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Healthcare Priority Setting and Rare Diseases

What Matters When Reimbursing Orphan Drugs

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To my parents
Eva and Henrik
I owe you everything!

CONTENTS

ABSTRACT

The rarity of a disease can give rise to challenges that differ from conventional diseases. For example, rarity hampers research and development of new drugs, and patients with severe, rare diseases have limited access to qualified treatments. When drugs are available, clinical evidence has higher uncertainty and the drugs can be very expensive. When setting priorities in the healthcare sector, treatments aimed at patients with rare diseases, so called *orphan drugs*, have become a source of concern. Orphan drugs seldom show solid evidence of effectiveness or cost-effectiveness. Still, treatments for rare disease patients, available on the European market, has increased rapidly since the adoption of a regulation offering incentives for research and development of orphan drugs. The question arises as to whether the publicly funded health care system should provide such expensive treatments, and if so, to what extent.

This doctoral thesis aims to investigate healthcare priority setting and rare diseases in the context of orphan drug reimbursement. Priority setting for orphan drugs is located at the intersection of economic, ethical and psychological perspectives. This intersection is explored by studying the public's view on the relevance of rarity when setting priorities for orphan drugs, and by examining how orphan drugs are managed when making reimbursement decisions in practice. Papers I and II in this thesis employ quantitative, experimental methods in order to investigate preferences for prioritising rare diseases, and the extent to which psychological factors influence such preferences. Papers III and IV employ qualitative methods to further explore what factors (apart from rarity) influence priority-setting decisions for orphan drugs, as well as how decisions regarding orphan drugs are made in practice in England, France, the Netherlands, Norway and Sweden. Combining quantitative and qualitative methods has provided a more comprehensive understanding of the topic explored in the thesis, and the methods have complemented each other.

Paper I shows that there is no general preference for giving higher priority to rare disease patients when allocating resources between rare and common disease patients. However, results show that preferences for treating the rare patients are malleable to a set of psychological factors, in particular

"proportion dominance". Paper II shows that the identifiability of an individual has no, or a negative, influence on the share of respondents choosing to allocate resources to him/her (compared to a non-identified individual). Paper III confirms that rarity *per se* is not seen as a factor that should influence priority-setting decisions (i.e. accept a greater willingness to pay for orphan drugs), however, other factors such as disease severity, treatment effect and whether there are treatment alternatives were seen as relevant for consideration. Paper IV explores the challenges with and solutions for orphan drug reimbursement, as perceived by different actors in five European countries. Perceived challenges are related to the components involved when making reimbursement decisions, to the reimbursement system, and to the acceptance of the final decision. Solutions are either specific for orphan drugs, or general measures that can be used for orphan drugs as well as for other drugs.

In conclusion, priority setting for orphan drugs is complex and requires particular attention from decision makers. There are many factors to consider when making reimbursement decisions for orphan drugs. The consequences of a decision are potentially severe (both for rare disease patients and for common disease patients, depending on the decision) and psychological factors can potentially influence decisions.

SVENSK SAMMANFATTNING

Sällsynta sjukdomar kan ge upphov till utmaningar, till exempel så kan ett tillstånds sällsynthet hindra forskning och utveckling av nya läkemedel, och patienter med allvarliga, sällsynta sjukdomar har begränsad tillgång till kvalificerade behandlingar. När läkemedel finns tillgängliga, så är den kliniska evidensen ofta förknippad med osäkerhet och läkemedlen kan vara väldigt dyra. Behandlingar riktade till patienter med sällsynta sjukdomar, så kallade särläkemedel, har kommit att bli en utmaning vid prioriteringar inom hälso- och sjukvården då de sällan är kostnadseffektiva givet traditionella gränsvärden. Trots det har antalet särläkemedel snabbt ökat på den europeiska marknaden efter att en förordning antagits i EU som erbjuder incitament för forskning och utveckling av särläkemedel. Frågan uppstår om huruvida den offentligt finansierade hälso- och sjukvården bör tillhandahålla väldigt dyra läkemedel för behandling av endast få patienter, och om så är fallet, i vilken utsträckning?

Denna doktorsavhandling har som syfte att undersöka prioriteringar inom hälso- och sjukvården kopplat till sällsynta sjukdomar, och mer specifikt inom ramen för subvention av särläkemedel. Prioriteringar gällande särläkemedel befinner sig i gränslandet mellan ekonomiska, etiska och psykologiska perspektiv. Detta gränsland utforskas genom att studera allmänhetens syn på huruvida sällsynthet ska spela roll vid prioriteringsbeslut gällande särläkemedel, och genom att undersöka hur särläkemedel hanteras när beslut om subvention av särläkemedel fattas i praktiken. I artikel I och II används kvantitativa, experimentella metoder för att undersöka om det finns preferenser för att prioritera sällsynta sjukdomar och om dessa preferenser påverkas av psykologiska effekter. I artikel III och IV används kvalitativa metoder för att vidare undersöka vilka faktorer (förutom sällsynthet) som påverkar prioriteringsbeslut gällande särläkemedel och hur prioriteringsbeslut görs i praktiken för särläkemedel i England, Frankrike, Nederländerna, Norge och Sverige. De kvantitativa och kvalitativa metoderna har kompletterar varandra, och möjliggör en djupare förståelse för ämnet.

Artikel I visar på att det inte finns en generell preferens för att ge högre prioritet för patienter med sällsynta sjukdomar när resurser ska fördelas

mellan patienter med sällsynta och vanliga sjukdomar. Resultaten visar dock att preferenser för att behandla sällsynta patienter påverkas av psykologiska faktorer, särskilt ”proportion dominance”. Artikel II visar att om en person är identifierad så har det ingen, eller en negativ, effekt på andelen respondenter som väljer att fördela resurser till honom/henne (jämfört med om personen inte är identifierad). I artikel III bekräftas det att sällsynthet i sig inte ses som en faktor som borde påverka prioriteringsbeslut (dvs. att acceptera en högre betalningsvilja för särläkemedel). Dock så visar studien att andra faktorer som svårighetsgrad, behandlingens effekt och om det finns andra tillgängliga behandlingsalternativ är relevanta att beakta. I artikel IV utforskas vilka utmaningar som kopplas till subvention av särläkemedel och vilka lösningar som använts för att hantera dessa utmaningar. Identifierade utmaningar är kopplade till olika faktorer som tas i beaktande när subventionsbeslut fattas, till subventionssystemet i sig, och huruvida det finns acceptans för det slutliga beslutet. Lösningar som presenterats för att hantera subvention av särläkemedel är antingen specifika för särläkemedel, eller generella åtgärder som kan användas både för särläkemedel och för andra läkemedel.

Sammanfattningsvis så har prioriteringsbeslut för särläkemedel en hög grad av komplexitet och detta gör att beslutsfattare måste vara särskilt uppmärksamma i denna typ av prioriteringsbeslut. Många faktorer ska beaktas vid subventionsbeslut för särläkemedel, konsekvenserna kan vara potentiellt allvarliga (både för sällsynta patienter och för vanliga patienter, beroende på vilket beslut som fattas), och psykologiska faktorer kan potentiellt påverka dessa beslut.

LIST OF PAPERS

I. Wiss J, Levin L-Å, Andersson D, Tinghög G. Prioritizing rare diseases: Psychological effects influencing medical decision making. Medical Decision Making, 2017. Published online ahead of print. DOI: 10.1177/0272989X17691744

II. Wiss J, Andersson D, Slovic P, Västfjäll D, Tinghög G. The influence of identifiability and singularity in moral decision making. Judgement and Decision Making, 2015, 10(5):492-502.

III. Wiss J, Tinghög G, Levin L-Å, Nedlund A-C. Why rarity matters in healthcare decision making after all. Submitted.

IV. Wiss J, Levin L-Å, Nedlund A-C, Carlsson P. Priority setting for reimbursement of orphan drugs in five European countries: Challenges and solutions. Manuscript.

ABBREVIATIONS

aHUS	atypical Hemolytic Uremic Syndrome
CEA	Cost Effectiveness Analysis
EBDM	Evidence Based Decision Making
EMA	European Medicines Agency
HST	Highly Specialised Technology evaluation
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
NICE	National Institute for Health and Care Excellence
NT	New Technologies Council
PKU	Phenylketonuria
PNH	Paroxymal Nocturnal Hemoglobinuria
RR	Rule-of-rescue
QALY	Quality-Adjusted Life Year
SALAR	Swedish Association of Local Authorities and Regions
SEK	Swedish currency [Swedish crowns]
TLV	The Dental and Pharmaceutical Benefits Agency [Tandvårds- och läkemedelsförmånsverket]
USD	US currency [US Dollars]

INTRODUCTION

Rarity fascinates people. Rare items are perceived as special, worth investing money in, and give rise to feelings of exclusivity and exquisiteness. Rare gemstones have for long been symbols of power and wealth. Collectors invest considerable time and money to acquire rare samples of coins, paintings, vintage model cars, and records. Nevertheless, rarity can give rise to challenges. In the healthcare sector, such challenges can arise when setting priorities for patients suffering from rare diseases. Healthcare priority setting in the case of rare diseses and reimbursement of treatments aimed at these patients has a high degree of complexity. To illustrate this I will draw on a well-known case in Sweden, regarding a rare disease patient.

When Kalle, a 20-year-old suffering from Hunters disease, was denied a new drug treatment, this was followed by a public outcry and numerous media reports regarding the case (Svenska dagbladet, 2007a, Svenska dagbladet, 2007b, Aftonbladet, 2007, Dagens nyheter, 2007, Sveriges Television, 2007). Kalle had been part of a clinical trial financed by the pharmaceutical company. When the clinical trial ended, the responsible decision makers for the healthcare services for Kalle decided not to finance the drug because of the high cost (10 million SEK per year and per patient). After public pressure, the county council stepped forward and contributed financially, allowing Kalle continued access to the drug. There are numerous examples of similar stories across the world (MacKenzie et al., 2008, Smit, 2015). These cases illustrate the complexity of the provision of expensive treatments for patients with rare diseases—they all involve identified, severely ill patients, there is an (apparently) effective drug, but the price of the drug far exceeds what is normally accepted by decision makers. Priority setting regarding reimbursement of such drugs is at the intersection of economics, ethics and psychology. Decision makers, at different levels of the healthcare organisation, face economic and ethical challenges when making decisions related to orphan drugs, and these decisions are likely to be influenced by psychological factors.

Treatments aimed at patients with rare diseases, so called *orphan drugs*, have become a highly topical issue for researchers in the fields of ethics and economics, for the pharmaceutical industry, and, not least, for decision makers in healthcare. *But why is rarity problematic in healthcare priority setting?* From an *economic perspective*, orphan drugs seldom show solid

evidence of effectiveness, or prove to be cost-effective. Still, treatments for rare disease patients available on the European market have increased rapidly in number since the adoption of a regulation offering incentives for research and development of orphan drugs (European Commission, 2000). Although the emergence of new drugs for rare diseases is positive for patients previously lacking treatment alternatives, it poses challenges for decision makers in publicly funded healthcare systems. Concerns for cost-effectiveness and budget control need to be balanced against other criteria, such as patient need, severity and the availability of treatment alternatives. The orphan drug Soliris highlights why rarity can be a problem in a healthcare priority setting. Soliris is aimed at treating patients with the rare disease atypical hemolytic uremic syndrome (aHUS). The drug is very expensive — in Sweden the costs are estimated to 12-29 million SEK per quality-adjusted life year (QALY) gained (The Dental and Pharmaceutical Benefits Agency, 2015). Although the budget impact as a share of the total drug budget is small, given the small number of patients, providing the drug would mean that society put a premium on rare diseases, and is willing to pay numerous times more for a health gain than what would be considered normal for an equally severe common disease. The question arises as to whether the publicly funded health care system should provide such expensive treatments.

The issue of priority setting and rare diseases is also controversial from an *ethical perspective*. *Should rarity matter when setting healthcare priorities?* Different theories of distributive justice lead us to reach different conclusions on how scarce resources should be allocated between rare and common disease patients. If one general cost-effectiveness threshold was strictly applied as a decision criterion, many orphan drugs would not be made available to patients. Whether or not this is acceptable from an ethical perspective can be questioned, based on competing theories of what constitutes distributive justice (Gericke et al., 2005, Juth, 2014, Sandman and Gustavsson, 2017). In addition, maximising health gains, no matter the distributional consequences, is not always in line with public preferences for allocating resources (Nord et al., 1995a). Thus, when allocating scarce resources, decision makers have to consider concerns for distributive justice with concerns for effectiveness. On the one hand, it might be considered unfair not to provide effective orphan drugs to severely ill patients where no other treatments are available. It could be argued that society has an obligation to treat rare, severely ill patients regardless of costs, if there is an effective drug available. Accordingly, this would imply accepting a

higher willingness to pay for rare diseases compared to common diseases (as of the economic consequences described above). On the other hand, the consequences of providing non-cost-effective orphan drugs could be to forsake cost-effective treatments for other, equally severely ill, patients with common diseases.

Evidently, emotions and the human psyche also play a vital role when setting priorities involving rare disease patients — *but how does the rarity of a disease influence decision making?* In order to understand these issues, a *psychological perspective* on priority setting and rarity needs to be applied. Healthcare decision making is influenced by a plethora of psychological factors (Blumenthal-Barby and Krieger, 2014, Stiggelbout et al., 2015), and priority setting related to rare disease patients and for orphan drug reimbursement is much likely to be subject to the influence of such factors. For example, it is probable that rare disease patients are identified as a consequence of the small group size, and decision makers face decisions where they might have to deny patients treatment because of the high costs. In addition, given a certain amount of available resources, a larger share of rare disease patients is likely to be treated given the small group size. Still, little research has been conducted to explore how these psychological factors actually influence priority-setting decisions for rare diseases.

Orphan drug reimbursement is an interesting case for examining healthcare priority setting. First, as the cost per health gain for orphan drugs commonly exceeds established thresholds, even when weighing in the disease severity and other potentially relevant factors, there is an inevitable need to prioritise among treatments and to be aware of the alternative use of resources (economic perspective). Second, decision makers must consider distributive justice when allocating resources. This makes it particularly important that the values on which the decisions are based are clearly stated, publicly accepted, and perceived as fair (ethical perspective). Third, decision making is complex, and rare disease patients have characteristics that are likely to influence decision makers, e.g. emotionally, and influence decision makers in a way that might conflict with scientific evidence and ethical principles (psychological perspective).

Aims

This doctoral thesis aims to investigate healthcare priority setting and rare diseases in the context of orphan drug reimbursement. Priority setting for orphan drugs is located at the intersection of economic, ethical and psychological perspectives. This intersection is explored by studying the public's view on the relevance of rarity when setting priorities for orphan drugs and by examining how orphan drugs are managed when making reimbursement decisions in practice. More specifically, the following research questions are investigated:

- Is there a general preference toward rarity among the population? Is such a preference malleable to psychological factors? (paper I)
- As rare disease patients are easily identified and often presented as single individuals in need, how do these factors (a patient's identifiability and singularity) influence priority setting? (paper II)
- What is the public's view on rarity and other factors influencing decision making, such as disease severity, treatment efficacy and availability of treatment alternatives, in relation to the reimbursement of orphan drugs? (Paper III)
- How are reimbursement decisions regarding orphan drugs made internationally and what are the views of the various actors on the challenges and solutions related to the reimbursement of such drugs? (Paper IV)

Outline of the thesis

The outline of this thesis is as follows. First, a background section introduces rare diseases and orphan drugs, priority setting in healthcare and describes economic, ethical and psychological perspectives important to the understanding of priority setting and rare diseases. Second, the methods section presents the quantitative and qualitative methods used in the thesis studies. Third, the results from each of the studies included in this thesis are presented in relation to the specific aims of each paper. Fourth, based on the results from the different studies, there is a discussion on whether or not rare diseases should be prioritised differently when setting priorities in healthcare, what factors influence priority setting regarding orphan drugs and how priority setting regarding orphan drugs can be improved. Lastly, the major conclusions drawn from the thesis are presented.

BACKGROUND

The background chapter will put the four papers into context and will contribute to the understanding of the results presented in this thesis. The background is divided into five sections. The first section introduces the concepts of rare diseases and orphan drugs, and followed by a brief introduction to priority setting in healthcare. The subsequent three sections present the economic, ethical, and psychological perspectives respectively. These perspectives are closely linked, and are important in understanding the complexity and the multidisciplinary nature of setting priorities for orphan drugs.

