of impact on condition

Lower	Medium	Higher
●Poor impact on quality of life ●unable stabilize the disease progression	●improve quality of Life ●Stabilize the disease.	●Cure/Stop the disease ●Establish normal quality of life/life expectancy

- **Use in unique indication:** is also measured on a three point ordinal scale as shown in Table 4.9 where the attribute "Higher" is assigned to DRDs that don't have any other actual or promising indications (even off label) to treat other conditions. The attribute "Medium" is assigned to DRDs that are actually indicated only for the disease in question but show potential for multiple indications. The attribute "Lower" is assigned to DRDs that are indicated to existing other diseases.

Table 4.9: Use in unique indication

Lower	Medium	Higher
Other indication exist	No other indication exists but promising indications would exist	No actual or promising indications (even Off-Label)

4.3 Selecting the Set of Reference Drugs and the Decision Maker Preferences

Drugs for rare diseases account for thousands. However, in this study, we needed not only a set of DRDs but also funding decisions made by decision makers to use as a reference set. To do so, we had two options. First option was to select any set of DRDs and then present to decision maker to perform the decisions. For lack of resources, such an option was impracticle for the case of this study. An alternative option was to work reversely, that is instead of proceeeding by selecting the DRDs and then ask for evalution from decision maker, we tried to find a set of DRDs that has been evaluated already to use as our reference set.

Indeed, this work opted for the alternative solution. The set of alternatives employed in the study has been selected from the evaluation of DRDs for funding made in Ontario between March 2008 and February 2013 (Winquist et al., 2014). Threfore, we will have the reference set of alternatives but also the decision maker preferences regarding the sorting of the set of drugs. We shall note though that in this case, the preferences of the decision maker are not primarily based on this model (criteria of evaluation).

This list includes the following drugs (and the corresponding indication): Idursulfase (Hunter Syndrome), Alglucosidase (Adult & Infant onset Pompe Disease), Miglustat (Niemann Pick, Type C), Laronidase (MPSI), Galsulfase (MPSVI), Voronistat (Cutaneous T-Cell Lymphoma), Canakinumab

(Cryopyrin-associated periodic syndrome), Eculizumab (Paraxysmal nocturnal Hemoglobinuria).

Evaluating Matrix

The study retained 8 drugs to form the reference set of drugs for rare diseases and 8 criteria of evaluation. On each criterion, the evaluation of DRDs has been based on literature review. For the criterion "rarity of the disease", since the decision making was for the case of the province of Ontario, we tried to collect the data regarding the prevalence rate in Ontario. Such a task though was very hard since the data were not always available majorly because of the rarity of the disease. In such a case, we tempted to find the best prevalence rate to represent the rarity of the disease. Hence, we tried to find it on the national level, US level and then on the international level. A similar approach has been adpoted for the evaluation on all criteria.

The evaluation of the different drugs on each of the criteria will be presented in the following :

Idursulfase

Idursulfase is a treatment used for Hunter Syndrome. The treatment is an enzyme replacement therapy. It uses man made or genetically engineered enzymes to replace missing or defective enzymes and ease the disease symptoms. In the following , we shall present the evaluation of Idursulfase for Hunter Syndrome on the different criteria.

1. Rarity: Hunter syndrome affects a calculated estimate of approximately

1 in 155,000 live male births, and affects an estimated 30 to 40 people in Canada (Shire, 2015). Based on the previous statistics, we shall assign the attribute **"Medium"**.

2. Level of research conducted: The drug sponsor performed 3 different RCT. As a consequence, we shall evaluate the level of research undertaken as "Higher" (ClinicalTrials.gov, 2015*j*).

3. Level of uncertainty of effectiveness: Market authorization of Idursulfase for Hunter Syndrome was based on three different randomized clinical trials (ClinicalTrials.gov, 2015*j*). Meanwhile, Only surrogate end points were considered to measure the efficacy of the drug. Consequently, we shall assign the attribute "Medium " for the level of uncertainty of effectiveness.

4. Follow up measures: After market authorization of the drug, the sponsor company has been performing other clinical trials for better assessment of Idursulfase for Hunter Syndrome (ClinicalTrials.gov, 2015*j*). As a result, we shall attribute "Higher" on this criterion.

5. Disease Severity : "MPS II (Hunter syndrome) is a severe progressive multisystemic disorder that has the potential to cause disease in most body systems and is usually fatal in the second or third decade of life. (Da Silva et al., 2011). This data supports that the drug should be assigned the attribute "Medium".

6. Available alternatives/ unmet medical need : no other alternative is available (National MPS Society, 2015a). We shall assign "Higher" on this criterion.

7. Level of impact on condition/ disease modification: Clinical trials support strong evidence about ameliorating functional capacity which may lead to a better quality of life. However, there is no evidence suppporting ameliorating outcomes as improvement in growth/ cardiac function/ quality of life/ mortality. Also, there is no evidence that the treatment will reduce mortality rates, simply it will slower the progression of the disease (Coyle et al., 2013). Thus, we conclude that the treatment shows positive considerable impact on the condition because it helps alleviating disease burden and inhibit the development of the disease without stopping it completely. Hence, we shall evaluate the impact as "Medium".

8. Use in unique indication or not :There is no evidence showing that the treatment is or would be used to treat other conditions. The attribute "Higher" will be assigned on this criterion (Shire, 2015).

Alglucosidase

1. Rarity: Incidence : We estimate the incidence rate to be around 1:40,000 (National Insitute of Neurological..., 2015). Therefore, we shall attribute "Medium" on this criterion.

2. Level of research undertaken: 2 RCT have been performed to provide evidence of the product in order to get market authorization (Genzyme, 2015a). Therefore, we shall assign "Higher" as an evaluation for this attribute.

3. Level of uncertainty of effectiveness: Surrogate endpoints were used to measure the efficacy of the treatment. The treatment showed significant improvement . Meanwhile, high levels of uncertainty still remain about survival and progression rates and quality of life in the long-run (Castro-Jaramillo, 2012). We conclude that "Medium" will be the attribute to assign on this criterion.

4. Follow up measures : We register at least one clinical trial performed after market authorization of the treatment (Genzyme, 2015a). Hence, we attribute "Higher" on this measure.

5. Disease severity : The disease is very severe and presents a high mortality rate for infants (Genzyme, 2015b). We attribute "Higher" on this measure.

6. Available alternatives/unmet medical need: Alglucosidase is actually the only available alternative present to treat Pompe disease (National Insitute of Neurological..., 2015). Therefore we attribute "Higher" on this criterion.

7. Level of impact on condition/disease modification : The treatment does

not cure the disease. However, it increases significantly life expectancy for infantile patients (Kanters et al., 2014). Therefore, we shall attribute "Medium " on this criterion.

8. Use in unique indication or not : Alglocusidase is not prescribed for other indications. Also, there is no proof supporting any promising indication even off label in the near future (FDA, 2015a). Then, we shall attribute "Higher" on this criterion.

Miglustat

1. Rarity : The prevalence of NPC has been estimated at 1:150,000 in Western Europe (Patterson, 2000). Then, we shall attribute "Medium" on this criterion.

2. Level of research undertaken : 3 RCT had been performed that concluded the research undertaken (Actelion, 2015).Accordingly, we shall attribute "Higher " on this criterion.

3. Level of uncertainty of effectiveness: Appropriate surrogate points were used in the different RCT performed. Meanwhile, the therapeutic effects of Miglustat in stabilizing or slowing disease progression have been confirmed in other reports in the clinical experience setting (Lyseng-Williamson, 2014). We shall conclude then that "Medium" is the attribute to assign on this criterion.

4. Follow up measures : We did not register any clincial trial to follow up the effect of treatment on the disease. We shall attribute "Lower " on this criterion.

5. Disease severity : The lifespan of the patients varies between a few days until over 60 years of age, although a majority of cases die between 10 and 25 years of age (Vanier, 2010). This supports the high degree of severity of the disease. Even though data are scattered, we will retain that the disease presents a high risk of mortality during infant hood. Hence, we shall attribute "Higher" on this criterion.

6. Available alternatives/unmet medical need: Miglustat is so far the only available treatment for NPC (National Nieamann-pick ..., 2015). Accordingly, we shall attribute the "Higher" on this criterion.

7. Level of impact on condition/disease modification : Miglustat improves or stabilizes several clinically relevant markers of NPC. This is the first agent studied in NPC for which there is both animal and clinical data supporting a disease modifying benefit (Patterson et al., 2007) also, in their evaluation of the efficacy of Miglustat in Niemann-Pick C disease, the authors concluded the effect of the treatment in slowing the progression of neurological symptoms in NPC patients (Ginocchio et al., 2013). Miglustat delayed the expected deterioration of neurological functions in patients with p.S940L-homozygous late-infantile-onset Niemann-Pick disease type C and provided important quality-of-life

benefits (Skorpen et al., 2012). We conclude then that the drug shows positive impact on the disease progression. Therefore, we shall attribute "Medium" on this criterion.

8. Use in unique indication or not : Beside NPC, Miglustat is used as a treatment for Gaucher Disease (Orphanet, 2015e). Then, we shall attribute "Lower" on this criterion.

Laronidase

1. Rarity : Birth prevalence is between 1 in 43,261 and 1 in 1,505,160 life births (Valayannopoulos et al., 2010). Prevalence is estimated at 1/100,000, with Hurler syndrome (the severe form) accounting for 57 % of cases, Hurler-Scheie syndrome accounting for 23% of cases and Scheie syndrome accounting for 20% of cases (Orphanet, 2015a). Hurler syndrome is the most frequent phenotype, we shall consider its prevelance. Therefore, we shall attribute "Medium" on this criterion.

2. Level of research undertaken: 3 clinical trials had been done to assess the safety and the efficacy of ALDURAZYME among them only one RCT (Clinicaltrials.gov, 2015a). Hence, we shall attribute "Higher" on this criterion.

3. Level of uncertainty of effectiveness: Surrogate end points were measured as primary outcomes (FVC//6MWT) (FDA, 2015c). The results

showed a positive impact of the treatment. Hence, we shall assign "Medium" on this criterion.

4. Follow-up measures: A list of clinical trials have been or are being performed to better ascertain the effect of the treatment (Clinicaltrials.gov, 2015c). Thus, we shall attribute "higher" on this criterion.

5. Severity of the disease: Severe MPS I shows the following caracteristics of disease progression: After normal birth, early manifestation appears before age 1. By age of 3, linear growth ceases. Intellectual disability is progressive and profound. Hearing loss is common. Death typically caused by cardiorespiratory failure usually occurs within the first ten years of life. On the other hand, Attenuated MPS I shows the similar characteristics: Clinical onset is usually between ages three and ten years. Hearing loss and cardiac valvular disease are common. Severity and rate of disease progression range from serious life threatening complications leading to death in the second to third decades to a normal life span complicated by significant disability from progressive joint manifestations Clarke and Heppner (2002). MPS I shows a continuum spectrum of symptoms of progression ranging from severe to attenuated. All in all, MPS I is relentlessly progressive and potentially fatal during infanthoud. As a consequence, we shall attribute "Higher" on this criterion.

6. Availability of other treatments/unmet medical need: Yes. HSCT

(more effective, but conditioned) (De Ru et al., 2011).

7. Level of impact on condition/disease modification: The treatment shows positive impacts in relation to reducing biochemical parameters and functional capacity (Jameson Elisabeth, 2013) with no effect in preventing neurocognitive decline as the recombinant enzyme will not cross the blood brain barrier in sufficient quantity (De Ru et al., 2011). Despite the positive improvement in morbidity and quality of life, no evidence was found in the literature suggesting a positive impact on mortality levels. Therefore, we shall attribute "Medium " on this criterion.

8. Use in unique indication or not: Laronidase is only indicated for MPS I. There is no proof supporting its promisisng near future indication even off label. (Orphanet, 2015a). Therefore, we shall attribute "Higher" on this criterion.

Galsulfase

1. Rarity : It has been estimated that about 1 in 215,000 births are affected by MPS VI (National MPS Society, 2015b). We therefore shall attribute "Higher" on this criterion.

2. Level of research undertaken : Only one RCT was fully completed and was considered as a basis for the evaluation of Galsulafase (Clinicaltrials.gov, 2015d). Then, we shall attribute "Medium " on this criterion.

3. Level of uncertainty of effectiveness : Four clinical trials were perfomed to assess the effectiveness of the treatment. Among them, we register RCT. However, we note that to measure the efficacy, the trials were refering to surrogate endpoints (as 12-MWT, 3M stair Claimbing test) (FDA, 2015d). So, we shall assign "Medium " on this criterion.

4. Follow up measures: A list of other clinical trials have been and are being performed to better understand the natural history and evaluate the efficacy and the safety of the treatment (Clinicaltrials.gov, 2015d). We shall then attribute "Higher" on this criterion.

5. Disease severity : The disease presents severe and progressive symptoms and usually leading to death in the first decades of life (Giugliani et al., 2014b). Therefore, we shall attribute "Medium" on this criterion.

6. Available alternatives/unmet medical need: hematopoietic stem cell transplantation (HSCT) represents an alternative treatment (Giugliani et al., 2014b). However HSCT is not easily feasible neither an automatic treatment as it requires finding first the donor that matches the selection criterion which is rarely available. For this reason, we will just assume, for simplicity reasons, that Galsulfase reamains the only automatic indication for MPS VI. Hence, we shall attribute "Higher" on this criterion.

7. Level of impact on condition/ disease modification: clinical studies support a significant improvement of patient quality of life (Harmatz

et al., 2006). Also Long-term galsulfase ERT was associated with improvements in pulmonary function and endurance, stabilized cardiac function and increased life expectancy (Giugliani et al., 2014a). Therefore, we shall conclude that "Medium" will be the attribute to assign on this criterion.

8. Use in unique indication or not: Galsulfase is only indicated for MPS VI and there is no proof of other promising indications in the near future. Therefore, we shall attribute "Higher" on this criterion (Orphanet, 2015c).