Rare diseases and orphan drugs

"Rare diseases" and drugs for treating these diseases, "orphan drugs", are core concepts for understanding priority setting regarding orphan drugs.

Rare diseases

Rare diseases is a collective term used to describe a large number of heterogeneous diseases affecting only a small number of individuals in a population. Currently, it is estimated that there are approximately 7000 identified rare diseases across the globe (Orphanet), but there are regularly new discoveries. These diseases are mostly genetic, but there are also e.g. autoimmune diseases, cancers and toxic diseases. Although each rare disease affects only a small number of patients, in aggregate, rare diseases affect millions of people around the world. The rarity of a condition commonly leads to inaccurate or delayed diagnosis. Rarity hampers research and development of new treatments, and the clinical evidence of available treatments will often be associated with uncertainty. In Box 1, four examples of rare diseases are presented, illustrating the heterogeneity of rare diseases, but also the commonly high degree of severity.

Box 1: Examples of rare diseases.

Atypical hemolytic uremic syndrome (aHUS) is a life-threatening disease that primarily affects a patient's renal function. The syndrome causes anaemia because red blood cells are breaking down (hemolysis); patients have low levels of platelets and suffer from kidney failure (uremia). The syndrome can occur at any point in life. The disease is very rare. In Sweden, approximately 10-20 people are diagnosed with aHUS each year. There is no cure for aHUS, but there is a treatment (eculizumab, Soliris) that has shown to decrease relapses and improve the renal function. Another alternative treatment is to give patients plasma therapy, although this is not as effective. Patients having developed acute kidney failure generally require dialysis.

Hunter's syndrome is a hereditary, rare metabolic disease. The syndrome is caused by a malfunctioning or missing enzyme, iduronare-2-sulfase, which is used for breaking down mucopolysaccharides. People suffering from Hunter's syndrome lack the enzyme and the mucopolysaccharides build up in the body's cells, which causes permanent damage in the body's tissues and organs. The syndrome most commonly affects boys, and symptoms usually show at the age of 2-4 years. In Sweden, fewer than 10 people are affected by Hunter's syndrome. There is no cure for Hunter's syndrome; however, the lacking enzyme is available as a drug that, when used, is given intravenously every week. The treatment has shown to improve the function of the joints, reduce the breathing difficulties and improve the patient's general condition.

Phenylketonuria (PKU) is a hereditary, rare metabolic disease. The disease is caused by a malfunctioning or missing enzyme, which is needed to transform the aminoacid phenylanine to tyrosine. High levels of phenylanine in the body leads to brain damage. In Sweden, 5 newborns per year are diagnosed with PKU (which equals approximately 5 per 100 000 in the population). Since 1965, when a screening programme of newborns was introduced in Sweden, approximately 260 children have been diagnosed with PKU. With treatment, children develop normally. The standard treatment is a diet where the intake of proteins is reduced, but there is a drug therapy that can complement or replace the diet.

Dermatomyositis is a chronic, inflammatory muscle disease. The disease occurs in both children and adults and causes a gradual deterioration in the muscle's strength and function. Dermatomyositis classifies as an autoimmune rheumatic disease. In Sweden, between 3 and 7 children under 16 years old are diagnosed with juvenile dermatomyositis every year. In the population of 16 year olds and above, approximately 20 people are diagnosed with the disease every year. If diagnosed with the disease, a rheumatologist or neurologist is consulted. The general treatment is high doses of cortisone for a longer period of time. Cortisone in high doses is usually associated with side effects, and thus the treatment is generally complemented with an immunosuppressant to decrease the use of cortisone.

Reference: (Socialstyrelsen, 2017)

What is viewed as rare differs between countries and regions. A disease can have a high prevalence in one country or region, while considered rare in another. Consequently, there has been a need to define rarity; for example, when developing incentives for orphan drug research and development, or when designing policies in countries regarding the organisation of care for rare disease patients. There are multiple, more or less inclusive definitions of rarity in the context of healthcare policy and decision making. In Table 1, we find a number of examples of rarity definitions across the globe. As can be observed, these definitions are sometimes presented as relative (European Union and Sweden), but sometimes as absolute (USA, Japan and Australia).

Table 1: Rare disease definitions.

Country/region	Definition of rare disease	Context
European Union	<5 per 10 000 individuals	Orphan drug legislation
Sweden	<1 per 10 000 individuals	National definition
USA	<200 000 individuals	Orphan drug legislation
Japan	<50 000 individuals	Orphan drug legislation
Australia	<2000 individuals	Orphan drug legislation

References: (FDA, 1983, European Commission, 2000, Commonwealth of Australia, 1990, Socialstyrelsen, 2010., Ministry of Health, 2009)

Orphan drugs

Most rare diseases have no cure; however, those affected can have improved quality of life and extended life expectancy if offered appropriate treatments and care. There have previously been few effective drugs available for rare disease patients. Because of the small patient groups, there has been a limited commercial interest in the research and develop-ment of such products. In order to provide incentives for pharmaceutical companies to increase research on, and develop orphan drugs[1], dif-ferent countries and regions have adopted various laws and regulations. The incentives offered to pharmaceutical companies usually include prolonged market exclusivity, reduced fees, protocol assistance and tax benefits (Mariz et al., 2016). See Table 2 for examples of the extent of these in-centives in a number of countries.

[1] It should be noted that not all treatments aimed at patients suffering from rare diseases have obtained an orphan drug designation. In this thesis, however, "orphan drugs" and "treatments aimed at patients with rare diseases" are employed synonymously.

Table 2: Incentives for orphan drugs.

	EU	USA	Japan	Australia
Year of original policy	2000	1983	1993	1997
Market exclusivity	10 years	7 years	10 years	5 years
Financial incentives	Regulatory fee reductions Price and reimbursement incentives in different member states	Tax credits for clinical development costs User fee waivers	Financial subsidies User fee waivers	User fee waivers No annual registration fees
Protocol assistance	Yes	Yes	Yes	Yes
Research programme grants	Yes	Yes	Yes	n/a

References: (Mariz et al., 2016, Gammie et al., 2015)

The US was the first country to introduce incentives for developing orphan medicinal products with the passing of the Orphan Drug Act in 1983 (FDA, 1983). Since its passing, there has been a substantial increase of the number of orphan drugs marketed in the US (Divino et al., 2016b). Nearly twenty years later, the EU adopted the regulation (EC) 141/2000 of the European Parliament and of the Council on orphan medicinal products, with the underlying objective that:

> ...patients suffering from rare conditions should be entitled to the same quality of treatment as other patients; it is therefore necessary to stimulate the research, development and bringing to the market of appropriate medications by the pharmaceutical industry... (European Commission, 2000)

A medicinal product qualifies for orphan drug designation if it is used to diagnose, prevent, or treat a condition affecting fewer than 5 per 10 000 individuals in the European Union (European Commission, 2000). In addition, the product should be intended for a life threatening or chronically debilitating condition, and there should exist no other method to diagnose, prevent or treat the condition. If meeting these criteria, the medicinal product is eligible for incentives such as protocol assistance (article 6), community marketing authorisation (article 7) and market exclusivity (article 8). Because of these incentives, a number of orphan drugs have been developed and have been granted market authorisation. Once granted market authorisation, the orphan drugs are judged to have the quality, efficacy and safety appropriate for their intended use, and the pharmaceutical company is free to market their product in the member states. However, healthcare

and reimbursement systems differ between countries and so does the criteria upon which reimbursement decisions are based. Thus, each country need to set priorities regarding what healthcare to offer their citizens.

Priority setting in healthcare

There is a need to set priorities in healthcare because available resources are not sufficient to provide the best care for all patients. Healthcare priority setting can take place at many levels of the healthcare organisation, and by different actors. The various levels can be the clinical level, hospital level, regional/local level or national level. The various levels of priority setting and actors involved are of course dependent on the context and on how the healthcare is organised in a specific country. However, roughly, physicians are responsible for providing patients with adequate treatment, politicians make decisions regarding overarching health policies, and decision makers in governmental organisations are responsible for determining what care should be available to patients through the national reimbursement system.

In Sweden, decision makers at all levels must follow three principles when setting healthcare priorities that are included in the Health and Medical Services Act: (i) the human-dignity principle, (ii) the needs-solidarity principle and (iii) the cost-effectiveness principle (Ministry of Health and Social Affairs, 1995, Swedish Government proposition 1996/97:60). These principles are defined as follows:

- The human-dignity principle states that all individuals have the same value. Individuals have right to equally qualitative care regardless of personal characteristics or social function (e.g. age, income, ethnicity or social standing).
- The needs-solidarity principle states that healthcare resources should be allocated to patients with the greatest needs and the worse quality of life. In addition, weaker groups should be given special consideration (e.g. children, elderly with dementia).
- The cost-effectiveness principle states that, when choosing between different services or treatments, the aim should be to strive for a reasonable relationship between the costs and the effects of the health intervention.

This example from Sweden show that, when making priority setting decisions, such as which drugs to offer patients in publicly funded health care systems, there is a need to balance principles such as human dignity, patient need and, cost-effectiveness. These values can conflict and, at times, decision makers have to make difficult choices regarding complex cases. Orphan drug reimbursement is a perfect example of such complex cases; rare disease patients are severly ill but some of the orphan drugs available are highly expensive, and thus are seldom cost-effective given commonly specified threshold values. Obviously, such principles are not the only components to consider in a well-functioning system for setting priorities for orphan drugs—there is also a need for functioning organisations, rules and routines to assist priority setting.

Economic factors inevitably need to be considered when making priority-setting decisions in healthcare, given scarce resources. Regarding priority setting for orphan drug reimbursement, the economic perspective is particularly salient. In the following section, we will look more closely at why rarity causes orphan drugs to be very expensive, the budget impact of orphan drugs as well as their (lack of) cost-effectiveness.

Health economic perspectives on orphan drugs

The economic perspective is important in order to understand why rarity matters when setting healthcare priorities. Are orphan drugs a challenge for health budgets, or will the budget impact remain reasonable over time? What are the implications of providing non-cost-effective orphan drugs? This section will start by looking at the diffusion and budget impact of orphan drugs. Next, some basics related to the cost-effectiveness of drug treatments will be presented toghether with the concept of opportunity costs.

Diffusion and budget impact of orphan drugs

Orphan drug legislations and regulations have fulfilled their purpose and increased the number of treatments available for rare disease patients. Up until today, 136 drugs with orphan medicinal status have obtained market authorisation from the European Medicines Agency (EMA) (EURORDIS, 2017). As some of these orphan drugs are highly priced, it raises questions regarding the sustainability of providing these treatments. A number of studies have calculated the budget impact of orphan drugs and have forecast the expected future budget impact of these drugs.

In Europe, orphan drugs as a share of the total hospital drug expenditures or total pharmaceutical expenditures has been estimated. For example, in Belgium, orphan drugs accounted for 5% of the hospital drug budget in 2008 (Denis et al., 2010), and it was estimated that this share would more than double over the coming five years. Another study (Hutchings et al., 2014) predicted that the budget impact of orphan drugs, as a share of the total drug expenditure, would increase from 2.7%/3.2% in Sweden/France to 4.1%/4.9% by 2020. Shey et al. (2011) estimated the future budget impact of orphan drugs in Europe as the share of the total pharmaceutical expenditures (2010-2020). The results predicted an increase in the orphan drug share of the total pharmaceutical market, from 3.3% in 2010 to a peak of 4.6% in 2016.

In USA and Canada, Divino et al. (2016a, 2016b) measured the current orphan drug expenditure and predicted the future expenditures. Expenditures for orphan drugs, as a share of total Canadian pharmaceutical drug expenditures, rose from 3.3% in 2007 to 5.6% in 2013 (Divino et al., 2016a). Only a minor increase in orphan drug expenditures as a share of the total drug expenditures from 2014-2018 was predicted. In the US, Divino et al. (2016b), made a historical and prospective analysis of orphan drug expenditures between 2007-2018. In 2007, the share of orphan drug expenditures was 4,9% of total drug expenditure, and in 2013 this share had increased to 8,9%. For the period 2014-2018, they predicted that the growth of orphan drugs, as a share of total drug expenditure, would slow down.

The above presented studies all predict an increase in orphan drug expenditures over the following years. The predicted extent of this increase varies, as do the conclusions from the various papers. It should also be noted that these studies looked at orphan drugs as a share of the total drug expenditure (or hospital drug expenditure); however, orphan drugs can have a significant impact on local hospital budgets. This section shows that although each individual disease is classified as rare, taken toghether, orphan drugs as a share of the total pharmaceutical budget can be substantial. In addition, focusing only on the budget impact disregards the distributional consequences of providing drugs which do not meet regular criteria for cost-effectiveness. In the next section, we will move from the budget impact analyses to the the assessment of cost-effectiveness.

Cost-effectiveness and orphan drugs

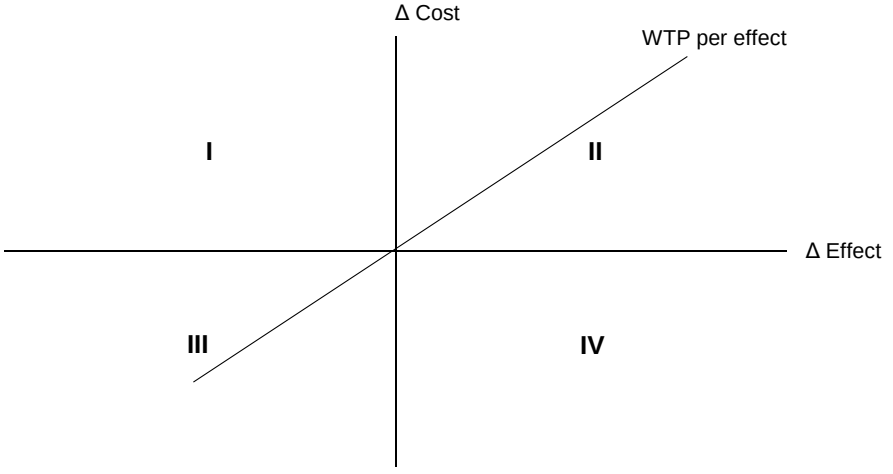
Health economic evaluations are used to assess new (and existing) health technologies and to ensure the effective use of available resources. Results from health economic evaluations are used as an input to priority setting decisions and give information about how to allocate scarce resources optimally. For example, Cost-Effectiveness Analysis (CEA) compares the costs and effects of two or more interventions, e.g. providing a new treatment versus providing standard care. In CEA, an effect could for example be percentage cholesterol reduction, episode-free days, or life-years gained (Drummond, 2005). However, the most preferred outcome measure when assessing healthcare interventions is Quality-Adjusted Life Years (QALYs). QALY is a measure that combines the expected life-years gained and the expected quality of life gained from an intervention.

The incremental cost-effectiveness ratio (ICER) is the main outcome of a CEA.

$$\text{ICER} = \frac{\text{Costs treatment A} - \text{Costs treatment B}}{\text{Effects treatment A} - \text{Effects treatment B}}$$

As depicted in the formula, the costs and effects of a new intervention (A) are compared with the costs and effects of a comparator (i.e. the best available alternative). The results from a CEA can be graphically illustrated in a diagram, i.e. the cost-effectiveness plane (see Figure 1).

Figure 1: Cost-effectiveness plane.



Adapted from Drummond (2005).

The cost-effectiveness plane consists of four quadrants (I-IV). If the analysis shows that the new intervention is both more costly and less effective than the comparator (quadrant I), the comparator dominates the new intervention. If the new intervention is less costly and more effective than the comparator (quadrant IV), the new treatment dominates the comparator. However, if the result of the analysis shows that one of the treatments is more costly but also more effective (quadrants II and III), none of the treatments is dominant, and there is a need to weigh the additional costs of implementing a more expensive treatment against the additional effect gained from it. In these two cases, the decision on which intervention to implement is clear. However, if we find ourselves in quadrants II or III, the answer is not as straightforward and the choice will depend on what cost-effectiveness ratio is judged acceptable, i.e. the threshold value or the willingness to pay for a health gain (e.g. a QALY).