Vorinostat

1. Rarity : with approximately 3,000 diagnosed cases in Canada. (Claimsecure, 2015). Approximate prevelance is around 1-5:10,000 (Orphanet, 2015h). Thus, we shall attribute "Lower" on this criterion.

2. Level of research undertaken : 2 main pivotal RCTs had been conducted that summarize the researh effort undertaken by the drug sponsor (FDA, 2015h). Therefore, we shall assign "Higher" on this criterion.

3. Level of effectiveness: RCT were used to assess the effectiveness of the treatment through primary endpoints. They showed satisfactory results (FDA, 2015b). Thus, we conclude that "Higher" is the attribute to assign on this criterion.

4. Follow-up measures: A list of other Clinical trials have been and are being performed to better assess the safety and the efficacy of the drug (Clinicaltrials.gov, 2015e). Thus, we shall attribute "Higher" on this criterion.

5. Disease severity : Even though, the disease has negative impact on mortality rate, the great majority of patients with CTLT do not die of their disease (Zackheim et al., 1999). Since, we can not report a direct and obvious life threatning character for the disease, we shall attribute "Lower" to the disease severity criterion.

6. Avaialble treatments/ unmet medical need: Other alternatives are available. We shall cite for instance : Radiation / chemotherapy and others (Bortezomib (Velcade) Denileukin diftitox (Ontak) Pralatrexate (Folotyn) Romidepsin (Istodax))(Lymphoma Research Foundation, 2015).Thus we shall attribute "Lower " on this criterion.

7. Level of Impact on Condition/disease modification : the effectiveness of the treatment is varying according to the stage of the disease. But, overall, the treatment has shown significant improvement in inhibiting and controlling the disease with no evidence of curing or stopping it completely (FDA, 2015h). We shall thus attribute "Medium" on this criterion.

8. Use in unique indication or not : Vorinostat is also indicated for Mesothelioma (Orphanet, 2015f). Thus, we shall attribute "Lower" on this

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criterion.

Canakinumab

1. Rarity : This related disease is extremely rare with few than 1000 cases have been reported in the world. with around 5500 of potential cases (Novartis, 2009). In the United States, we estimate the prevalence ratio to be around 1 in 360,000 individuals Boor et al. (2015). Hence, we shall attribute "Higher" on this attribute.

2. Level of research undertaken : 2 RCTs had been performed to assess the safety and the efficacy of the drug (Novartis, 2015). Thus, we shall attribute "Higher" on this criterion.

3. Level of uncertainty of effectiveness: The main measure of effectiveness in the different studies was the number of patients who did not have a disease flare (relapse of symptoms) after a 24-week treatment period (EMA, 2009). Overall, the treatment was more effective than placebo and the treatment was even capable to stop the disease progression. Therefore, we shall conclude that "Higher" will be assigned on this criterion.

4. Follow up measures: Other clinical trials are or have been developing to assess the long term safety, efficacy of the drug (Clinicaltrials.gov, 2015b). We therefore shall assign "Higher" on this criterion.

5. Disease severity : It is varying across the different disease phenotypes ranging from fever to hear loss, central nervous system dysfunction and musculoskeletal disorders, renal failure (Boor et al., 2015). We conclude that the disease presents severe impact on quality of life but we were not able to report any direct life threatening characteristics. Therefore, we shall attribute "Lower" on this criterion.

6. Available alternatives/unmet medical need: The drug is not the only treatment option for CAPS. For instance, these drugs are also indicated for the same disease: Anakinra, Rilonacept. (AutoInflammatory Alliance, 2015). Thus, we shall attribute "Lower" on this criterion.

7. Level of impact on condition/disease modification: The clinical trials proved that treatment with ILARIS resulted in clinically significant improvement of signs and symptoms that leads us to conclude that the treatment is efficient in controlling and stopping the disease progression (Novartis, 2015; EMA, 2009). We shall then attribute "Higher" on this criterion.

8. Use in unique indication or not: the treatment is also indicated for other indications shuch as: Systemic-onset juvenile idiopathic arthritis (SoJIA), Gout arthritis, Rheumatoid arthritis. (Dhimolea, 2009). Thus we shall conclude that "Lower" will be assigned on this criterion.

Eculizumab

1. Rarity : The disease is extremely rare. We estimate the prevalence ratio to be around 1:500,000 (Orphanet, 2015*g*). We shall attribute "Higher" on this criterion.

2. Level of research undertaken: Two clinical trials had been conducted to assess the safety and the efficacy of the treatment. Thus, we shall conclude that "Higher " will be the attribute to assign on this criterion (FDA, 2015*f*).

3. Level of effectiveness: We report that the drug sponsor refered to RCT to assess the effectiveness of the disease where primary endpoints were measured supporting a positive impact of the treatment on the disease (FDA, 2015*f*). Thus, we shall attribute "Higher" on this attribute.

4. Follow up measures: Other clinical trials are or have been developing to assess the long term safety, efficacy of the drug (ClinicalTrials.gov, 2015*g*). We therefore shall assign "Higher" on this criterion.

5. Disease severity : The disease can occur at any time, but affects especially young adults. The disease is severe and significantly lowers down the quality of life and it presents a life threat with a median survival of about 10.3 years (Orphanet, 2015*g*). Thus, we shall conclude that "Medium " will be the attribute to assign on this criterion.

6. Available alternatives/ unmet medical need: Bone marrow transplan-

tation is another alternative to treat PNH. It is more effective as it is the only treatment that permanently abolishes the hematopeietic defect(Orphanet, 2015g). However, this treatment is not automatically available as we need to find a donor that matches with the patient. So, for simplicity purposes, we shall neglect this option. Therefore, we shall assign "Higher" on this criterion.

7. Disease modification/ impact of the treatment : The treatment shows positive effects on the natural progress of the disease. In fact, a model assessing the cost and opportunity cost (Coyle et al., 2014) revealed that Eculizumab is associated with greater life years as well as QALYs. It remains unable to completely cure the disease though(Orphanet, 2015g). Therefore, we shall assign "Medium" on this criterion.

8. Use for other indications: The drug is indicated for other 5 indications (Orphanet, 2015g). Thus we shall assign "Lower" on this criterion.

4.4 Evaluation Matrix

The evaluation matrix presented in Table 4.10 constitues our main data input. We represented the different alternatives (reference alternatives) on the rows. The columns represent the criteria of evaluation. And of course, the evaluation of alternative i on citeirion j is represented as the intersection cell between row i and column j. We retained only the first letters H, M an L to

represent the evaluation Higher, Medium and Lower respectively. Similarly, on a second turn and for the ease of compuation later on, we coded H, M and L by 3,2 and 1 respectively as shown in Table 4.11.

4.5   Decision Maker Preferences

After presenting the matrix of evaluation, we complete it with the decision maker preferences. Normally, the decision maker is asked to explicitly express his/her preferences on the reference set of criteria and sort the DRDs into two different categories. In this case, we adopted the categorization of DRDs made by the Drugs for Rare Diseases Working Group (DRDWG) through the DRDs evaluation framework used in Ontario (Winquist et al., 2014). The DRDWG evaluated a number of eight drugs through the framework. Among them, drugs were received recommendation for funding as shown in Table 4.12.