The result from a CEA is put in relation to some threshold of what has been judged acceptable to pay per health gain in order to maximise health. The determination of the cost-effectiveness threshold is subject to discussion (McCabe et al., 2008). Three approaches have been proposed to determine the threshold value for cost-effectiveness; (i) looking at previous decisions, (ii) being determined by the optimal health care budget, and (iii) being determined by an exogenously determined budget (McCabe et al., 2008). I will not go in detail into the pros and cons of these approaches here. However, it can be noted that very few countries have an explicit threshold for what is considered acceptable to pay for a QALY. In Sweden, there is no explicit threshold value for what is acceptable to pay per health gain when making decision regarding which pharmaceuticals to reimburse. However, a commonly stated indication of the threshold value is 500.000 SEK per QALY (Socialstyrelsen, 2011). In priority setting practice, the distribution of health is also considered and there is a higher willingness to pay for severe treatments. During the last decade, the Swedish reimbursement agency, TLV, has worked with several thresholds in order to balance aspects such as the severity of the condition in the patient population (Svensson et al., 2015).

Health economic evaluations show that orphan drugs are rarely cost-effective in relation to what is normally acceptable to pay for pharmaceuticals (Drummond et al., 2007), even when adjusting for disease severity. Thus, if considering accepting orphan drugs that are not cost-effective, it is also

important to be aware of the opportunity costs associated with these choices.

> The true opportunity cost of health care in a community, where the effectiveness of interventions is determined by their impact on health, is not to be measured in money – but in health itself. (Culyer, 2016)

Providing orphan drugs that do not meet the demands for cost-effectiveness implies that other treatments qualifying as cost-effective might not be provided or that the overall quality of health care will deteriorate. Thus, decision makers need to be aware of the opportunity costs of providing non-cost effective care. The opportunity costs for providing non-cost-effective orphan drugs can be substantial. A recent study by Coyle et al. (2014) showed that eculizumab for treating patients with the rare disease Paroxymal Nocturnal Hemoglobinuria (PNH) provided significant health benefits. However, providing treatments for patients with PNH is associated with an opportunity cost of 102.3 discounted QALYs for each patient funded (assuming a threshold of 50 000 USD per QALY; ICER per QALY 5.24 million USD).

The substantial opportunity costs of some orphan drugs will lead to a situation where health (QALYs) is not maximised given the available resources. But could there be reasons to accept a situation where health is not maximised? From an ethical perspective, there may be arguments for why rarity should matter depending on different theories of distributive justice.

Ethical perspectives on orphan drugs

The economic perspective on orphan drugs is closely linked to the ethical perspective. While the economic perspective gives insight into why rarity matters when setting healthcare priorities, the ethical perspective gives an important input in the discussion regarding whether rarity should matter when setting healthcare priorities. In this section I will briefly present a number of theories on distributive justice relevant in the context of orphan drug reimbursement. Then, the focus will be on the debate in the scientific literature on whether rarity should matter when making reimbursement decisions for orphan drugs. For example, which considerations regarding distributive justice are there for and against providing non-cost-effective orphan drugs? Lastly, I will present the idea of procedural justice and the link to public's views and values in relation to healthcare priority setting.

Theories of distributive justice in healthcare

People are likely to agree that some idea of fairness in the distribution of public resources is important. However, to reach a consensus about what "fairness" means in practice is not always straightforward. In healthcare, theories of distributive justice can give us insights into how resources should be allocated fairly, but also what it is that should be distributed fairly. I will briefly account for five theories of distributive justice in light of which priority setting for orphan drugs can be understood differently: *utilitarianism*, *prioritarianism*, *egalitarianism*, the *Difference Principle* and *sufficientarianism*. I will also present the *rule-of-rescue*, often referred to in the context of orphan drugs, which is more of a moral intuition about how to allocate resources.

In line with *utilitarian views* on fair allocation in healthcare, a desirable distribution of resources is a maximisation of some utility (e.g. QALYs). Thus, if accepting utilitarian principles, we would strive to maximise the total sum of QALYs gained in society, and adherents to utilitarianism would argue spending resources on cost-effective treatments. An alternative view of distributive justice, close to the ideas behind utilitarianism, is *prioritarianism* or the *priority view* (Parfit, 1991). There is a desire to maximise the relevant outcome, but there is also an idea that it matters more to benefit people the worse of they are. Fair allocation of resources according to an *egalitarian view* is what leads to the most equal distribution of a relevant outcome, e.g. health, access to healthcare, or resources to obtain health. The *Difference Principle*, as suggested by John Rawls (1971), is a less strict version of the egalitarian view. The Difference Principle allows for situations deviating from strict equality, although inequalities are accepted only in situations where it would make the least privileged in society better off than under strict equality. *Sufficientarianism* is a version of egalitarianism, but requires that such principles should be applied only up to a specified minimum level of health (or some other entity). Lastly, although it could be argued not qualifying as a theory of distributive justice, a commonly presented moral intuition in the orphan drug debate is the *Rule-of-Rescue* (RR) (Largent and Pearson, 2012, Hughes et al., 2005). RR describes the intuitive response to help identified individuals in desperate need of rescue, no matter the costs.

These theories of distributive justice can be used to analyse the case of providing non-cost-effective orphan drugs to patients with rare diseases.

Several commentators have argued for or against providing such treatments with support from various theories of distributive justice.

Views on whether rarity should matter in priority setting

A number of scientific papers, arguing for or against providing non-cost-effective treatments in light of theories of distributive justice, have been presented in recent years (see e.g. McCabe et al., 2005, McCabe et al., 2010, McCabe et al., 2006, McCabe et al., 2007, Gericke et al., 2005, Sandman and Gustavsson, 2017, Juth, 2014, Hughes et al., 2005, Largent and Pearson, 2012, Picavet et al., 2012, Rai, 2002). In this section, I will present arguments from some selected articles, showing the range of ethical considerations that have been brought to the table regarding the provision of orphan drugs.

Opponents of assigning a special status for orphan drugs, which would motivate paying premium prices for orphan drugs, most commonly argue from a utilitarian point of view. McCabe et al. (2005) ask whether it is reasonable to value health gains differently depending on the size of the patient group. They provide the following example:

> Consider two groups of people who have similar diseases (J and K). J is a rare disease (1 per 10 000) and K a more common disease (1 per 1000). Imagine these people have the same personal characteristics, the same prognosis without treatment, and the same capacity to benefit from the treatments. Is it acceptable that people with J do not get treatment simply because they have a rare disease? Most would say not. (McCabe et al., 2005, p. 1018)

Given that orphan drugs are commonly more expensive, the authors proceed in their argument by assigning a higher treatment cost for the rare disease patient (£1000) than for the common disease patient (£100). If all else is equal apart from the prevalence, this would imply that the rare disease patients in this case would be valued 10 times higher as compared to the common disease patients. Thus, to maximise health in society, the rare disease patients would not have priority. The authors further argue that allocating healthcare resources has an influence at the population level, and funding treatment for one patient implies not funding treatment for someone else.

However, there may be other objectives in the allocation of healthcare resources rather than maximising health gains. Whether other theories of distributive justice can be used to motivate paying premium prices for orphan drugs has been discussed by e.g. Juth (2014). Juth (2014) assesses

three arguments of justice and fairness in the case of orphan drugs: the argument related to group size, the argument in relation to principles of need, and the identifiability argument. However, in line with Juths reasoning, none of these arguments gives any support to the acceptance of premium prices for orphan drugs. In relation to the first argument, group size, he puts forward the need to distinguish between directly and indirectly operative factors. For example, cost is a direct operative factor influencing patient access to treatment, and is thus a relevant factor to take into consideration when setting priorities in healthcare. However, some indirect operative factors may influence cost, but Juth argues that these are not morally relevant considerations. In relation to the second argument, principles of need[2], Juth presents and discusses a number of theories of distributive justice — sufficientarianism, prioritarianism, outcome egalitarianism and opportunity egalitarianism. In conclusion, he finds no support from these theories that rare disease patients should be prioritised differently (as compared to patients with common diseases). Lastly, the third argument, identifiability, he argues that the identifiability of a patient cannot be considered morally relevant.

As a reply to Juth (2014), in relation to the argument on irrelevance of group size, Sandman and Gustavsson (2017) argue that indirectly operative factors are already compensated for in healthcare, and that there are no reasons why group size should not be compensated for. Thus, the group size *per se* is not a relevant factor, but for reasons of formal equality, the negative effects caused by the size of a group should be compensated for. The authors give some examples of where society already compensates for indirectly operative factors, for example because the signs of myocardial infarction are not as easily detected among women compared to men, society accepts spending extra resources on specific tests for diagnosing women. Sandman and Gustavsson argue that group size is another indirectly operative factor that society could compensate for. For rare disease patients, they argue that:

> ...these groups are often disadvantaged in that their conditions are chronic, start at a young age, and have a great degree of severity. Moreover, the healthcare system generally lacks competence to identify and care for these diseases in a consistent way. Hence, even though group size might not be unique in this respect, there is a systematic disadvantage in belonging to a

[2] A collective term for ideas of distributive justice where the worse off should be prioritised even if this leads to a situation where healthcare resources are not maximised (e.g. some egalitarian or prioritarian ideas).

> small patient group when it comes to the distribution of healthcare, compared to a large number of indirectly operating factors. (Sandman and Gustavsson, 2017, p. 28-29)

These factors, in line with the authors' reasoning, would motivate compensating for indirect operating factors, such as group size. They conclude that there needs to be a discussion on which indirect operative factors should be candidates for compensation, but also to what extent.

Other articles have discussed various theories of distributive justice and brought forward further arguments that could be potentially relevant for consideration in the context of orphan drug reimbursement, e.g. rights-based arguments, non-abandonment, moral obligations, etc. (Gericke et al., 2005, Hughes et al., 2005, Picavet et al., 2012). In addition, one frequently occurring consideration is the Rule-of-Rescue (RR), which has been used both as an explanation for the moral impulse of non-abandonment of patients with rare diseases, but also as an argument for why society should pay a premium for orphan drugs. The RR can give us some insight into why denying treatments to severely ill patients is so difficult. It has been brought up as an impulse that needs to be considered when setting priorities, as:

> …any plan to distribute health care services must take human nature into account if the plan is to be acceptable to society. In this regard, there is a fact about the human psyche that will inevitably trump the utilitarian rationality that is implicit in cost-effectiveness analysis: people cannot stand idly by when an identified person's life is visibly threatened, if rescue measures are available. (Hadorn, 1991)

The various definitions of RR differ somewhat, but some general features recur: (1) an individual is identified, (2) it is an emergency, (3) the outcome if no action is taken is death (or severe disability), and (4) there is a way to save/rescue the individual. There is disagreement on whether the RR can be used as a valid argument to motivate paying for highly expensive treatments for rare disease patients (McCabe et al., 2006, Hughes et al., 2005).

These theories of distributive justice will not give a straightforward answer on whether to give priority to rare disease patients, in the context of orphan drug reimbursement and accepting to pay premium prices for orphan drugs. Is there a middle way?

Procedural justice and public preferences

Rather than ruling out the various theories of distributive justice, e.g. utilitarianism versus egalitarianism, it is possible to shift focus to the procedures of healthcare priority setting, and whether this procedure can be considered fair. Procedural justice can be seen as an effort to find a middle way between various views on how to allocate healthcare resources (Rawlins, 2005, Daniels and Sabin, 2008). When setting health care priorities, both scientific value judgements and social value judgements are important to consider (Rawlins, 2005). The former type of judgement relies on scientific evidence, whereas the latter concerns society and "the ethical principles, preferences, culture and aspirations that should underpin the nature and the care provided by a health service" (Rawlins, 2005, p. 472).

Thus, when making challenging healthcare priority setting decisions, decision makers can gain valuable input from the public. Citizens contribute to the public health care system through taxes, and are directly affected by priority setting in health care, as this influences which health care needs are met. The trust in the healthcare system might be negatively affected if citizens do not share the values on which priority setting decisions are based. Making rationing and priority setting in health care more explicit has shown to be in line with the preferences of patients and professionals (Owen-Smith et al., 2010). In addition, the public has much to contribute when it comes to complementing the inputs of health care professionals or decision makers in health care (Litva et al., 2002). Consequently, there is a desire among decision makers to include the views of the public and to be open about health care priority setting decisions. Input from the public is relevant on a general level but in complex cases, e.g. orphan drug reimbursement, this type of input can be particularly valuable.

In relation to the case of orphan drug reimbursement, previous research has indicated that people show a preference for providing treatments to patients, even if this implies not maximising the health gained in society (Nord, 1999, Nord et al., 1995b), and that there is a desire among the public to reduce inequalities in health (Dolan et al., 2005). In addition, NICE in England has, in its citizen councils, discussed in which cases departing from the threshold can be accepted (National Institute for Health and Care Excellence, 2008), and whether society should pay premium prices for ultra-orphan drugs (National Institute for Clinical Excellence, 2004). A majority of the members of the citizen council considered that life-saving treatments, treatments aimed at children, treatments aimed at rare disease

patients, and extremely severe diseases could justify departing from the NICE threshold. Cases where the citizen council would consider justifying the payment of premium prices for ultra-orphan drugs are cases where there is a high degree of disease severity, the treatment provides significant health gains, and the disease is life-threatening. In contrast, a number of studies have shown that there are no preferences for treating rare disease patients over common patients (Desser, 2013, Desser et al., 2010, Desser et al., 2013, Mentzakis et al., 2011, Dragojlovic et al., 2015, Linley and Hughes, 2013, Wiss et al., 2017).

Concluding this section, the various theories of distributive justice give us different interpretations on whether rarity should matter when setting healthcare priorities. Procedural justice can be a way in which to accommodate various views on priority setting in healthcare and it is possible to include the public's view. However, patients', the public's and decision makers' preferences for various resource allocation outcomes are likely to be influenced by emotions and psychological factors. Psychological perspectives on priority setting and orphan drugs are presented in the following section.

Psychological perspectives on orphan drugs

The psychological perspective is important to understand in what ways the rarity of a disease influences practical decision making, i.e. how rarity influences decision making.

Decision making in healthcare can be a highly emotional task. Decisions concern the life and death of patients, as well as their wellbeing over time. Decisions are often irreversible and the expected outcomes from decisions are surrounded by uncertainty. In addition, decisions affect not only individual patients, but also their close family and relatives. Decision making related to orphan drugs have features that, combined, can make the decision process incredibly complex. The patients are easily identified because of the small number of patients, and the severity of the diseases is generally high. Furthermore, patients are often in need of highly specialised treatments, where the scientific evidence is associated with a high degree of uncertainty and where the costs per patient are substantial.

The complex nature of decision making related to orphan drugs will increase the probability of decision makers using "decisional short cuts", so called *heuristics*. Research has shown that individuals often use heuristics to facilititate decision making, i.e. handling complex problems or tasks by using simplifying rules or guidelines. Many times, heuristics are helpful when making decisions, but it may also lead to systematic and predictable *biases*. In the scientific literature, there are many examples of psychological effects that have proven to influence choice-behaviour and preferences for given alternatives (Blumenthal-Barby and Krieger, 2014, Stiggelbout et al., 2015, Gilovich et al., 2002, Chapman and Elstein, 2000). In a healthcare decision-making context, most of the research has been done regarding the patient-doctor encounter, i.e. the micro-level (Stiggelbout et al., 2015). The focus in this thesis, however, is on decisions pertaining to the societal level, where decisions are made on which care to offer citizens, i.e. the macro-level. Thus, this thesis expands the knowledge on psychological effects in macro-level decision making.

Linked to healthcare decision making in general, and orphan drug reimbursement in particular, a number of psychological effects are likely to influence decisions. The focus in this thesis is on the influence of the *identifiability* of a patient, of *giving vs denying treatment* to patients, of *individual level vs group level* decisions and of presenting the number of patients treated in *absolute vs relative numbers*. These effects are described in more detail in the following sections.