4.6   Drugs to Evaluate

In this section, we shall select 3 drugs to evaluate through the model. The choice of three drugs was dictated mainly by the number of drugs we have in the reference set. The drugs in question are Elosulfase alfa for mucopolysaccharidosis type IV-A (MPS IVA), Imiglucerase for Gaucher disease and Agalsidase beta for Fabry disease. There is no specific reason for choosing these

Table 4.10: Evaluation of DRDs

Drugs	Criteria							
	Rarity	Research	Effectiveness	Follow up measures	Disease severity	Alternatives	Medical Impact	Unique use
Idursulfase	M	H	M	H	M	H	M	H
Alglucosidase	M	H	M	H	H	H	M	H
Miglustat	M	H	M	L	H	H	M	L
Laronidase	M	H	M	H	H	H	M	H
Galsulfase	H	M	M	H	M	H	M	H
Vorinostat	L	H	H	H	L	L	M	L
Canakinumab	H	H	H	H	L	L	H	L
Eculizumab	H	H	H	H	M	H	M	L

H:Higher; M: Medium; L:Lower

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Table 4.11: Evaluation of DRDs-Coded

Drugs	Criteria							
	Rarity	Research	Effectiveness	Follow up measures	Disease severity	Alternatives	Medical Impact	Unique use
Idursulfase	2	3	2	3	2	3	2	3
Alglucosidase	2	3	2	3	3	3	2	3
Miglustat	2	3	2	1	3	3	2	1
Laronidase	2	3	3	3	3	3	2	3
Galsulfase	3	2	2	3	2	3	2	3
Vorinostat	1	3	3	3	1	1	2	1
Canakinumab	3	3	3	3	1	1	3	1
Eculizumab	3	3	3	3	2	3	2	1

3:Higher; 2: Medium; 1:Lower

Table 4.12: Classification of DRDs

received funding	Not received funding
Idursulfase for Hunter Syndrome	Galsulfase for MPS VI
Alglucosidase for Adult and Infant onset Pompe disease	Vorinostat for Cutaneous T-cell Lymphoma
Miglustat for Niemann Pick Type C	Eculizumab for Paroxysmal nocturnal Hemoglobinuria
Laronidase for MPS I	
Canakinumab for Cryopyrin-associated periodic syndrome	

drugs except the fact that they are merely drugs for rare diseases. In the following, we shall present their evaluation on the different criteria. Table 4.13 and Table 4.14 will summurize those evaluations.

Elosulfase alfa for MPS IVA

1. Rarity : The disease is very rare. Its prevalence around the world is estimated to range between 1:76,000 and 1:640,000. Thus we shall assign "Higher" on this criterion (Tomatsu et al., 2005).

2. Level of research undertaken : Data report that the drug sponsor has performed more that one clinical trial to assess the product. Hence, we shall attribute "Higher " on this criterion (European Clinical Trials Register, 2015).

3. Level of uncertainty of effectiveness: An RCT has been performed as a mean to measure the level of effectiveness of the treatment. However, the major clinical endpoint measured is just a surrogate endpoint (6MWT). Therefore, even though, the product showed significant positive impact, we shall attribute "Medium" on this criterion (FDA, 2015*g*).

4. Follow up measures: We report that even after receiving market authorization, the drug sponsor is still performing other clinical trials to better assess the quality of the treatment (Clinicaltrials.gov, 2015*i*). We shall attribute "Higher" then on this criterion.

5. Disease severity: The disease manifests whether as a severe form or a slow progressive form. The severe form is associated with an early onset at the age of 1 to three. The slow progressive one is associated with a later onset usually at late childhood or adolescence. Both types represent severe morbidity (Regier et al., 2013). The disease will have negative effect on growth, physical appearance, eyes, ears, conductive deafness and other serious problems (MPSIV). The life expectancy for patients with MPS IV is also effected. Severe cases may face high risks of mortality at late childhood or adolescence. Other patients may survive till adulthood, although their life expectancy may be reduced (Genetics home reference, 2015). Therefore, we conclude that the disease is very severe and life threatening during childhood. Consequently, we shall assign "Higher" on this attribute.

6. Available alternatives/unmet medical need: Elosulfase alfa is the only drug available to treat MPS IVA (The Canadian Society..., 2015). Thus, we shall attribute "Higher" on this criterion.

7. Level of impact on condition/disease modification: The disease has shown a positive impact in ameliorating patients health status but without the capacity of a complete cure. Then we shall assign "Medium" on this criterion (The Canadian Society..., 2015).

8. Use in unique indication or not: Elosulfase alfa is only indicated for MPS IVA and no evidence was found that stipulates its eventual use

even off-label for other indications. Thus, we shall assign "Higher" on this criterion (The Canadian Society..., 2015).

Imiglucerase for Gaucher disease

1. Rarity: The prevelance rate of Gaucher disease is estimated around 1:100,000. Thus, we shall assign "Medium" on this criterion (Orphanet, 2015*d*).

2. Level of research undertaken : The effectiveness of the drug in question was assessed through three randomized trials (EMA, 2015).Thus, we shall assign "Higher" on this criterion.

3. Level of uncertainty of effectiveness: The effectiveness of the disease has been evalaluated through randomized trials. However, only surrogate endpoints were taken into consideration. Thus, we shall assign "Medium " on this criterion (EMA, 2015).

4. Follow up measures: The drug sponsor has been performing other clinical trials to better assess the effectiveness and safety of the drug in question. Thus, we shall assign "Higher" on this criterion (ClinicalTrials.gov, 2015*h*).

5. Disease severity : Gaucher disease is a multi system disease associated with striking variation in its clinical manifestation, severity and course. Symptoms may vary. They may include but not limited to

bone pain and fractures, cognitive impairment, enlarged spleen, enlarged liver, seizures. This will categorize the disease as very harmful for the health quality (Cox and Schofield, 1997). However, except for type 2 Gaucher disease which is not a frequent one, other types of Gaucher do not present a high risk of mortality at infant age. Yet a study showed though that type 1 Gaucher disease (the most frequent type) patients have seen their life expectancy reduced by only 8 years at birth compared to reference population (Weinreb et al., 2008). We generally conclude that Gaucher disease has slight impact on mortality. Therefore, we shall assign "Lower" on this criterion.

6. Available alternatives/unmet medical need: Cerezyme is not the only available alternative to treat Gaucher disease. Other alternatives with at least similar technological and effectiveness level also exist. Thus, we shall assign "Lower" on this criterion (National Gaucher Foundation, 2015).

7. Level of impact on condition/disease modification: The drug shows positive impact on patient condition and significantly improves their health status however without the capability to completely cure the disease. Thus we shall assign "Medium " on this criterion (National Gaucher Foundation, 2015).

8. Use in unique indication or not: The drug is indicated only for Gaucher disease. No information available proves its use for other indications

even off label. Thus, we shall assign "Higher" on this criterion (Orphanet, 2015*d*).