Identifiability & Singularity

> Let a 6-year-old girl with brown hair need thousands of dollars for an operation that will prolong her life until Christmas, and the post office will be swamped with nickels and dimes to save her. But let it be reported that without a sales tax the hospital facilities of Massachusetts will deteriorate and cause a barely perceptible increase in preventable deaths—not many will drop a tear or reach for their check books. (Schelling, 1968)

People tend to be more willing to help individuals that are presented as identified rather than anonymous (i.e., the identifiable victim effect). This effect has been shown in numerous studies on helping behaviour (Västfjäll et al., 2014, Kogut and Ritov, 2005a, Kogut and Ritov, 2005b, Kogut and Ritov, 2011, Jenni and Loewenstein, 1997). Moreover, people often feel a sense of a moral duty to help identified individuals presenting themselves to health services with a severe, life-threatening condition. The feeling of moral obligation towards a single, identified individual, regardless of cost,

is often termed the rule of rescue. Media coverage and the public debate on reimbursement decisions regarding orphan drugs commonly involve a reference to the rule of rescue (Jonsen, 1986, McKie and Richardson, 2003). Mackenzie and others (2008) analyzed the media coverage preceding the funding decision regarding the drug Herceptin (Trastuzumab) for women suffering from HER2 breast cancer in Australia. They found that a majority (54%) of the news statements featured "desperate, sick women in double jeopardy because of callous government/incompetent bureaucracy". The straightforward prediction, based on previous literature on the identifiable victim effect and rule of rescue, is that preferences for rarity should increase when presenting a patient with a name and a picture. However, it should also be noted that the tendency to offer greater aid to specific identified victims is context dependent (Lee and Feeley, 2016).

Attribute framing

Framing equivalent decision problems as either gains or losses has been shown to affect choices. Tversky and Kahneman (1981) described the "Asian disease problem": a scenario where participants could choose between two medical programs to combat an unusual disease. One program was described as a secure option (some lives will be saved for sure) and the other as a risky option (some probability that everyone will be saved and some probability that no one will be saved). The two versions of the scenario were randomly allocated to participants: one version where the outcomes were expressed in lives saved and one version where the outcomes were expressed in expected deaths. The results showed that presenting outcomes either in terms of gains or in terms of losses led to a reversal of preferences for the otherwise identical medical programs.

When discussing resource allocation in health care on a policy level, a "give-frame" is typically referred to as priority setting, whereas a "deny frame" is typically referred to as rationing. It is probable that rationing evokes negative emotions in individuals, as it associates with a situation of scarcity and forced choice. In contrast, priority setting is likely to be regarded in a more positive way, a situation where informed choices are made to benefit the society at large. In the public debate regarding orphan drugs, focus is often on cases where patients have been denied a treatment. Given that denying (rationing) care is likely to be a more emotionally burdensome decision, it is not unreasonable to believe that this framing could increase preferences for rarity.

Proportion dominance

A preference for maximising relative savings at the expense of absolute savings is commonly referred to as proportion dominance (Slovic et al., 2007, Baron, 1997, Bartels, 2006, Markowitz et al., 2013). Individuals generally prefer to help a larger proportion (e.g., 100 out of 100 people) rather than a smaller proportion (e.g., 100 out of 10,000 people) even though the number of people helped is identical. The proportion dominance effect is often linked to a "drop-in-the-bucket" feeling, implying that people are tempted to shut down emotionally and ask "what is the point?" when facing problems of large magnitude (Markowitz et al., 2013). This indicates a tendency among people to prefer actions that eliminate a problem over actions that only eliminate some part of a problem. Accordingly, people have a general preference for dealing with smaller problems before moving on to bigger problems, thereby sometimes ignoring efficiency concerns.

The effect of proportion dominance is likely to be important when setting priorities for patients with rare diseases, given that the relative share of patients with a rare disease that can be treated is bound to be higher than the relative share of patients with a common disease that can be treated. For example, if we assume that costs and effects for treating patients with rare and common diseases are identical, we can treat 80 out of 80 patients with a rare disease but only 80 out of 10,000 patients with a common disease. Being able to treat a higher proportion of patients with rare diseases could potentially create preferences for rarity to avoid the dropin- the-bucket feeling. Importantly, to avoid this feeling, people might also be willing to sacrifice overall efficiency (Bartels, 2006); e.g., prioritise the health gain for 80 out of 80 patients rather than for 100 out of 10,000 patients.

Individual vs. group level decision making

Priority setting takes place on many different levels of the health care organisation—from decisions made by the physician directly in relation to a patient (bedside rationing) to high-level policy decisions (desktop rationing) (Tinghög, 2011). Redelmeier and Tversky (2004) showed that physicians, as well as lay people, make different decisions when evaluating an individual patient than when considering a group of comparable patients. More specifically, physicians gave more weight to efficiency concerns at the group level. Previous studies have also shown that an individual, in contrast to a group, is viewed as a psychologically coherent unit and that this leads to stronger impressions about individuals than groups (Hamilton and Sherman, 1996). Policy decisions regarding patients with rare diseases,

who are often in need of specialized care, are more likely to concern individual patients rather than groups.

METHODS

To achieve the thesis aim, both quantitative, experimental and qualitative methods have been employed. This approach was considered suitable given the complexity involved when setting priorities for orphan drug reimbursement. Relying only on quantitative methods would have left many questions unanswered and the use of qualitative methods provided the opportunity to gain a deepened understanding of how priorities for orphan drugs are set and what influences how decisions are made.

Use of methods

My background lies in economics; however, this thesis sprang from a multidisciplinary context. In the context of my research, I collaborated with social scientists, psychologists, ethicists and other economists specialising in e.g. behavioural economics and health economic evaluations. Reaserch in the field of healthcare priority setting in general, and orphan drug reimbursement in particular, comprises complex and multidimensional problems to be analysed. Consequently, in this thesis' papers both quantitative, experimental methods (papers I and II) and qualitative methods (papers III and IV) have been employed. It has been acknowledged that combining quantitative and qualitative approaches can be particularly useful for studying multidimensional and complex issues, such as healthcare interventions (Tariq and Woodman, 2013).

In this methods section I will begin with presenting the quantitative, experimental methods used in paper I and II. In these two studies, collecting data involved distributing a population survey and performing decision experiments based on moral dilemmas. Subsequently, I will describe the qualitative methods used in papers III and IV. In these two studies, the data was collected from focus group discussions and from semi-structured interviews with various actors with knowledge about setting priorities for orphan drugs. Table 3 gives an overview of the design and the data collection in papers I-IV.

Table 3. Overview of the design and data collection of papers I-IV.

Paper	Title	Design	Data & Participants
I	Prioritising rare diseases: Psychological effects influencing medical decision making.	Quantitative, experimental	Postal survey distributed to a representative sample of the nationally registered population (n=1270).
II	The influence of identifiability and singularity in moral decision making.	Quantitative, experimental	Moral dilemmas distributed to students in Sweden and to a population-representative subjects pool in the US (n=1232).
III	Why rarity matters in healthcare decision making after all	Qualitative focus group study	Four semi-structured focus group discussions were conducted with participants from various backgrounds (n=19).
IV	Reimbursement of orphan drugs in five European countries: challenges and solutions.	Semi-structured interviews	Semi-structured interviews and a study of relevant literature/documents (n=22).

Quantitative, experimental methods: Papers I and II

Paper I: Population survey

In order to investigate if there is a general preference toward rarity among the population, and if such a preference is malleable to psychological factors, we conducted a survey of the general population in Sweden.

Data collection

A postal questionnaire was sent out to a randomly selected sample of the population in Sweden (living in the county of Östergötland), aged between 20 and 75 years. A total number of 3000 questionnaires were distributed. Two reminders were sent out. Before sending out the survey it was pilot tested and respondents were interviewed to make sure instructions and scenarios were interpreted as intended.

Survey design

To introduce the topic to respondents, the questionnaire started with a short description of rare diseases, and why treatments aimed at patients

with rare diseases might be challenging when setting priorities in health care. This information was kept as short and neutral as possible to avoid influencing respondents' choices in the following scenarios.

Figure 2 gives a general overview of the questionnaire, where variations in choice options are presented for each scenario. The questionnaire was designed to allow for both within- and between-subject comparisons. Thus, three different versions of the questionnaire were sent out (versions A-C).

Figure 2: Overview of the survey

	Version A Baseline	Version B Attribute Framing	Version C Prop. Dominance + Identifiability
Scenario 1 (group level, equal cost)	• 100 rare patients • 100 common patients • Indifferent	• 10 rare patients • 10 common patients • Indifferent	• 80/80 rare patients • 100/10 000 common patients • Indifferent
Scenario 2 (group level, unequal cost)	• 100 rare patients • 800 common patients • Indifferent	• 10 rare patients • 80 common patients • Indifferent	• 80/80 rare patients • 800/10 000 common patients • Indifferent
Scenario 3 (individual level, equal cost)	• Patient X (rare) • Patient Y (common) • Indifferent	• Deny patient X (rare) • Deny patient Y (common) • Indifferent	• Eric (rare) • Patient Y (common) • Indifferent
Scenario 4 (individual level, unequal cost)	• Patient X (rare) • Patient Y+7 (common) • Indifferent	• Deny patient X (rare) • Deny patient Y+7 (common) • Indifferent	• Eric (rare) • Patient Y+7 (common) • Indifferent

Within-subject comparisons

Each questionnaire contained four allocation scenarios where participants were asked to make a choice between allocating health care resources to patient(s) with a rare disease, patient(s) with a common disease or to be indifferent. The rare and the common diseases were described as equal in severity using EQ-5D health state descriptions.

In scenarios 1 and 2, respondents were asked to allocate health care resources to either a group of 100 patients with a rare disease, or a group of 100 patients with a common disease. In scenarios 3 and 4, respondents were asked to allocate health care resources to either one patient with a rare disease, or one patient with a common disease. We label scenarios 1 and 2 as group-level scenarios and scenarios 3 and 4 as individual-level scenarios.

The costs for treating the rare and the common disease patient(s) were described as equal in scenarios 1 and 3, whereas the costs for treating the rare disease patient(s) were increased in scenarios 2 and 4. We label scenarios 1 and 3 as equal-cost scenarios and scenarios 2 and 4 as unequal-cost scenarios. The increased opportunity cost for treating the rare disease patients reflects the higher costs of rare disease treatments compared to common disease treatments.

The exact phrasing of scenario 1 (group level, equal cost) was as follows:

> Imagine that the county council has obtained additional resources that can be used to treat 100 patients. The county council must decide which one of two similar diseases should be treated: Disease A, a rare disease (100 cases per year in Sweden), or Disease B, a common disease (10 000 cases per year in Sweden). Diseases A and B are equally severe. Patients can walk with some difficulty and they suffer from severe pain. Both patient groups will regain full health with treatment. The costs of treating patients with Disease A and with Disease B are identical. How do you think that the additional resources should be used?

The respondents were then asked to choose one of the following options: to treat 100 patients with Disease A (rare disease), to treat 100 patients with Disease B (common disease) or to be indifferent.

Scenario 2 (group level, unequal cost) was also described as a group-level decision, but where the cost of treating a patient with a rare disease was eight times higher than treating a patient with a common disease. Respondents were asked to make a choice between treating 100 patients with a rare disease, 800 patients with a common disease, or to be indifferent.

Scenario 3 (individual level, equal cost) was presented as an individual level decision where respondents were asked to make a choice between treating Patient X with a rare disease, treating Patient Y suffering from a common disease or to be indifferent.

Scenario 4 (individual level, unequal cost) was presented as an individual-level decision, but with the cost of treating Patient X (rare disease) being eight times higher than treating Patient Y (common disease). Respondents were asked to make a choice between treating Patient X (rare disease), Patient Y (common disease) plus seven other patients also suffering from the common disease, or to be indifferent.

Between-subject comparisons

To test for differences in respondents' preferences for rarity due to information presentation, three versions (A-C) of the questionnaire were randomly distributed. Scenarios 1-4 were identical across versions A-C, except for minor variations in the way information was presented. The variations in information, related to the effects described in the introduction, were the following:

i) Identifiability: The patient suffering from the rare disease was presented either with a picture and a name, or as an anonymous patient without picture and name.

ii) Proportion dominance: The number of patients it was possible to treat was expressed either in absolute terms (i.e. treating 100 rare patients vs treating 100 common patients) or as a proportion (i.e. treating 80 out of 80 rare patients vs treating 100 out of 10 000 common patients). Thus, the scenario used to test for the proportion dominance effect (i.e. scenario 1 in survey version C), did not reflect equal cost between rare and common disease.

iii) Attribute framing: The respondents were asked to either give priority to one patient, or deny and ration care to one patient.

Paper II: Decision experiments

As rare disease patients are easily identified and often presented as single individuals in need, we wanted to investigate how these factors (a patient's identifiability and singularity) influence priority setting. In order to manipulate the identifiability and singularity of a victim, we decided to perform a decision experiment based on a realistic scenario.

Data collection

Three separate data collections including in total 1 232 subjects were carried out. More specifically, the sample included 581 subjects from Linköping University in Sweden (Experiments SWE I and SWE II) and 651 subjects from the population-representative subject pool at Decision Research in Eugene, Oregon (Experiment USA). In all experiments identifiability and singularity were varied orthogonally across four experimental treatments to which subjects were randomly assigned.

Experiment SWE I

Data collection SWE I was conducted as a classroom experiment at Linköping University, with undergraduate students from the faculty of arts and sciences. Subjects were randomly assigned to one of four treatments in a 2x2 between-subjects design. Each treatment presented the same moral dilemma, but differed with respect to which choice option[s] was [were] presented as identified to the subject. The moral decision entailed choosing to give measles vaccines to either one or five children presented as either identified or non-identified. The identification details included information on the child's [children's] age and name[s] and a photograph [photographs]. The photographs depicted children of similar age and appearance. Subjects were informed that they were participating in a decision-making experiment with real outcomes, i.e., that their choice would result in an actual donation of measles vaccines to UNICEF according to their decision.

Following the structure of the bystander dilemma, there was a default option. Subjects could either stay with the default, which meant that a potentially life-saving vaccine would be given to the single child (i.e. the deontological option), or make an active choice to re-allocate so that five other children received vaccine (i.e. the consequentialist option). The structure of the four treatments is described below.

Treatment 1 (1 id vs 5 non-id): the single child was presented to the subjects with a picture, a name and an age, while the other five were presented without pictures, names and ages. The exact phrasing of the vaccine allocation dilemma in treatment 1 was as follows:

> Benge is five years old and lives in Kenya. He lives in a poor and inaccessible mountain village where outbreaks of measles frequently occur. The disease can cause serious injury and even death. We will donate enough money for one dose of measles vaccine that will protect Benge from the disease and its side effects. A vaccination offers him an opportunity for a better and more secure future. For the same amount of money, we can vaccinate five children living in another more accessible, poor area in Kenya. You can choose to deny Benge the vaccine in favour of the other children. Do you choose to give Benge the vaccine?

Treatments 2, 3 and 4 were identical except for the following differences:

Treatment 2 (1 non-id vs 5 non-id): both the single child and the group of five children were presented as non-identified.

Treatment 3 (1 id vs 5 id): both the single child and the group of five children were presented as identified.

Treatment 4 (1 non-id vs 5 id): the single child was presented as non-identified and the five children as identified.

After making their choice, subjects were asked three follow-up questions related to their emotional response: (1) how difficult did you find the question was to answer? (2) how much sympathy did you feel for the single child? and (3) how much sympathy did you feel for the five children? A Likert scale ranging from 1 to 6 was used, where 1 was defined as "not difficult at all" and 6 was defined as "very difficult" for the first question and "no sympathy"/ "much sympathy" for the second and third questions.

Experiment SWE II

The second experiment was also conducted as a classroom experiment at Linköping University, with undergraduate students from the faculty of arts and sciences. The structure and instructions pertaining to this experiment were very similar to experiment SWE I, but three modifications were made in the design. First, the sentence "He lives in a poor and inaccessible mountain village" was excluded because this information could potentially make subjects believe that the "more accessible" place might have alternative ways of getting the vaccine, thus influencing subjects to choose the single child. Second, the wording related to the default option was changed so that it was expressed more clearly. The exact wording of treatment 1 in experiment SWE II was as follows:

> Benge is five years old and lives in Kenya. He lives in an area where outbreaks of measles frequently occur. The disease can cause serious injury and even death. We will donate one dose of measles vaccine that protects Benge from the disease and its side effects. A vaccination offers him an opportunity for a better and more secure future. Instead of vaccinating Benge it is possible to vaccinate five other children, living in a similar situation to Benge. Right now the vaccine is designated to Benge. However, you can choose to deny Benge the vaccine in favour of the other children. Do you choose to give Benge the vaccine?

The third modification compared to experiment SWE I, was the addition of a series of follow-up questions in order to explore emotional reactance and emotional upscaling as possible psychological processes influencing responses. For example, subjects were asked to state their agreement with

the statement "I felt that Benge should not get 'special treatment'" (emotional reactance) and "My feelings for the single child made me feel more intensely for the five children" (emotional upscaling). A Likert scale ranging from 1 to 6 (where 1 = completely disagree and 6 = completely agree) was used.

Experiment USA

The third experiment was run in collaboration with Decision Research in Eugene, Oregon. Subjects were drawn from a diverse sample of the adult U.S. population included in the subject pool of Decision Research. The experiment was conducted as a web survey. Instructions were identical to experiment SWE II but translated into English. In addition, experiment USA included four treatments to control for potential order effects related to the presentation of the single child and the group of children. In the additional experimental treatments with reversed order, the group of children was presented first and the single child second.

Qualitative methods

Paper III: Focus group discussions

To get more nuanced understanding of preferences for rarity, we wanted to further explore the public's view on rarity and other factors influencing decision making, such as disease severity, treatment efficacy and available treatment alternatives, in relation to the reimbursement of orphan drugs. It was decided that focus groups would be an appropriate method for exploring such factors. Focus group discussions are useful when it comes to exploring not only what people think but also why they have a certain point of view. The participants' present their own view, but they also listen, reflect on what is said, and consider their own standpoint further. Thus, the method allows for a dynamic interaction where participants mutually can develop their way of reasoning and generate a broader scale of ideas than from an individual interview.

Sample selection & data collection

Four focus group discussions were carried out in a medium-sized city in Sweden in January and February 2014. Each group consisted of 4-6 participants. Participants were recruited by e-mail by the focus group leader (author JW). We employed a purposive sampling approach with the aim of selecting groups displaying variation regarding some characteristics

(Patton, 2002). The selection criteria were group belonging and age (see Table 4). Also, an even gender distribution was aimed for. The selection criteria were chosen aiming for a broad range of participants. The purpose of the group selection was to include lay people with an interest in discussing social issues, but not necessarily with a background in the healthcare sector. The groups comprised university students in social science, first aid volunteers, care staff at special housing for people with mental disabilities, and senior administrators at a government agency or a larger company.

Table 4: Focus group composition.

Group	n	Female (n)	Age (youngest-oldest)
Students in social science (S)	5	2	20-24
First aid volunteers (V)	6	3	22-35
Care staff (CS)	4	2	33-55
Senior administrators (SA)	4	2	50-63

Participants in each group were acquainted with one another. Previous research suggests that participants are more comfortable sharing personal opinions when the group is homogenous regarding personal characteristics, such as age and social belonging (Krueger and Casey, 2009). Thus, the purpose of using pre-existing groups was to create favourable conditions for discussing a topic that many people perceive as sensitive—rare diseases and the limitations of the publicly funded healthcare system. In particular, questions concerned subsidised healthcare with the possible effect of withholding potentially effective drugs from some patients, or giving one patient priority over another.

The focus group discussions were moderated by the focus group leader and followed a predefined structure. The content and the structure of the focus group discussion were pilot tested in two smaller groups of researchers from the faculty, prior to the actual discussions, in order to see if the information was understood correctly and if the design stimulated discussion. The goal was to have a setup where participants would present their own view, but also listen, reflect on what has been said, and consider their own standpoint further.

Each focus group discussion lasted between 55 and 90 minutes, with an average of 75 minutes, excluding the introduction by the focus group leader. Participants were seated around a table. The focus group leader gave information on the structure of the discussion, the concepts of rare

diseases, orphan drugs, and cost-effectiveness as well as why orphan drugs sometimes pose a challenge when setting priorities in healthcare. The discussion was based on a basic priority setting dilemma regarding orphan drug reimbursement: A new drug is introduced onto the market. The cost per health gain is 20 times higher than what is normally accepted when including drugs in the national pharmaceutical benefit scheme. The high cost per health gain is due to the fact that the drug treats a group of patients with a rare disease. After being presented with the dilemma, participants were asked to consider a number of decision-making components when discussing whether or not the drug in question should be reimbursed. The decision-making components were identified, prior to the focus group discussions, based on the literature on resource allocation in healthcare related to rare diseases. Paper cards with each decision-making component were placed in the centre of the table. The paper notes were used in order to facilitate the discussion. Participants could move the paper cards around while discussing and could rank the components in order of importance. First, the decision-making components severity, treatment effect, cost-effectiveness, rarity (prevalence) and the treatment alternatives, were introduced to the participants. Second, the following components were added to the table: budget impact, advancing scientific knowledge, double jeopardy, rule-of-rescue, vulnerable group, and identifiability of a patient. Presenting the decision-making components in two rounds allowed the focus group participants to focus on a few components at a time and not to be overwhelmed by the task. In each round, participants were asked to discuss which decision-making components society should consider when making a decision on whether or not to reimburse the drug in the given example. The participants were also encouraged to add alternative decision-making components that they believed were important in the discussion (by writing them on additional paper cards). At the end of the discussion a brief summary of what had been discussed was given by the focus group leader, and participants were asked if they agreed with the summary and if they missed, or wanted to add, any important aspect.

Data analysis

Discussions were recorded and transcribed. Data was analysed using a thematic analysis (Braun and Clarke, 2006). The analysis was primarily deductive, using the decision components identified prior to the discussions as the basis of the analysis. The data was also analysed inductively by identifying components presented by participants that were not explicitly presented by the focus group leader.

The data analysis was an iterative process. Transcripts were carefully reviewed several times. All sections were highlighted where it appeared that the participants argued for or against a predefined decision-making component, or where the participants argued for other components relevant for orphan drug reimbursement (not linked to the predefined components). The highlighted text was coded and later labelled into four overarching themes related to the decision-making components: the patient, the treatment, economic aspects, and societal concerns. Quotes presented in the results section were translated from Swedish to English.

Paper IV: Semi-structured interviews

In order to explore how reimbursement decisions regarding orphan drugs are made and the views of various actors on the challenges and solutions related to the reimbursement of such drugs, we performed semi-structured interviews with relevant decision makers and other stakeholders in England, France, the Netherlands, Norway and Sweden.

Sample selection and data collection

Countries with both similarities and differences regarding their healthcare systems were included for a relevant overview of the challenges linked to orphan drug reimbursement and the solutions used to deal with these. All included countries have healthcare insurance schemes covering a large majority of the population. Sweden, Norway and England have a large share of public providers, whereas France and the Netherlands have an insurance-based system with a mix of private and public providers. The countries have different processes for making reimbursement recommendations.

A strategic sampling approach, with the aim of recruiting actors with knowledge about orphan drug reimbursement, was employed. Informants were involved in the reimbursement process for orphan drugs, or were national experts with knowledge about orphan drug reimbursement (national experts, NE), or were in some way affected by these decisions (pharmaceutical industry representatives, PI, and patient group representatives, PR) (see Table 5). The purpose of consulting different actors was to have different perspectives on the challenges and solutions in orphan drug reimbursement. Representatives from all actor groups were interviewed in each country, except for France where we did not manage to arrange an interview with a patient representative. To get a deeper understanding of the

healthcare systems and the reimbursement processes in each country, relevant documents were reviewed before the interviews. After the interviews, these documents were used to fill information gaps or to get detailed information on some matters.

Semi-structured interviews, N=22 were conducted in 2015-16. Some interviews included more than one informant and the total number of informants was 27. Informants were recruited by e-mail. Each interview lasted between 25 and 103 minutes, with an average of 59 minutes. The interviews were conducted face-to-face or, if a personal meeting was not feasible, by phone. The interviews followed a topic guide. Depending on the expertise of the informant, certain topics were given more attention.

Data analysis

All interviews were recorded and transcribed. The transcripts were analysed using a thematic analysis, and the analysis was a continuous and iterative process. Each transcript was reviewed in detail and all sections were highlighted where it appeared that the informant described issues related to orphan drug reimbursement. Subsequently, the highlighted text was coded and sorted into broader themes and sub-themes. Quotes were translated from the language of origin into English.

Table 5: Informants in each country, informants' roles and the organisations represented.

Country	N	n	Role[a]	Organisations/other	Original name of organisations/other
England	3	1	NE	NICE Highly Specialised Technologies (HST) Committee	
		1	PI	The Association of the British Pharmaceutical Industry (ABPI)	
		1	PR	Genetic Alliance UK	
France	7	4	NE	The French National Authority for Health, The Transparency Committee, The Economic Committee on Health Care Products	Haute Autorité de Santé (HAS), La Commission de la Transparence, Le Comité Économique des Produits de Santé (CEPS)
		3	PI	The French Pharmaceutical Companies Association	Les entreprises du médicament (LEEM)
the Netherlands	5	2	NE	The National Health Care Institute, Scientific Advisory Board	Zorginstituut, Wetenschappelijke Adviesraad (WAR)
		1	PR	Appraisal committee	Adviescommissie packet (ACP)
		2	PI	Association Innovative Medicines	Nefarma
Norway	7	4	NE	The Norwegian Medicines Agency, The Norwegian Health Economics Administration, University researchers	Statens Legemiddelverk (SLV), Helseøkonomiforvaltningen (HELFO)
		2	PR	The Norwegian Association of Disabled, Oslo University Hospital	Norges Handikapforbund, Oslo Universitetssykehus
		1	PI	The Pharmaceutical Industry in Norway	Legemiddelindustrien (LMI)
Sweden	5	3	NE	The Dental and Pharmaceutical Benefits Agency, New Therapies (NT) council at the Swedish Association of Local Authorities and Regions (SALAR), Government advisor	Tandvårds- och läkemedelsförmånsverket (TLV), NT-rådet vid Sveriges Kommuner och Landsting (SKL)
		1	PI	The Swedish Association of the Pharmaceutical Industry	Läkemedelsindustriföreningen (LIF)
		1	PR	Rare diseases Sweden	Riksförbundet Sällsynta Diagnoser

RESULTS

Preferences for rarity and psychological effects influencing such preferences (Paper I)

Data collection and respondent characteristics

Data was collected between April and June, 2014. The return rate was 42.3% (n = 1,270). Respondent characteristics regarding age, gender, education and monthly salary were mostly representative of the Swedish population. Mean age among respondents was 50.9 years, and 53.9% of subjects in the sample were women. There were no significant differences between survey versions regarding age, gender, education, or monthly income.

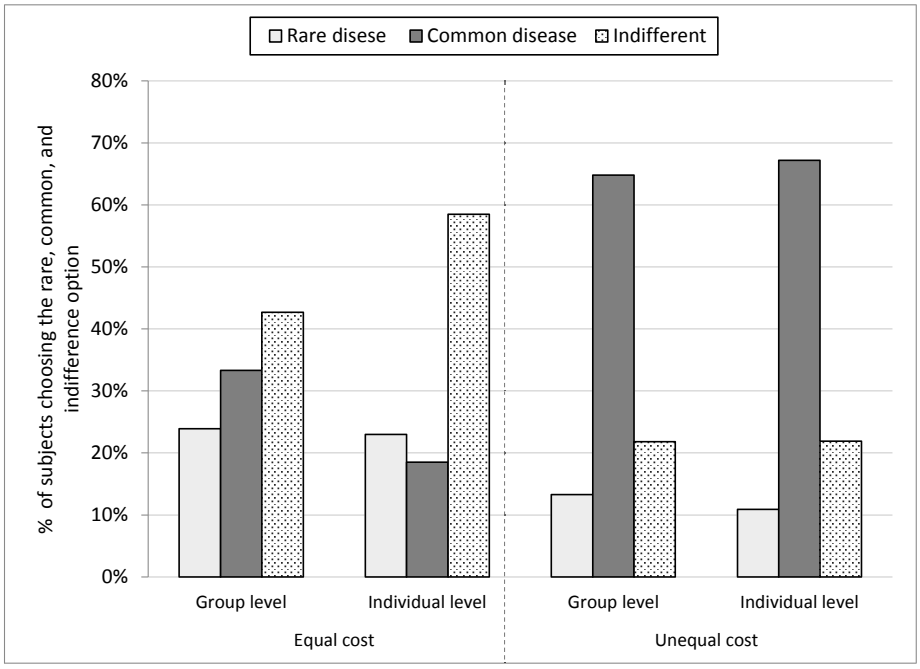
General preferences for rarity

Figure 3 shows the proportion of respondents that chose to allocate funds to patients with a rare or common disease for the four scenarios across all versions (A, B, C) of the survey. It also shows the fraction of respondents who stated that they were indifferent to the two choice options. The two left clusters of bars in Figure 3 show responses when treatment costs were described as equal. At the group-level, where respondents faced a decision to fund treatment for either 100 patients with a rare disease, or 100 patients with a common disease, 23.9% of the subjects chose to treat the rare disease group. A larger share, 33.3%, chose the common disease group, whereas 42.7% were indifferent. Thus, a larger proportion of the respondents prioritised the common disease group when treatment costs were described as identical. At the individual level, where respondents faced a decision to fund treatment for either one patient with a rare disease or one patient with a common disease, 23.0% of the subjects chose to treat the rare disease group. A smaller share, 18.5%, chose the common disease group, whereas 58.5% were indifferent. Thus, there were notable differences in responses between the individual level compared with the group level.

The two right clusters of bars in Figure 3 show responses in the scenarios where treatment costs between rare and common diseases were unequal. More specifically, they show responses in the scenarios where it was eight times costlier to treat patients with a rare disease than those with a common disease. As expected, most respondents, 64.8%, chose to maximise the

number of patients treated, and prioritised the common disease, with only 13.3% choosing patients with the rare disease at the group level. The results were similar at the individual level, where 67.2% chose to treat patients with a common disease and 10.9%, the patients with a rare disease.

Figure 3: Share of respondents choosing to treat patients with rare or common diseases across all scenarios.

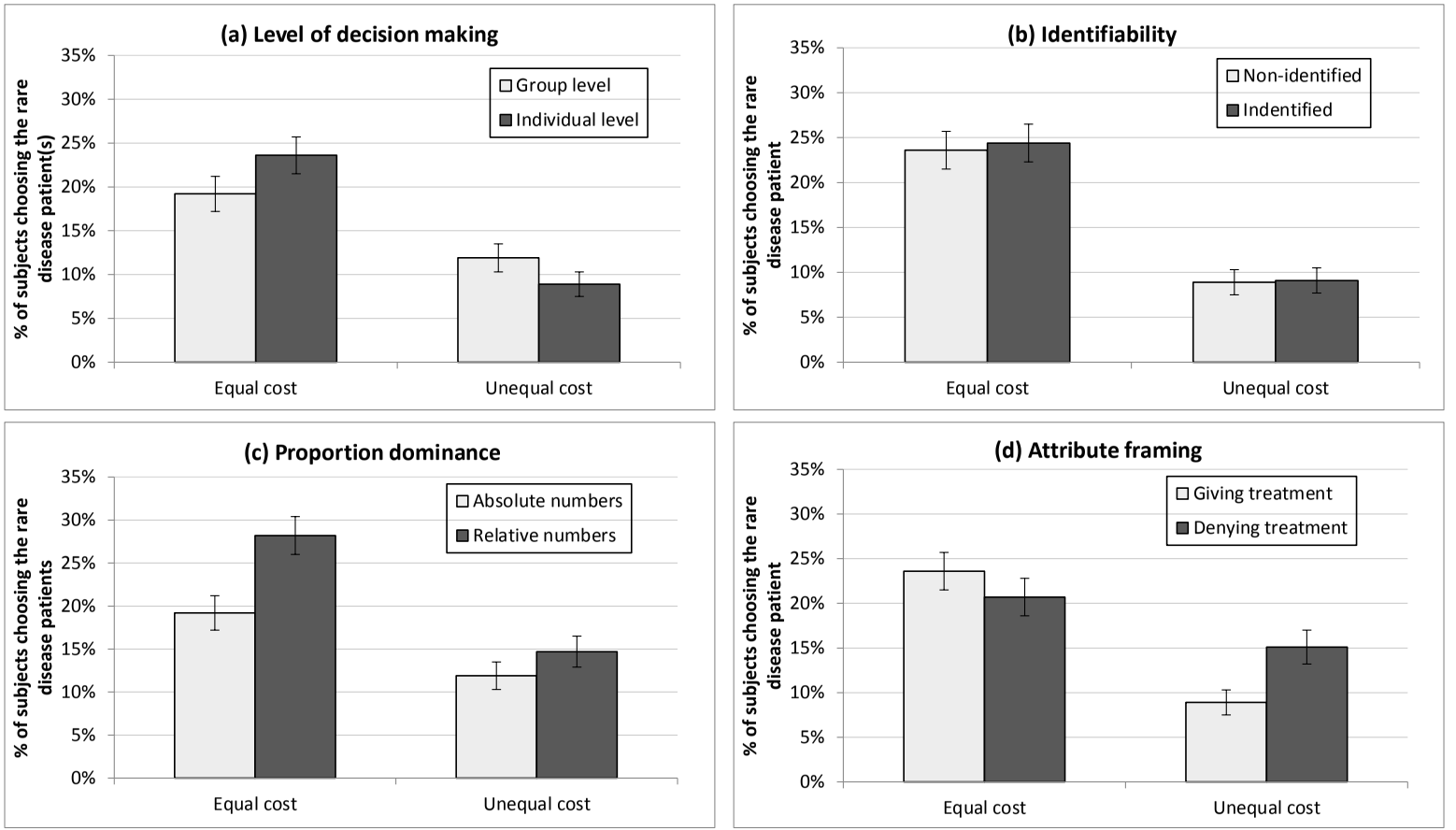


As could be expected, the fraction of respondents choosing to prioritise patients with a rare disease decreased in the unequal-cost scenarios, as compared with the equal-cost scenarios, both at the individual (23.0% v. 10.9%) and group (23.9% v. 13.3%) level (McNemar's test, $P < .01$). Consequently, the scenarios that are arguably closest to the real-world decision problems in orphan drug funding, were also the ones where support for prioritising rarity was the lowest.