Agalsidase beta for Fabry disease

1. Rarity : Fabry disease prevalence is estimated to be around 1-5 : 10,000 (Orphanet, 2015*b*). Thus we shall assign "Lower" on this criterion.

2. Level of research undertaken : The market approval of agalsidase beta was based on only one RCT that assessed the effectiveness of the treatment (FDA , 2015*e*). We shall assign "Medium" on this criterion.

3. Level of uncertainty of effectiveness: The effectiveness of the treatment was assessed based on a RCT. However, it used surrogate endpoint as a primary outcome measure (GL-3). The study reported postive impact on GL-3 inclusion reduction. However, the relationship between GL-3 inclusion reduction to specific clinical manifestations of Fabry disease has not yet been established (FDA , 2015*e*). We shall assign "Medium" on this criterion.

4. Follow up measures: We report a list of other clinical trials that had been or are being perfomed by the sponsor to better ascertain the drug efficacy and safety (ClinicalTrials.gov, 2015*f*). Then, we shall assign "Higher" on this criterion.

5. Disease severity : The disease shows negative impact on patient quality

of life ranging from mild to severe. With age, life-threatening cardio-vascular or cerebrovascular complications limit the life-expectancy of untreated males and females with reductions of 20 and 10 years, respectively, versus the general population (Orphanet, 2015b). Thus, we shall assign "Medium " on this criterion.

6. Available alternatives/unmet medical need: Beside Agalsidase beta, Fabry disease patients have the option to receive another treatment which is (Agalsidase alpha). In a commentary paper, (Pisani et al., 2015) reported that based on the available scarce data, the two alternatives are not significantly different. Hence we shall attribute "Lower" on this criterion.

7. Level of impact on condition/disease modification: A 10 year study documents that treatment was capable to control and stabilize the disease stressing that the most benefit is reached with patients who initiated the treatment early (Germain et al., 2015). Thus, we shall attribute "Medium" on this criterion.

8. Use in unique indication or not: Agalsidase beta is only indicated for Fabry disease and there is no proof that shows other promising indication even off label in the near future (Orphanet, 2015b). Thus, we shall assign "Higher" on this criterion.

Table 4.13: Evaluation of new DRDs

Drugs	Rarity	Research	Effectiveness	Follow up measures	Disease severity	Alternatives	Medical Impact	Unique use
Elosulfase alfa	H	H	M	H	H	H	M	H
Imiglucerase	M	H	M	H	L	L	M	H
Agalsidase	L	M	M	H	M	L	M	H

H:Higher; M: Medium; L:Lower

Table 4.14: Evaluation of new DRDs Coded

Drugs	Criteria							
	Rarity	Research	Effectiveness	Follow up measures	Disease severity	Alternatives	Medical Impact	Unique use
Elosulfase alfa	3	3	2	3	3	3	2	3
Imiglucerase	2	3	2	3	1	1	2	3
Agalsidase	1	2	2	3	2	1	2	3

3:Higher; 2: Medium; 1:Lower

Chapter 5

Results and Analysis

In this chapter we will present the results of the application of UTADIS-GMS to the data presented in Chapter 4 (Section 5.1). These results will be analyzed and discussed in Section5.2.

5.1 Results

This section presents different steps and aspects of the application of UTADIS-GMS using R software. Outputs are displayed at the end of the section.

5.1.1 Explanation of the Procedure

The application of the UTADIS-GMS has been possible through Rorutadis (Robust Ordinal Regression UTADIS), an R package implemented in R v3.2.1. ran on a Windows 7 machine. The package had been developed

by Krzystof Ciomek from Poznan University of Technology for the purpose of implementation of a Robust Ordinal Regression for value based sorting. It is the software implementation of Rorutabis, an MCDA sorting method as a generalization of UTADIS-GMS (Kadzinski et al., 2015).

In the following we shall introduce the different steps performed and the results obtained.

5.1.2   Representation of the Problem

Building the problem with R starts by entry data phase. The data consist of the evaluation matrix, the number of classes, as well as the decision maker's preferences expressed in terms of assigning the reference alternatives into one of the designed classes. In addition, other technical information is also needed such as the nature of the criteria (gain, or cost). Then the function *buildproblem* is used to build a representation of the problem. As shown in Figure 5.1, the problem is represented by the performance matrix *perf* where the columns represent criteria of evaluation and the rows the alternatives (the DRDs). The coding for the different criteria is as follows:

1. : Rarity

2. : Level of research

3. : Level of uncertainty

4. : Follow up measures

5. : Disease severity

6. : Available alternative

7. : Level of impact

8. : Use in unique indication

The coding for the different alternatives is as follows :

1. : Idurslfase

2. : Alglucosidase

3. : Miglustat

4. : Laronidase

5. : Galsulfase

6. : Vorinostat

7. : Canakinumab

8. : Eculizumab

9. : Ecosulfase

10. : Imiglucerase

11. : Agalsidase

It also shows the number of sorting classes *nrClasses*, two in our problem. Class 1 represents drugs not eligible for funding and consequently class 2 represents the pool of drugs eligible for funding. We shall be interested also to look at the preferences of the decision maker presented in the form of constraints of lower class assignments. The matrix *assignmentsLB* represents the set of reference alternatives on the rows (the 8 drugs already evaluated) while its second column indicates which class each alternative is at least assigned to. The result shown is perfectly matching our data.

Figure 5.1: Representation of the problem: The output of builproblem function

5.1.3 Checking the Consistency of the Problem

Once a representation of the problem is created on R, we shall proceed to check its consistency, that is if the preferences on the reference set of alternatives are not contradictory with the natural performances of each alternative. For that purpose, Rorutadis provides us with a function called *checkConsistency*. The output of this function is binary (True or False). In our case, the result shows that the problem is indeed consistent which allows us to move on to the next step as shown in Figure 5.2 . If it happens that the model is inconsistent, we shall revise our data by asking the decision maker to review his/her preferences for instance.

```
> isConsistent <- checkConsistency(problem)
> isConsistent
[1] TRUE
>
```

Figure 5.2: The R command and output to check the consistency of the problem

5.1.4 Outputs

The method returns different outcomes as a result. We shall consider the categorisation of alternatives as our main outcome. Other results will be shown as well.

Categorization of alternatives

The three alternatives to sort are *Elosulfase for MPS IVA, Imiglucerase for Gaucher disease and Agalsidase beta for Fabry disease.* They corresponds to alternatives 9, 10 and 11 respectively in our problem representation. The results obtained appears on Figure 5.3 where we have a vector representing the assignments of the different alternatives. Alternative 9 is assigned to class 2 while alternative 10 and 11 are assigned to class 1. We can deduce that our model indicates the following result:

Elosulfasse for MPS IV will be categorized as eligible for funding. While the other two drugs are not eligible for funding.

```
> assignments <- getAssignments(problem, representativeFunction)
> assigments
Error: object 'assigments' not found
> assignments
 [1] 2 2 2 2 1 1 2 1 2 1 1
> |
```
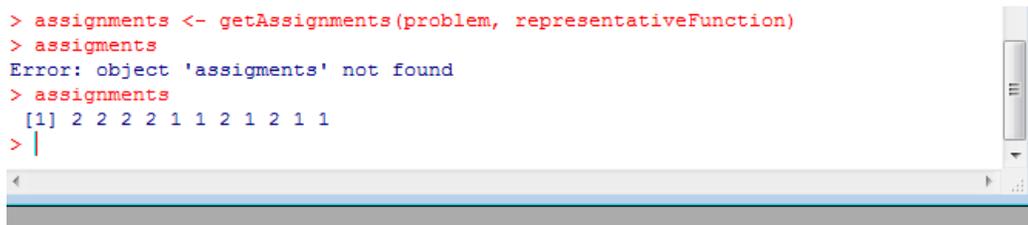
Figure 5.3: Assignments: The R command and output to get the assignment of alternatives

Other results

Secondary outcomes can also be retrieved as part of the result. We picked the following outcomes that are relevant for further analysis.

Marginal Utilities and Characteristic Points Here we present the different marginal utilities achieved by all the different criteria as shown in

Figure 5.4. In the figure, a matrix appears where the rows constitute the alternatives and the columns represent the criteria of evaluation. Hence, each element on the matrix represents a marginal utility of an alternative on a particular criterion.

Beside that, we shall retain the following characteristic points. They are merely the different possible values for each alternative. We provide their corresponding marginal utilities as indicated in Figure 5.5. Each number respectively matches a criterion. Therefore, each matrix provides the charactertic points on its rows and two columns the first is for the code of the charactersitic point itself and the second is for its corresponding marginal utility. For instance, in matrix 2, we retain two characteristic points, the value 2 and 3 on the scale of measure of criterion 2 (level of research). Value 2 presents aboslutely no marginal utility. While value 3 represents an added utility of 0.166 on criterion 2

```
> marginalUtilities <- getMarginalUtilities(problem, representativeFunction)
> marginalUtilities
      [,1]      [,2] [,3]          [,4]      [,5]      [,6]      [,7]      [,8]
 [1,]    0 0.1666667    0 -9.251859e-17 0.0000000 0.1666667 0.0000000 0.1666667
 [2,]    0 0.1666667    0 -9.251859e-17 0.1666667 0.1666667 0.0000000 0.1666667
 [3,]    0 0.1666667    0  0.000000e+00 0.1666667 0.1666667 0.0000000 0.0000000
 [4,]    0 0.1666667    0 -9.251859e-17 0.1666667 0.1666667 0.0000000 0.1666667
 [5,]    0 0.0000000    0 -9.251859e-17 0.0000000 0.1666667 0.0000000 0.1666667
 [6,]    0 0.1666667    0 -9.251859e-17 0.0000000 0.0000000 0.0000000 0.0000000
 [7,]    0 0.1666667    0 -9.251859e-17 0.0000000 0.0000000 0.3333333 0.0000000
 [8,]    0 0.1666667    0 -9.251859e-17 0.0000000 0.1666667 0.0000000 0.0000000
 [9,]    0 0.1666667    0 -9.251859e-17 0.1666667 0.1666667 0.0000000 0.1666667
[10,]    0 0.1666667    0 -9.251859e-17 0.0000000 0.0000000 0.0000000 0.1666667
[11,]    0 0.0000000    0 -9.251859e-17 0.0000000 0.0000000 0.0000000 0.1666667
> |
```

Figure 5.4: Marginal Utilities: The R command and output to obtain the marginal utilities

```
> > characteristicPoints <- getCharacteristicPoints(problem, representativeFunction)
Error: unexpected '>' in ">"
> > characteristicPoints
Error: unexpected '>' in ">"
> representativeFunction <- findRepresentativeFunction(problem, 0)
> characteristicPoints <- getCharacteristicPoints(problem, representativeFunction)
> characteristicPoints
[[1]]
     [,1] [,2]
[1,]   1    0
[2,]   2    0
[3,]   3    0

[[2]]
     [,1]      [,2]
[1,]   2 0.0000000
[2,]   3 0.1666667

[[3]]
     [,1] [,2]
[1,]   2    0
[2,]   3    0

[[4]]
     [,1]          [,2]
[1,]   1  0.000000e+00
[2,]   3 -9.251859e-17

[[5]]
     [,1]      [,2]
[1,]   1 0.0000000
[2,]   2 0.0000000
[3,]   3 0.1666667

[[6]]
     [,1]      [,2]
[1,]   1 0.0000000
[2,]   3 0.1666667

[[7]]
     [,1]      [,2]
[1,]   2 0.0000000
[2,]   3 0.3333333

[[8]]
     [,1]      [,2]
[1,]   1 0.0000000
[2,]   3 0.1666667

> |
```

Figure 5.5: Characteristic points: The R command and output to obtain the characteristic points

Utility After demonstrating the marginal values, we shall represent the overall utility scored by the different alternatives as indicated in Figure 5.6. The figure represents a graph with 2 axes. The horizontal axis is for alternatives. While the vertical one represents the corresponding utilities. Every alternative could score a utility value ranging from 0 to 1. In our case, 0.67 was the maximum utility value scored by alternatives 2, 4 and 9 while the minimum value is 0.17 and was achieved by alternatives 6 and 11.

Thresholds : Another relevant result to consider would be the utility value considered as a threshold to pass from a class to an upper one. As we only have two classes in our model, we expect to have only one threshold valued
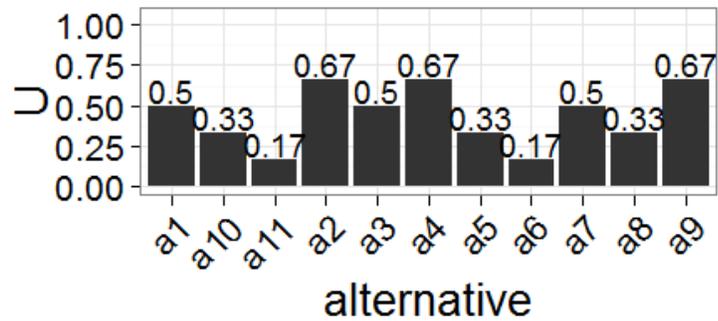
Figure 5.6: Alternatives and correspondingutility

0.334 as shown in Figure 5.7.

```
> thresholds <- getThresholds(problem, representativeFunction)
> thresholds
[1] 0.3343333
>
```