Effects of the psychological manipulations

Figure 4 shows how preferences for treating patients with a rare disease changes with regard to key psychological manipulations, and these results were confirmed by logistic regression analyses.

Figure 4: Share of respondents with a preference for treating patients with rare diseases dependent on psychological manipulations.



The percentage of respondents that chose to treat the patients with a rare disease at different levels of decision making is shown in Figure 4a. As opposed to the results shown in Figure 3, the results depicted in Figure 4a represent within-subject differences only from the baseline version of the questionnaire. When costs were equal, 19.2% of respondents allocated funds to patients with a rare disease at the group level. This proportion of subjects increased to 23.6% at the individual level (McNemar's test, P=.09). In the unequal-cost scenarios, the effect of moving from group to individual level of decision making was in the opposite direction. The proportion of respondents giving priority to rarity decreased from 11.9% to 8.9%. This decrease in preferences for rarity was statistically significant (McNemar's test, P<.05).

The percentage of respondents that chose to treat patients with a rare disease dependent on identifiability is depicted in Figure 4b. Identifying the patient with the rare disease did not increase the share of respondents choosing to allocate resources to the patient in either the equal- (Chi-Sq, P=.77) or the unequal-cost scenario (Chi-Sq, P=.89). Although identifiability had no effect on preferences for rarity per se, in the unequal-cost scenario, fewer subjects were indifferent and more prioritised patients with a common disease when the patient with a rare disease was identified, rather than not identified (Chi-Sq, P<.05). Thus, there was an indication that identifiability had a negative effect on preferences for rarity when costs were unequal.

The effect of the proportion dominance manipulation is shown in Figure 4c. In the equal-cost scenario, the share of respondents who stated a preference for rarity increased from 19.2% to 28.2% when outcomes were presented in relative terms (i.e., treating 80 out of 80 patients with a rare disease or 100 out of 10,000 patients with a common disease), compared with when outcomes were presented in absolute terms (i.e., treating 100 patients with a rare disease or 100 patients with a common disease). This effect was statistically significant (Chi-Sq, P<0.01). Thus, more participants chose to maximise the relative number of treated patients, so-called proportion dominance, at the expense of the absolute number of treated patients. In the unequal-cost scenarios, stated preferences for rarity increased from 11.9% to 14.7% (Chi-Sq, P=.24). Thus, the effect of proportion dominance becomes less prevalent as opportunity cost increases. Still, it should be noted that rational choice theory predicts that the share of participants that allocate funds to the rare disease group should be lower (not higher)

in the scenarios testing for proportion dominance, since allocating funds to treat patients with a common disease maximises the number of treated patients.

The percentage of respondents that chose to treat the patient with a rare disease dependent on attribute framing is depicted in Figure 4d. In the equal cost scenario, when asking respondents to deny funding to patients as opposed to prioritise who should receive funding, the percentage who chose the patient with a rare disease decreased from 23.6% to 20.7% (Chi-Sq, P=.34). In the unequal cost scenario, the share of respondents who preferred rarity increased from 8.9% when prioritising to 15.1% when rationing care. This increase was statistically significant (Chi-Sq, P<.01).

The influence of identifiability and singularity on decision making (Paper II)

Descriptive results

Table 6 presents the descriptive results divided by treatment from the three experiments SWE I, SWE II and USA. The table also shows collapsed percentages for experiments SWE I and SWE II, as well as for USA and USA reversed order.

Table 6: Descriptive results for Exp. SWE I, Exp. SWE II and Exp. USA.

	Treatment 1:	Treatment 2:	Treatment 3:	Treatment 4:
Exp. SWE I	**1 id vs. 5 non-id**	**1 non-id vs. 5 non-id**	**1 id vs. 5 id**	**1 non-id vs. 5 id**
n	81	92	84	77
Subjects choosing the single child - n, (%)	23, (28.4%)	37, (40.2%)	20, (23.8%)	25, (32.5%)
Women - n, (%)	42, (52.5%)	51, (55.4%)	44, (52.4%)	39, (50.7%)
Mean age	20.9	21.2	20.8	21.3
Exp. SWE II				
n	60	61	63	61
Subjects choosing the single child - n, (%)	15, (25.0%)	15, (24.6%)	11, (17.2%)	12, (19.7%)
Women - n, (%)	39, (65.0%)	29, (47.5%)	45, (70.3%)	37, (59.7%)
Mean age	22.8	22.3	22.1	21.9
Exp. SWE I + II				
n	141	153	147	138
Subjects choosing the single child - n, (%)	38, (27.0%)	52, (34.0%)	31, (21.1%)	37, (26.8%)
Women - n, (%)	81, (57.5%)	80, (52.3%)	89, (60.5%)	76, (55.1%)
Mean age	21.9	21.8	21.5	21.6
Exp. USA				
n	82	84	84	81
Subjects choosing the single child - n, (%)	44, (53.7%)	35, (41.7%)	42, (50.0%)	20, (24.7%)
Women - n, (%)	42, (51.2%)	42, (50.0%)	50, (59.5%)	52, (64.2%)
Mean age	46.8	45.5	45.9	43.6
Exp. USA reversed order	**5 non-id vs. 1 id**	**5 non-id vs. 1 non-id**	**5 id vs. 1 id**	**5 id vs. 1 non-id**
n	80	80	82	78
Subjects choosing the single child - n, (%)	35, (43.8%)	24, (30.0%)	31, (37.8%)	22, (28.2%)
Women - n, (%)	43, (53.8%)	39, (48.8%)	46, (56.1%)	45, (57.7%)
Mean age	45.4	43.2	46.5	44.0
Exp. USA + USA reversed order				
n	162	164	166	159
Subjects choosing the single child - n, (%)	79, (48.8%)	59, (36.0%)	73, (44.0%)	42, (26.4%)
Women - n, (%)	85, (52.5%)	81, (49.4%)	96, (57.7%)	97, (61.0%)
Mean age	46.1	44.4	46.2	43.8

The influence of identifiability and singularity on choice

Figures 5a-d further illustrate the descriptive results from experiments SWE I, SWE II and USA. The percentage of subjects choosing to give the vaccine to the single child, irrespective of identifiability, is presented in Figure 5a. Overall, a dominant share of subjects chose the benefit maximising option when rationing vaccines to children. That is, there was a general

preference for the group of five children over the single child. It is nevertheless notable that a non-negligible share of subjects chose the non-benefit maximising option — on average, across all experiments, 32.6 % distributed the vaccine to the single child. The percentage choosing to allocate the vaccine to the single child was highest in Experiment USA (42.5%), and lowest in Experiment SWE II (21.6%). Also, the percentage choosing the single child was significantly higher in Exp. SWE I (31.4%) than in Exp. SWE II (Chi-Sq, p=.009), suggesting that the difference with regard to the circumstances of the single child, potentially affecting the perceived vulnerability of the single child, had an effect on choice.

Figure 5: Proportion (±s.e.) of subjects allocating vaccine to the single child in Exp. SWE I, Exp. SWE II and Exp. USA.

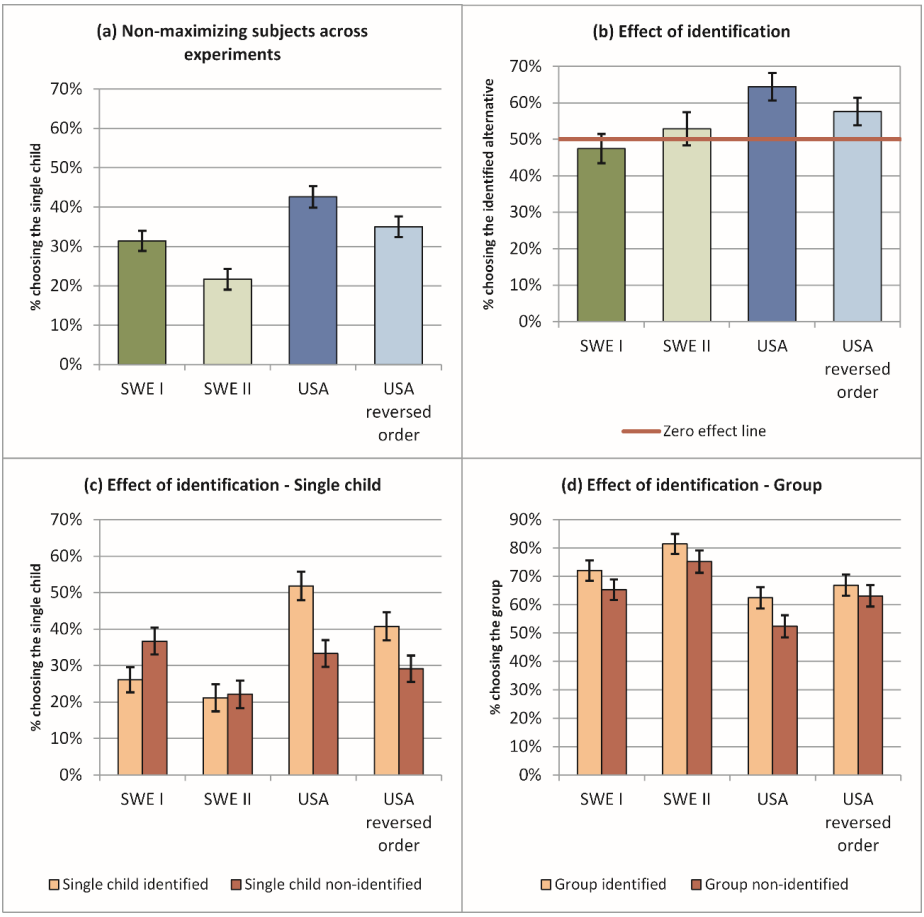


Figure 5b illustrates the general effect of identification in each experiment. Subjects' proneness to give vaccines to children presented as identified was tested by pooling responses where subjects chose the identified option and pooling responses where subjects chose the non-identified option across treatments 1 (1 id vs. 5 non-id) and 4 (1 non-id vs. 5 id). A binominal test was conducted with the null hypothesis h0=0.5 — meaning that, on average, 50% of subjects would choose the identified option if identification had no impact on choice. The "zero-effect line", depicted in Figure 5b, represents h0. The null hypothesis cannot be rejected based on responses in Exp. SWE I and Exp. SWE II, implying that there was no impact from identifiability alone on moral decisions in these experiments. The overall effect of identification in Exp. SWE I was slightly negative — only 47.5% gave vaccines to the identified option. In Exp. SWE II the general effect of identification was slightly positive since 52.9% chose the identified option. In Exp. USA, however, the overall effect of identifiability on choice was strongly positive ($p<.001$). In total, 61.1% of subjects in Exp. USA chose the identified option. Thus, our first hypothesis that subjects will allocate relatively more vaccines to identified children (with name and picture), compared to children presented as non-identified, is confirmed by the results in Exp. USA while this is not the case in Exp. SWE I and SWE II.

Figures 5c and 5d show the share of subjects choosing to distribute the vaccine to the single child (Figure 5c), and the group of children (Figure 5d), when presented as either identified or non-identified. In Exp. SWE I, 26% of the subjects chose the single child when presented as identified, as opposed to 37% when presented as non-identified (Chi-Sq, $p=.037$). Thus, a statistically significant negative effect of identifiability was found for the single child in Exp. SWE I. When the group of children was presented as identified, 72% of subjects chose to allocate vaccines to the group. This share decreased to 65% when the group was presented as non-identified (Chi-Sq, $p=.186$). Although this positive effect of identification related to the group is not statistically significant, Exp. SWE I suggests an inverse effect of identification for a group and a single child.

In Exp. SWE II, where information about the inaccessible mountain village was excluded from the instructions, less variation between treatments is seen. As shown in Figure 5c there was practically no difference in subjects' willingness to choose the single child when identified (21%), compared to when non-identified (22%) (Chi-Sq, $p=.850$). The effect of identification for the group of children (Figure 5d) was weakly positive with the share of

subjects choosing to give vaccines to the group increasing from 75% to 81% when identified (Chi-Sq, p=.235).

The results of Exp. USA differ considerably from those of Exp. SWE I and Exp. SWE II. Notably, the share of subjects who chose to allocate vaccine to the single child increased from 33% to 52% when presenting the single child as identified (Chi-Sq=11.55, p<.001). The effect of identification was also positive for the group of children, although not as striking as for the single child. The share of subjects who chose to allocate vaccines to the group of children increased from 52% to 62% when presented as identified (Chi-Sq=3.39, p=.065). Running the experiment with reversed order of presentation (i.e., the group of children was presented first and the single child second), the effect of identifiability on allocation choice remained similar. Interaction analyses showed no significant interaction between identifiability and order of presentation, and thus confirmed a stable effect of identifiability. However, there was a significant order effect related to allocation choice. Independent of identifiability, subjects were more likely to choose the alternative presented first in the scenario. The share of subjects who chose to allocate vaccines to the single child decreased from 43% to 35% when the group of children was presented first in the scenario (Chi-Sq=3.95, p=.047). Thus, our second hypothesis that the effect of identifiability is larger for a single child compared to a group of children (singularity effect) was supported by the results in Exp. USA but not by Exp. SWE I and SWE II.

To further explore the descriptive results, we conducted logistic regression analyses on giving the vaccine to the single child (controlling for age and gender). Table 7 shows the results from these analyses, where the effects are presented as odds ratios. Analyses of interactions (using logistic regression) showed that the pattern of results regarding the effect of identifiability did not significantly differ between SWE I and SWE II (single child: p=.417; group: p=.844). Thus, we merged data from these experiments in the logistic regression analyses presented in Table 7, using the label SWEDEN.

Table 7: Logistic regressions on giving vaccine to the single child, effects presented as Odds Ratios (OR).

	SWEDEN		USA	
	OR	sig.	OR	sig.
Single child identified	0.72 (0.50 - 1.06)	0,093	2.20 (1.40 - 3.46)	0,001
Group identified	0.66 (0.45 - 0.97)	0,032	0.66 (0.42 - 1.03)	0,068
Age	0.93 (0.86 - 1.01)	0,088	1.00 (0.98 - 1.01)	0,586
Female	1.67 (1.34 - 2.46)	0,009	0.79 (0.50 - 1.26)	0,317

In line with what is shown in Figure 5c, the identifiability of the single child reduced the likelihood of subjects choosing the single child in the Swedish sample. However, identification of the group decreased the odds-ratios of choosing the single child by 0.34 (i.e. a positive effect of identification for the group). The logistic analysis for the American sample showed a highly significant positive effect of identifiability of the single child, also when controlling for age and gender. An additional finding was that females in the Swedish sample were significantly more likely to give the vaccine to the single child than males were. Thus, females adhere to a greater extent to a deontological no-harm principle, while men were more likely to adhere to a consequential benefit-maximising principle. In the American sample, no such gender differences were detected.

To test for differences in effect between SWEDEN and USA an interaction analysis was conducted. This interaction analysis showed that the effect of identifying the single child differed significantly between USA and SWEDEN ($p<.001$). This admittedly post-hoc result suggests that the difference between Sweden and USA in the effect of identification of the single child cannot be explained (solely) as a chance finding. The positive effect of identifying the group, however, was similar for USA and Sweden ($p=0.749$ for the difference).