Figure 5.7: Threshold: The R command and output to obtain thresholds

Necessary and Possible relations   Another relevant outcome, we could retrieve from our model is the necessary and possible preference relations between the different alternatives. Let us remind that a necessary preference

relation exists between two different alternatives if the preference relation holds the same for all the different possible utility functions. A possible preference relation exists when the preference relation is supported by at least one possible utility function. Unfortunately, this version allows us to only compute the necessary relations between the different alternatives. Figure 5.8 shows the necessary relation between the different alternatives in form of a logic matrix crossing the different alternatives. The output of such a cross is TRUE if and only if row alternative is assigned to a class that is at least as good as the one for column alternative. For instance, if we look at row number 9 in Figure 5.8, we can see clearly that it is all TRUE values, which means that alternative 9 is necessarily at least as good as all the alternatives. In other words, this result is equivalent to say that all the possible utility functions computed are supporting the preference relation.

```
> resultOfComparison <- compareAssignments(problem)
> resultOfComparison
        [,1]  [,2]  [,3]  [,4]  [,5]  [,6]  [,7]  [,8]  [,9] [,10] [,11]
 [1,]   TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE
 [2,]   TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE
 [3,]   TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE
 [4,]   TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE
 [5,]  FALSE FALSE FALSE FALSE  TRUE FALSE FALSE FALSE FALSE FALSE  TRUE
 [6,]  FALSE FALSE FALSE FALSE FALSE  TRUE FALSE FALSE FALSE FALSE FALSE
 [7,]   TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE
 [8,]  FALSE FALSE FALSE FALSE FALSE  TRUE FALSE  TRUE FALSE FALSE FALSE
 [9,]   TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE  TRUE
[10,]  FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE  TRUE FALSE
[11,]  FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE FALSE  TRUE
> |
```

Figure 5.8: Necessary relations: The R command and output to obtain necessary relations

5.2 Analysis and Result Discussion

The model is a multi criteria decision aiding tool to help deciding about whether to fund DRDs or not. In this sense, we shall say that our model is an effective one as its primary output was indeed a categorization of the DRDs as shown in section 5.1.4. As a brief reminder, based on a set of alternatives (DRDs) already categorized into two groups (The reference set): the group of funded drugs and the group of drugs with no funding, the model is supposed to classify upcoming alternatives (DRDs) into one of the two groups. The model was not only able to do that but provides also, thanks to the necessary preference relations (*see Figure* 5.8), an explicit explanation of the classification. In fact, necessary relations constitute a tangible proof that any upcoming DRD that has been assigned funding is necessarily better (utility wise) than any drug that has been refused funding before. Similarly, any upcoming drug that will be denied funding is necessarily worse (utility wise) than any drug that has been funded before.

Moreover, the model computes a numerical threshold of classification. This value (0.3340) (*See Figure* 5.7) constitutes the utility threshold to overpass in order to belong to a superior class of alternatives, that is the class of drugs to fund. Even though this value is of minor relevance, at least compared to the categorization of alternatives itself, it would be a good index for decision makers to consider as a decision making threshold as the case for the Incremental Cost effectiveness ratio (ICER) in cost effectiveness studies.

Another question the model was able to provide an element of answer for is the relevance of criteria. In our model, we selected 8 different criteria. It seems then, that the criteria selected are not of an equal relevance. In fact, an analysis of the characteristic points figure (*see Figure* 5.5), we see that for criterion 1, the different values (1,2, and 3) score a null value as a marginal utility. This would be absurd because the values are ordinally scaled. That is the value 3 is better than 2 which is better than 1. However, this order was not respected in terms of marginal utilities that were all equivalent to a null value. This contradiction is explained by the constraints set by the decision maker in terms of the classification of the reference set of alternatives. Therefore, the null marginal utility assigned to all the values means that all the values are of neutral effect. Consequently, the whole evaluation under this criterion is of neutral effect. This analogy is applied also to criterion 3. Criteria 1 and 3 are respectively *"The rarity of the disease"* and *"the level of uncertainty of effectiveness"*. Therefore, the results of the model indicate that both criteria are not relevant to valuate drugs for rare disease.

Denying the evaluation and then implicitly funding drugs for rare diseases based on rarity finds its supporters. For instance, the Citizen's Council of the National Institute for Health and Clinical Excellence (NICE) recommended considering the payment of premium prices for very rare diseases based on the severity of the disease, evidence of health gain, and whether the disease is life threatening without considering the rarity of the disease as a considerable element for funding (NICE Citizens Council, 2004). Also, McCabe

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et al. go back to the roots of both the Orphan Drug Act in United States and The European regulation regarding rare diseases (McCabe et al., 2005). The regulation are indeed considering rare diseases, but equity purposes as well as the value of technology and innovation reflected in very high costs for DRDs were the major incentives behind such regulation.

If considering rarity as a criterion of evaluation was controversial, uncertainty of effectiveness is a big problem if not the major one related to DRDs and can not be neglected from any evaluation procedure. Broadly, evaluating the effectiveness of drugs and the uncertainty surrounding its effect is a mandatory step in any evaluation process. For DRDs in particular, this is again a step of a crucial importance as the drug usually doesn't go through a standard process of clinical trials due to its rarity and then the difficulty to perform such trials. That being said, neglecting the uncertainty of effectiveness from the evaluation criterion seems unrealistic. Therefore, finding an explanation for the reasons behind the uselessness of that criterion in our model should be the right question to ask rather than whether it is a relevant criterion of evaluation or not. Mainly, it is a measurement issue. Hence to obtain more accurate results, reviewing the definition of the item, a larger measurement scale, having a larger sample could be seen as potential solutions.

Chapter 6

Conclusion and Future Research

Evaluating drugs for rare diseases for the purpose of reimbursement and beyond, represents a tremendous challenge for most health care priorities. A consensus is set about the irrelevance of cost effectiveness analysis to evaluate such drugs. The appeal for multi criteria decision aid models seems reasonnable as the evaluation of DRDs is indeed multifaceted. However, the application of MCDA for the purpose of evaluating DRDs is yet primitive and simplistic. The present work tried to tackle the issue of evaluating DRDs from a decision maker angle by adopting an innovative robust ordinal regression MCDA method, UTADIS-GMS, that helps the decision maker discern between the DRDs based on their multi criteria value. It claims presenting a certain number of advantages evoked as follows.

From a conceptual point of view, this work presents a consistent literature review of the problems surrounding the funding and reimbursement decisions for DRDs. The reader will benefit from an up to date overview of the notion of DRDs and will found direct answers for questions as : What is drug for rare disease? What are the challenges in the assessment of DRDs and the actual main solutions presented?

Also, this work enlarges the spectrum of robust ordinal regression MCDA methods original and yet not so popular compared to classical outranking and weighting methods. In fact, the present work is considered as a direct application for UTADIS-GMS in particular and robust ordinal regression and preference disaggregation MCDA methods in general. These ones fit perfectly decision makers' needs of having before hands a practical decision making tool where they can exercise and evaluate their decisions.

Regarding DRDs, the present work claims presenting a practical method for evaluating DRDs for reimbursement and beyond decisions that take into consideration the different aspects of valuation of the drugs in question in an explicit way. Consequently, a noticeable gain in terms of the quality of the decision will be noted. In fact, decisions are more credible and accountable because they are supported by an explicit mathematical optimization program behind. Also, the decisions are more traceable and inter comparable. Moreover, with this method, decision makers enjoys a wider degree of flexibility at the moment of making the decision as the method enables different simulations by enlarging or restricting the set of reference alternatives in an

iterative way.