Follow-up questions

Responses from the follow-up questions related to subjects' emotional responses to the dilemma showed that elicited sympathy was higher for the identified child/children, compared to the non-identified child/children in all three experiments. The positive effect of identification on elicited sympathy was, however, more pronounced in the Swedish experiments. No differences were found regarding experienced difficulty in responding to dilemmas between the experiments. Thus, subjects did not find it increasingly hard to make moral decisions due to identifiability. In Exp. SWE II and Exp. USA subjects were asked if they believed that their choice would

result in a real donation. The average response was 3.51 in Exp. USA and 3.18 in Exp. SWE II, using a six-point scale ranging from 1 = "not convinced at all" to 6 = "very convinced".

Factors to consider when making reimbursement decisions regarding orphan drugs (Paper III)

The following section presents identified decision-making components related to reimbursement decisions regarding orphan drugs (see Table 8). Decision-making components are categorised into four overarching themes: the patient, the treatment, economic aspects, and societal concerns. Additional components derived inductively from the focus group discussions are also presented in Table 8, followed by an asterisk (*).

Table 8: Identified decision-making components and descriptions.

Decision-making components related to priority setting and rare diseases	Description
The patient	
Severity of the disease	How a condition affects a patient's quality or length of life.
Rarity (prevalence)	The number of individuals affected by a disease.
Vulnerable group	Whether rare disease patients can be viewed as a particularly vulnerable group, compared to other patient groups.
Double jeopardy	A patient should not be disadvantaged because he/she has been unfortunate enough to be affected by a severe disease that also happens to be rare and costly to treat.
Identifiability of a patient	Whether a patient is identified, e.g., through media coverage.
Personal characteristics*	E.g., age, gender, level of autonomy, social class, role in society and ethnicity.
Own responsibility*	Whether the patient's situation is self-inflicted.
The treatment	
Treatment effect	Whether a treatment is effective in terms of prolonging the patient's life or improving the patient's quality of life.
Treatment alternatives	Access to alternative therapies to treat a patient.
Economic aspects	
Cost-effectiveness	Whether the treatment provides value for money, i.e. the costs associated with the treatment are reasonable (or not) in relation to the health gain, compared to standard treatment.
Budget impact	Whether the healthcare budget is affected by the potential introduction of the new treatment.
Pharmaceutical company responsibility*	The pharmaceutical companies' role in setting prices.
Societal concerns	
Advancing scientific knowledge	Whether the study of rare diseases can lead to new insights or to the development of new treatments for other patients.
Rule-of-rescue	There is a moral obligation to treat a severely ill, identified patient suffering from a rare disease, no matter the costs.
A fair decision*	Decision makers should be able to motivate why they make certain choices.
Expectations on society*	The implications of living in a society. Obligations towards other members in a society.

*Components derived inductively from focus group discussions.

Components related to the patient

Focus group participants generally considered the *severity of the disease* as an important factor to consider when making priority-setting decisions regarding orphan drugs. It was expressed that society should be willing to pay more for drugs treating severely ill patients (and conversely, not pay more for drugs targeting diseases with a low degree of severity). The severity of the disease was often viewed in combination with other components, e.g. the treatment effect. *Rarity* should not be an argument for giving higher priority; however, it appeared that rarity was often confounded with conditions that are severe and life-threatening. The *vulnerable group* and *double jeopardy* components were not given much consideration by respondents. However, it was argued that some groups, such as children,

were more vulnerable than others. It was agreed that a patient's *identifiability* should not affect decision making. But it was argued that identifying patients through media can play an important role in exposing unfair priorities. Also, media can give people who are not affected by a rare disease a glimpse of the injustices that these patients can experience, and thereby raise awareness of some rare diseases. Other components, derived inductively from the interviews, were the patient's personal characteristics. For example, all groups discussed *age,* and it was generally agreed that children should have some priority. *Own responsibility* was also a component that was brought up as something that could influence priority-setting decisions.

Components related to the treatment

The *treatment effect*, and how a drug performed in comparison with other treatment alternatives, were seen as important components to consider when making a reimbursement decision. In some cases, it was argued that a lower degree of treatment effect could be accepted for very severe conditions. Participants generally argued that it was important to consider whether there were any other *treatment alternatives*, particularly if the severity of the disease was high and if the treatment was effective. Participants commonly used emotional language when discussing the lack of treatment alternatives. For example, participants stated that it is cruel to say no if there are no other treatment alternatives available, that you would deprive a patient of the feeling of hope that a drug can offer, and that if there is only one effective treatment a patient should have access to it otherwise "this is not a civilised society".

Economic components

Participants' view of the importance of the *cost-effectiveness* component varied. Some argued that it was the most important criterion, whereas others were more reluctant to take cost-effectiveness into consideration. One participant argued that society has to consider cost-effectiveness, but that the individual's own opinion on the matter is not as important. Also, it was noted that if cost-effectiveness was the only criterion when making a decision, a drug that costs 20 times as musch as you would normally pay per health gain in the publicly funded healthcare system would never be reimbursed. It is notable that the cost-effectiveness criterion was rarely brought up in the discussion and that it was often misunderstood. Also, participants more commonly referred to economic aspects in terms of "costs", "the economy" and "the money" rather than cost-effectiveness. This indicates that even though cost-effectiveness was presented and defined prior to the

discussion, the concept of cost-effectiveness might be hard for lay people to grasp and discuss. Regarding the *budget impact* of the drug, participants discussed what a budget restriction means in practice. They reasoned that society needs to take the budget into consideration and that everything has a "price tag". The budget sets the limits for what is possible to achieve. Participants often reasoned in terms of opportunity costs. In one group it was argued that if only one, or a few people, are affected by a disease then the cost related to the total budget is not very large, which would imply that the fewer individuals affected by a disease, the better, when viewed from a monetary perspective. Another group discussed ways of making room in the budget by means other than cutting costs related to the drug. These alternative methods included reducing high salaries for some employees and rearranging and adjusting the budget to make room for some expensive drugs. The price of the drug and the *responsibility of the pharmaceutical company* was considered in several groups. It was acknowledged that the pharmaceutical companies had an interest in making profits, and one participant suggested that there should be negotiations with the company in order to lower the prices.

Societal components

Participants argued that *advancing scientific knowledge* is an important component to consider. However, this component was discussed more in general terms than in relation to the specific priority setting dilemma. Innovation was seen as important because it gives hope to society (and patients), and because knowledge is intrinsically valuable. Also, with innovation, participants believed that there could be a reduction in the price of the drug, and that the drug could be made more effective and potentially be used for other indications. One group argued that the *rule of rescue* is important because it indicates what kind of society we live in. However, in reality there are factors that limit what is possible to achieve, such as the budget impact. The similarities between rule of rescue and situations where there are no other treatment alternatives were also discussed. It was argued that if a patient only had one effective treatment option, the treatment had to be given because "you can't just stand by and watch someone die". Also discussed was where to draw the line—should a life be saved at any cost? Thus, the importance of this component seems to depend on how the participants interpret the consequences of the rule of rescue. It was argued, in one of the groups, that whether the *decision is fair* should be considered. Decision makers should be able to justify their choices. But it was also argued that what is considered fair would depend on circumstance; for example, if you are affected yourself it is more likely that you would consider a

situation unfair. The *expectations on the society we live in* were brought up in the discussions and it was argued that in a functioning society individuals were not to be left to fend for themselves.

In sum, rarity in itself was not viewed as a component that should make society pay a premium in funding decisions for orphan drugs. However, in the focus group discussions, participants took many decision components related to rarity into consideration, and balanced them against one another. Three components were viewed as particularly important considerations when setting priorities regarding orphan drugs — disease severity, treatment effect and lack of other treatment alternatives. These components had a prominent role when participants argued for granting access to orphan drugs not meeting demands for cost-effectiveness. For example, in cases where a rare disease patient is severely ill, if the treatment effect is significant and if there are no other treatment alternatives, then society should possibly be willing to pay more per health gain for that drug. Thus, our results indicate that rarity is often confounded with conditions that are severe and life-threatening, which people in general do put a premium on when thinking about healthcare priorities.

Perceived challenges and solutions when setting priorities regarding orphan drugs (Paper IV)

The challenges and solutions related to orphan drug reimbursement presented in the following sections are summed up in Tables 9 and 10.

Perceived challenges

Given the current situation of orphan drug reimbursement, we have identified three types of challenges facing decision makers: (1) challenges regarding the components involved when making reimbursement recommendations, (2) challenges regarding the reimbursement system and the process that leads up to a recommendation, and (3) challenges related to the acceptance of the final recommendation.

Firstly, when assessing orphan drugs, decision makers often have to make recommendations on highly priced drugs based on limited scientific evidence. Consequently, the incremental cost effectiveness ratios (ICER) per QALY are uncertain and commonly exceed what is normally accepted for pharmaceuticals. In addition, rare disease patients are often severely ill and in great need of effective treatments. Secondly, informants brought up

challenges related to the reimbursement system and the process leading up to a recommendation. There are often parallel systems for the reimbursement and for the financing of orphan drugs, which can cause uncertainties for decision makers, physicians and patients. Furthermore, even if decision makers balance decision criteria in the process, it appears challenging to determine to what extent severity and lack of treatment alternatives can offset uncertain scientific evidence and a lack of cost-effectiveness. Thirdly, informants perceive the acceptance of the final reimbursement recommendation of orphan drugs as challenging in various ways. Informants saw that both positive and negative recommendations could be a source of injustice for patients suffering from rare and common diseases respectively. Giving positive recommendations for drugs not meeting demands for cost-effectiveness could crowd out urgent care for other patients. In addition, starting to accept higher prices for some drugs make it increasingly difficult to set limits in the future. In contrast, giving negative recommendations could lead to severely ill patients not having equal access to care, because the group is small and not sufficiently profitable for the pharmaceutical companies. In the case of giving negative reimbursement recommendations, the public does not always understand or accept the use of cost-effectiveness. It can therefore be difficult to set explicit and fixed thresholds of what is acceptable for a drug to be included in the reimbursement scheme.

Table 9. Challenges identified by informants regarding orphan drug reimbursement.

Themes	Sub-themes	Examples
High prices	Not meeting demands for cost-effectiveness High potential budget impact	
Lack of scientific evidence	Higher degree of uncertainty Conventional outcome measures not adapted for evaluating rare disease patients	
Lack of transparency	Price setting	Not clear how pharmaceutical companies are pricing orphan drugs Prices are kept secret after negotiation
	Parallel system for reimbursement & financing	Different processes regarding hospital drugs and prescription drugs National reimbursement organisation and local/regional health care budgets General reimbursement process and individual reimbursement Hard to navigate the system for manufacturers, patients, practitioners and decision makers
Lack of acceptance of decision criteria	Lack of acceptance of cost-effectiveness as decision criterion among the public Decision makers perceive that it is difficult to assess cost-effectiveness for orphan drugs	
Difficulties when balancing criteria and the goals for the healthcare system	How to balance conflicting criteria e.g. severity versus cost-effectiveness How to balance conflicting goals in the healthcare system.	
Influence of emotional factors	Negative media coverage can undermine the legitimacy of the decision-making process Decision makers can be influenced by emotional factors when making reimbursement recommendations	
Acceptance of the final recommendation	Positive reimbursement recommendation	Financial impact of orphan drugs Setting limits regarding what care to offer citizens Risk for injustices between patient groups (rare vs common diseases), e.g. crowding out treatments that are cost-effective
	Negative reimbursement recommendation	Risk for injustices between patient groups (rare vs common diseases), e.g. individual rare disease patients will not access treatment

Perceived solutions

In response to the challenges identified above, countries have employed various solutions. All countries in this study have presented more or less explicit solutions for dealing with orphan drug reimbursement, with the exception of France, who generally focused more on facilitating access to these drugs rather than imposing limitations. There are generally two broad themes regarding which solutions countries have employed to handle orphan drug reimbursement: special arrangements uniquely for orphan drugs, and general arrangements that can be used for orphan drugs as well as for other drugs. These solutions can be used simultaneously in each respective country.

In Norway and England, we find special arrangements for orphan drugs. The HST-evaluation in England have so far assessed only a few selected cases, for highly expensive drugs for very rare disease patients. In Norway, patient access to effective, but not always cost-effective orphan drugs is secured through individual reimbursement. In Sweden and the Netherlands there has been more focus on introducing specific or general measures within the existing system. For example, to compensate for the limited scientific evidence they have suggested creating disease specific committees, and creating registries to collect more data on the costs and effect of the drugs. To limit the overall costs of orphan drugs, the focus is on optimising the doses for patients and developing start/stop criteria for when patients should be given treatment, and for when to stop treatment in cases where the drug is not effective. In Sweden, there is a development towards collaboration between county councils and pharmaceutical companies under the supervision of the national reimbursement agency (TLV). Furthermore, TLV has recently stated that the rarity of a disease could increase the willingness to pay in cases where the drug is aimed at treating very rare diseases where no treatment alternatives are available, and in cases where patients are severely ill. In addition, cooperation between actors (such as the "three party collaboration" in Sweden), may increase trust between involved actors, and lead to a more transparent decision-making process.

Table 10. Solutions identified by informants for handling reimbursement of orphan drugs.

Themes	Sub-themes	Examples
Special arrangements for ODs	Use of a thorough procedure	**HST-evaluation** Compensate for limited scientific evidence Create legitimacy for giving positive/negative reimbursement decisions Cost-effectiveness is not assessed and considered explicitly
	Decentralised decision making	**Individual reimbursement** Limit the financial impact of expensive drugs Safety measure for patients that would not access treatment otherwise Cost-effectiveness is not assessed and considered explicitly
	Introducing alternative decision criteria/aspects	Rarity as a decision-criterion No treatment alternatives Vulnerable group Consequences for patients' family members Public health priority Balance criteria, e.g. put more weight on severity and less weight on cost-effectiveness to motivate paying more for some drugs
General arrangements used for ODs (and other drugs)	Price negotiations and risk sharing agreements	Between pharmaceutical companies and final decision maker, regional level decision makers or pricing committee Limit risks when introducing new pharmaceuticals Lower prices of orphan drugs Coordinate the introduction of new pharmaceuticals
	Conditional reimbursement	Defining subgroups Re-evaluation after a specified time Use of start/stop criteria
	Creation of disease specific advisory committees	To give advice on the clinical use of ODs
	Develop start/stop criteria	To ensure the effective use of ODs and to limit financial impact of expensive drugs
	Join disease specific registries to collect more data	Improve scientific evidence Make more reliable cost-effectiveness calculations
	Early access scheme	Give patients access to ODs (and other innovative drugs) in an early stage

DISCUSSION

In this thesis, I have explored healthcare priority setting from economic, ethical and psychological perspectives by looking at the case of orphan drug reimbursement. In the introduction, the individual case regarding Kalle, who suffers from Hunters disease and is in need of an expensive orphan drug, was introduced. How can we better understand this case in relation to what has been presented in the preceding sections of this thesis? Does rarity matter, should rarity matter, and how does the rarity of a disease influence healthcare decision making? In this chapter, I will discuss these questions in light of what has been found in studies I-IV and expand the analysis further. Lastly, I will present some recommendations and reflections on contemporary trends in relation to orphan drug reimbursement.

Does rarity matter in healthcare decision making?

Rarity matters in healthcare decision making in at least two ways. First, it causes a market failure as pharmaceutical companies previously ignored rare disease treatments because of the lack of profits. Thus, as we have seen, incentives are provided to increase the supply of orphan drugs. These incentives appear to have turned matters upside down — orphan drugs are now seen as an opportunity for pharmaceutical companies to make profits (Meekings et al., 2012, Hughes and Poletti-Hughes, 2016). This leads to the second reason rarity matters. As the number of patients is still small, when entering the market, the drug prices are often higher than for drugs aimed at patients suffering from equally severe common diseases. Other contributing factors to the high prices are the extended market exclusivity for orphan drugs, and that decision makers have shown to pay premium prices for orphan drugs.