Furthermore more, If there is only one question that summarizes the dilemma of orphan drugs, it would be undoubtedly how to value them. This work provides an element of answer for this question. It values DRDs multidimensionnaly through multiple criteria that represents such value in a numerical way in terms of utility. But also to determine the relative importance of each dimension.

Weaknesses   Despite the mentioned strength axes, this work does not lack of certain points of weakness. The following represent the major weaknesses detected.

The choice and evaluation of criteria: It would be possible to include other criteria for the better assessment of the value of DRDs. Adding monetary or budgetary criterion such as (The drug budget impact) would be reasonable, especially in a context where a special fixed budget is allocated to DRDs. Nevertheless, this work has among its purposes to understand the value, out of the financial one, of DRDs. This is the reason why we avoided to include monetary or budgetary criterion.

Measurement of criteria performance: The measurement of criteria had been effected through a three point ordinal scale. Even though such a small scale is sufficient enough for criteria such as (rarity of the disease) or (use in

unique indication), a wider measurement scale for more complex items such as (the level of uncertainty of effectiveness) or (disease severity) will provide a more thorough analysis and hence more accurate results. This limitation was not avoidable in this study majorly because the unavailibilty of relevant data.

We clearly recognize that the data available for the study was scarce. The result found were based on an evaluation of only 8 different alternatives. Enlarging the set of reference alternatives is highly recommended for more accurate results.

Future work and promissing areas of research : The weakness points mentioned above could be a subject of further investigation. Beside that, hereafter, we shall present other promising areas of research seen as an extension of the current work.

First of all, the application of Robust ordinal regression methods could benefit not only the evaluation of DRDs but also could be generalized to other Heatlth technology assessments (HTA) . The World Health Organization defines HTA as *"the systematic evaluation of properties, effects, and/or impacts of health technology. It is a multidisciplinary process to evaluate the social, economic, organizational and ethical issues of a health intervention or health technology. The main purpose of conducting an assessment is to inform a policy decision making. "* (World Health Organization, 2015). This definition recognized the multilevel evaluation of health technologies in a sys-

tematic way. Therefore, the use of MCDA methods seems obviously natural and consequently Robust ordinal regression methods.

The use of RORUTADIS will grant the decision maker with a wider degree of freedom to express his/her preferences in many other aspects beside the assignment examples provided on a set of a reference alternatives. For instance, a pairwise comparison of alternative in a form of a is better than b by at least k classes or preference regarding the structure of the class itself such as : At least 10 alternatives can be assigned to class C1.

Appendix A

Binary Relations

A.1   Definition

Binary relation: Let $A = \{a, b, c...\}$ a finite set of alternatives. A binary relation R on the set A is a subset of the cartesian product $A \times A$, i.e. a set of ordered pairs (a, b) of elements A. For an ordered pair (a, b) belonging to R, we note :

$$(a, b) \in R, \ aRb \text{ or } R(a, b)$$

Since, by defintion, binary relations are subset, all properties from set theory are applied to them. Let R and T be two binary relations on the same set A:

- **The Inclusion:** $\quad R \subseteq T \quad$ iff $\quad aRb \Rightarrow aTb$.

- **The Union:** $\quad a(R \bigcup T)b \quad$ iff $\quad aRb \text{ or} aTb$.

- **The Intersection:** $a(R \bigcap T)b$ iff aRb and aTb

- **The Relative Product:** $a(R.T)b$ iff $\exists c \in A : aRc$; and; cTb; $(aR^2b = aR.Rb)$

Given a binary relation R, we can define the following relations :

- The inverse(dual) relation $\hat{R}$: $a\hat{R}b \equiv bRa$:

- The complement relation : R^c: $aR^cb \equiv not(aRb)$

A.2   Properties

The binary relation R is said to be :

- **reflexive**, if $\forall a \in A, \ aRa$

- **irreflexive**, if $\forall a \ in A, \ aR^ca$

- **symmetric**, if $\forall a, b \in A, aRb \Rightarrow bRa$

- **antisymmetric**, if $\forall a, b \in A, (aRb, bRa) \Rightarrow a = b$

- **asymmetric**, if $\forall a, b \in A, aRb \Rightarrow aR^cb$

- **complete**, if $\forall a, b \in A, aRb$ or bRa

- **transitive**, if $\forall a, b, c \in A, aRb$ and $bRc \Rightarrow aRc$

- **negatively transitive**, if $\forall a, b, c \in A, aR^cb$ and $bR^cc \Rightarrow aR^cc$

A.3　Preference Structure

Faced to a set A of alternatives, the decision maker is supposed to answer the following question: *For all $a, b \in A$ is a at least as good as b?* Different elements of answer a decision maker could provide. In its simplest form of answer, the decision maker would have 3 possible elements of answer to the previous question : yes a is at least as good as b, no a is not at least as good as b, or i don't know the answer. The question is a at least as good as b will determine the preference of the decision maker faced to a decision problem (choosing, ranking or sorting among differnt a set of alternatives). A preference structure is the formal modeling of the elements of answer of this question. Therefore, we can define a preference structure as : a collection of binary relations defined on the set of A such that for each couple a, b in A there is one and only one relation satisfied. Each preference relation in the structure of preference is uniquely characterized by its properties (symmetry, transitivity, reflexivity...). Hence, the preference structure is a set of exhaustive and mutually exclusive preference relations. In this sens, a preference structure could also be defined as binary reference relation. In fact, according to Bouyssou and Vincke (2009), a preference structure on A is a reflexive binary relation R on A.

Let $\succsim$ be a binary preference relation on A such that, $\forall a, b \in A$; , $a \succsim b$ means that a is at least as good as b., in terms of $\succsim$ the possible four elements of comparision between a and b are the following:

- if $a \succsim b$ and *not* $(b \succsim a)$ then a is strictly better than b , and we note $a \succ b$.

- if *not* $(a \succsim b)$ and $(b \succsim a)$ then b is strictly better than a , and we note $b \succ a$.

- if $a \succsim b$ and $(b \succsim a)$ then a is equivalent (similar) to b , and we note $a \sim b$.

- if $not(a \succsim b)$ and *not* $(b \succsim a)$ then a and b are incomparable, and we note $a \,?\, b$.

-

A.3.1 Remarkable preference structures

Once applied, the preference $\succsim$ structure will lead to a certain arrangement of elements in A. These are some of the remarkable arrangements.

Total Order

A preference structure $\succsim = (\succ, \sim)$ is a total order if it is *reflexive, antisymmetric, complete and transitive.* A total order also referred as complete order, simple order or linear order brings a full arrangements of all elements from A from the best to the worst without any ex aequo. Hence, in a total order, the indifference relation holds only for identical items.

Weak Order

A preference structure $\succsim = (\succ, \sim)$ is a weak order if it is *reflexive, complete and transitive.* In other words a weak order is a complete order with ex aequo classing permitted. In this case, the indifference relation stands for an equivalence eventhough this is not always the case in practice.

partial Order

A preference structure $\succsim = (\succ, \sim, ?)$ is an order supporting incomparability situations. A structure is a partial order if it is *reflexive, antisymmetric, and transitive.*

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