The economic impact of expensive orphan drugs can be viewed from a budget impact perspective, or by considering the cost-effectiveness of these drugs. A commonly stated argument for why orphan drugs should be provided is that although they are very expensive, they are for only a few patients and thus the budget impact is limited. However, although each individual orphan drug represents only a small share of the total pharmaceutical budget, taken together the impact is not insignificant. Furthermore, looking only at the budget impact of orphan drugs completely disregards the health forgone by the other patients while providing non-cost-effective

drugs to the rare disease patients. In the study by Coyle et al. (2014), presented in the background, we saw that the opportunity costs of providing the drug Soliris for treatment of patients with the rare disease Paroxymal Nocturnal Hemoglobinuria (PNH) are potentially substantial. In the same article, given a Canadian context, the authors illustrate that an alternative to providing 47 patients[3] with Soliris (eculizumab) during a year would for example be to fund 470 000 half-hour physiotherapist appointments, to reimburse 200 000 co-payments for necessary ambulance trips or to offer a supplementary home visit for every newborn. If decision makers choose to provide non-cost-effective orphan drugs, there are implications for the overall performance of the healthcare system, and, ultimately, providing orphan drugs might crowd out other essential care for other patients.

Given the distributional consequences of providing expensive orphan drugs, are there indications that society is willing to sacrifice overall efficiency in order to provide orphan drugs to rare disease patients? That is, should rarity matter in healthcare decision making?

Should rarity matter in healthcare decision making?

In this thesis, we have explored the views of the public in three of the studies included (I-III). Studies I and II show that individuals generally want to maximise health when allocating resources. In these studies, the alternative use of resources is clearly stated, and subsequently the consequences of treating the rare disease patients are clearly visualised. Thus, if using these experiment based results as an input to priority setting in healthcare, it would indicate that a greater willingness to pay for orphan drugs should generally not be accepted. However, in Study I, it should be noted that a non-negligible share of respondents chose to be indifferent, or chose to treat the rare disease patients, even when the opportunity cost of treating one rare patient was to treat eight common disease patients. This can be interpreted as a willingness to provide treatment to patients, even though this will lead to a situation where health gains are not maximised. This is also seen in study II, where, across all treatments, in all three experiments, 32.6% of the subjects chose to stay with the deontological default option instead of actively choosing to maximise benefits.

[3] Which corresponds to approximately 20 % of PNH patients in Canada.

When people are given more time to discuss and deliberate hypothetical decision situations, as in study III, rare disease patients are given some priority. In addition, even though participants are aware of the scarcity of resources, there is less focus on economic factors. It is notable that the cost-effectiveness criterion was rarely brought up in the discussion, and that it was often misunderstood. Also, participants more commonly referred to economic aspects in terms of "costs", "the economy" and "the money" rather than cost-effectiveness. Even though participants generally argued that rarity *per se* should not be a factor determining whether a drug should be reimbursed, rarity was often confounded with conditions that are severe and life threatening, which people in general do put a premium on. In study IV, we saw that decision makers involved in practical decision making generally provide expensive orphan drugs to patients, especially in cases where the severity of the disease is great. However, it appears that the justification for providing such drugs is made more or less explicitly. On the one hand, some countries disregard or are not explicit about the lack of cost-effectiveness for orphan drugs. On the other hand, some countries take the influence of rarity into consideration when setting priorities and deal with this in various ways.

Thus, as seen in study IV, there appears to be some acceptance that rarity should matter when making reimbursement decisions for orphan drugs. In some countries, rarity as an explicit decision criterion has been suggested or implemented. In Sweden, rarity has formally been taken into consideration when making decisions both at the national reimbursement agency (TLV) and at the regional level by the NT-council, which is in charge of giving recommendations about the use of new pharmaceutical therapies to the county councils (The Dental and Pharmaceutical Benefits Agency, 2016, New Technologies Council, 2015). In Norway's guidelines for priority setting in healthcare, it has been concluded that rarity *per se* should not be used to motivate paying more for orphan drugs (Ministry of Health and Care Services, 2016). However, somewhat contradictorily, the possibility to give some priority for patients with rare diseases is not completely disregarded. For example, in the guidelines it is stated that there might be reasons to accept lower standards for scientific evidence for orphan drugs, and that higher costs could be accepted for very rare diseases with a high degree of severity.

Even when it is not explicitly stated that rarity should matter (or not), countries have implemented various measures to deal with the consequences of

rarity. Examples of such measures are separate procedures for dealing with the uncertainties connected to orphan drugs, such as the HST evaluations in England and the individual reimbursement in Norway, or more general measures used for reducing risks or limit the costs of orphan drugs. The development of the HST evaluation in England was a response to the challenges associated with reimbursing orphan drugs and an attempt to create an independent and transparent assessment process. In countries where no special arrangements are in place, or parallel to such arrangements, there are also general measures used to improve the process, increase acceptance of recommendations and to limit the financial impact of orphan drugs. These measures include e.g. start/stop criteria, conditional reimbursement, creation of disease specific committees, and joining registries to collect more data.

The results presented in studies I-IV seem to be inconsistent concerning whether rarity should matter. The inconsistency suggests that the answer to the question of whether rarity should matter is context dependent. Situations involving real patients are likely to become more emotionally burdensome (compared to hypothetical decisions), and the complexity of the decision is likely to increase with the number of individuals involved when making the decision, as well as with the number of factors that need to be taken into consideration. These discrepancies leads us to the question as to how rarity influences priority setting for orphan drugs.

How rarity influences decision making

The rarity of a disease is likely to influence priority-setting decisions in various ways. In this thesis, a number of psychological effects potentially influencing priority-setting decisions regarding orphan drugs are explored, and confirms its impact on allocation decisions in the experimental studies I-II. Results from the qualitative studies III-IV further show that individuals and decision makers are influenced by emotions when discussing orphan drug reimbursement or when making such reimbursement decisions. In this section, I will discuss the influence of psychological and emotional factors on healthcare priority setting, for example in relation to Evidence Based Decision Making (EBDM). I will also discuss priority setting on a clinical level and on a policy level and the discrepancy between these levels. Furthermore, the influence of proportion dominance and identifiability of a patient on priority setting in healthcare will be discussed more in detail.

The use of EBDM has gained prominence in the field of healthcare policy when making decisions about how to allocate resources in the healthcare sector. Although a seemingly rational approach to setting priorities, the potential influences of various psychological effects are rarely acknowledged. The ever-increasing body of research regarding the influence of heuristics and biases in priority setting implies that there is a need to challenge the underlying rationality assumptions in EBDM. The influence of psychological effects in medical decision-making may potentially weaken the reliability of the evidence and consequently undermine the decisions made. This suggests that there needs to be an awareness about cognitive limitations in decision making.

The influence of psychological effects in medical decision-making is not necessarily a bad thing. Heuristics can help decision makers at various levels of the healthcare organisation to make quick and (often) accurate decisions under time pressure. However, these kind of decisional shortcuts can have potentially important distributional consequences that may influence the availability or quality of the healthcare services for patients. At the clinical level, such shortcuts can be justified with reference to limited time or resources to fully take into consideration all relevant aspects important for the decision. The influence of psychological effects can also be present at the policy level, where the distributional consequences can be more severe as the decisions concern population level decisions rather than decisions related to individual patients. It is notable that previous research has primarily focused on heuristics and biases in clinical practice. In this thesis, the focus has been on the policy level perspective. The results obtained suggest that there is a need for more research on the influence of psychological effects on healthcare priority setting decisions from a policy-level perspective, particularly in relation to priority setting regarding orphan drugs.

A psychological effect that was shown to influence preferences for rarity was "proportion dominance". The share of respondents choosing to treat the rare patient group increased when the choice options explicitly stated that the entire rare disease group could be treated (80 out of 80 patients) versus only a fraction of the common disease group (100 out of 10 000 patients), even though this implied a loss in overall efficiency. In health policy, there are at least two ways in which proportion dominance can influence decisions regarding funding of orphan drugs. First, policy makers may want to eliminate the "smaller" problems before they move on to the "bigger" ones. Second, compared to the total health care budget, the cost of

treating a rare disease is relatively small. Paying for rare disease treatments, even though very expensive and non-cost-effective, may be perceived as having a limited impact in relation to the total health care budget. This would result in a case of cumulative cost neglect, where policy makers tend to overlook the aggregate outcome of many inefficient decisions. Results presented in this thesis further confirms the potential influence of psychological factors and emotions when making reimbursement regarding orphan drugs.

A notable difference between priority setting at a policy level and at a clinical level is that at the clinical level, the person responsible, e.g. the treating doctor, will meet the patient in person. This is likely to make priority setting even more emotionally burdensome for the one making a decision not to treat a rare disease patient with an available, but expensive, orphan drug. Although probably more pertinent in clinical decision-making, identifiability is also likely to influence policy decisions. For example, decision makers at a policy level might have met with rare disease patient representatives, might have read a newspaper article about some rare disease patient, or might have close relatives affected by a rare disease. Identifiability has shown to positively influence willingness to contribute to specified causes (Jenni and Loewenstein, 1997, Kogut and Ritov, 2005a, Kogut and Ritov, 2005b, Kogut and Ritov, 2011). However, in studies I and II in this thesis, the prediction that identifiability should increase preferences for rarity was not supported. In study I, identifying the rare disease patient when costs were unequal increased the share of respondents prioritising the common disease, indicating a negative effect of identifiability on preferences for rarity. However, it is possible that the effect of identifiability would have been positive had we used a separate evaluation design where individuals were not explicitly aware of the alternative use of resources. In cases where trade-offs are not explicit, identifiability is more likely to have a positive effect on allocation decisions. Thus, a difference between identifiability in study I and II and the identified patients brought forward by patient advocates, pharmaceutical companies and the media is the presentation (or lack thereof) of alternative costs.

Deciding whether to reimburse expensive treatments to severely ill patients is a highly emotional task. For example, in study III, participants commonly used emotional language when discussing the lack of treatment alternatives. For example, participants stated that it is cruel to say no if there

are no other treatment alternatives available, that you would deprive a patient of a feeling of hope that a drug can offer. They also stated that if there is only one effective treatment a patient should have access to it, otherwise "this is not a civilized society". In addition, the case of Pompe and Fabry disease in the Netherlands clearly shows how decisions can be highly sensitive when patients are denied treatment. This case illustrates how decisions can be influenced by emotions (affecting members of the reimbursement agency) and by the public opinion.

In conclusion, orphan drug reimbursement is an attractive case for examining priority setting decisions. Economic, ethical and psychological perspectives help to illustrate the complexity of these such decisions. There appear to be no straightforward answers to whether or not orphan drugs should be prioritised differently compared to other drugs. Accepting higher costs per health gain (or not) for these drugs appears delicate and can be highly political.

Recommendations and further reflections

In the next section, I will give some recommendations based on what previously has been presented. What can we learn from the results presented in the thesis and how can these results help improve priority setting regarding orphan drugs? From an economic perspective, being clearer about the alternative use of resources when making reimbursement decisions would make it easier to see the health forgone because of providing non-cost-effective orphan drugs. If choosing to reimburse such drugs, the consequences of doing so would be clearer to decision makers. In addition, when using cost-effectiveness in healthcare priority setting, decision makers should find pedagogical ways of communicating what cost-effectiveness means and the implications of providing non-cost-effective treatments, in order for the public to understand the outcome of the decisions made and to increase the acceptability of these decisions. From an ethical perspective, the lack of consensus regarding how to allocate resources between rare and common patients has generally led to attempts to select and balance various criteria against one another. Further clarity in the matter can be obtained by analysing decision outcomes in light of various theories of distributive justice, but it can also be important to include the views of the public, as the decisions ultimately have to be accepted by them. However, neither theories of distributive justice, nor the public's view, provide us

with a definite answer as to whether or not orphan drugs should be prioritised differently. Thus, in order to move forward on this question, these inputs would benefit from a factual political debate characterised by transparency. From a psychological perspective, in order to improve the decision process for orphan drugs, there needs to be an awareness about which psychological effects may potentially influence such decisions. Studies have shown that so called debiasing strategies can offset the influence of some heuristics and framing effects and make the decisions more conscious (Stiggelbout et al., 2015). Such strategies include, for example, paying attention to base rates or arguing both sides before making the final decision.

Orphan drugs are in many ways challenging for decision makers when setting healthcare priorities and are likely to continue to be increasingly challenging both in the short term and in the long term. The short-term challenges related to orphan drug reimbursement is to set priorities that are acceptable to the public, patients and decision makers. Decision makers have already started introducing measures to meet these challenges and they are on a quest to find potential solutions for managing orphan drugs. The long-term challenges are not as easily foreseen. As of today, the orphan drugs available to patients target only a small share of the total number of rare diseases. Thus, it is likely to believe that the number of orphan drugs will increase over time. As patient groups will still be small and development costs will remain high, the costs of some of these treatments will continuously be high. In addition, the development towards stratified and personalised medicine may lead to an increase in the number of patients classified as rare. Reimbursements systems will potentially have to redefine policies in order to meet these upcoming challenges. There is already a trend towards dividing larger patient groups into rare subgroups (Meekings et al., 2012). These developments might eventually lead to an increasingly unsustainable situation where there is a need to make more definite priority setting decisions and where explicit choices have to be made between treatments and patient groups.

This thesis has focused on priority setting for orphan drug reimbursement. However, it should not be forgotten that priority setting for orphan drugs is only one part of the puzzle for rare disease patients. Organising other aspects of rare disease patients' care should not be ignored. Finally, it cannot be stated enough that priority setting regarding rare disease patients is complex and that this case requires particular attention from decision mak-

ers. There are many aspects to be balanced, the consequences are potentially severe (both for rare patients and for common patients depending on the decision), psychological factors are potentially influencing decisions, and the future development of this matter is uncertain but is likely to be increasingly demanding in the future. This thesis gives insights in light of the economic, ethical and psychological perspectives influencing orphan drug reimbursement and increases the understanding of what matters when reimbursing orphan drugs.

CONCLUSIONS

This thesis offers new insights about the complex nature of priority setting for reimbursement of orphan drugs. The thesis has aimed to analyse the public's view on rarity as well as practical priority setting decisions for orphan drugs in light of economic, ethical and psychological perspectives. The results show that rarity *per se* is generally not considered a relevant factor when deciding whether to accept higher costs per health gain for orphan drugs. However, the indirect factors of rarity and rarity in combination with some other factors, such as severity, treatment effect and treatment alternatives, might be reasons to consider a higher willingness to pay for these drugs. These kind of considerations are also reflected in practical decision making in a number of European countries.

Specific conclusions from study I-III related to the public's view on rarity in healthcare priority setting, and the influence of psychological effects on such preferences, are:

- There is no evidence of a general preference for giving rare patients priority over common disease patients. All else equal, 23.9% of the subjects chose to treat the rare disease group. A larger share, 33.3%, chose the common disease group, whereas 42.7% were indifferent. When treating the rare disease patients were eight times costlier, a majority of subjects chose the option maximising health gains (i.e. the common patient group).
- Preferences for rarity are malleable to a set of psychological factors, most importantly "proportion dominance". When the treatment costs were equal for the rare and the common disease, the share of respondents who stated a preference for rarity increased from 19.2% to 28.2% when outcomes were presented in relative terms (i.e., treating 80 out of 80 patients with a rare disease or 100 out of 10,000 patients with a common disease), compared with when outcomes were presented in absolute terms (i.e., treating 100 patients with a rare disease or 100 patients with a common disease).
- The identifiability of a patient has no or a negative effect on allocation decisions. This is confirmed in two separate studies. It is possible that

the effect of identifiability would have been positive had we used a separate evaluation design where individuals were not explicitly aware of the alternative use of resources.

- Although rarity *per se* was not seen as a relevant factor by participants in focus groups, other factors were relevant to consider when making reimbursement decisions for orphan drugs, in particular: disease severity, treatment effect, and treatment alternatives. In addition, it was noted that participants in focus groups more commonly referred to economic aspects in terms of "costs", "the economy" and "the money" rather than cost-effectiveness. This indicates that even though cost-effectiveness was presented and defined prior to the discussion, the concept of cost-effectiveness might be hard for lay people to grasp and discuss.

Specific conclusions from study IV related to perceived challenges and solutions for manageing orphan drug reimbursement in England, France, the Netherlands, Norway and Sweden, are:

- Given the current situation of orphan drug reimbursement, three types of challenges facing decision makers were identified: (1) challenges regarding the components involved when making reimbursement recommendations, (2) challenges regarding the reimbursement system and the process that lead up to a recommendation, and (3) challenges related to the acceptance of the final recommendation.
- In response to the various challenges, countries have employed various solutions to manage orphan drug reimbursement. All countries in study IV have more or less explicit solutions for dealing with orphan drug reimbursement, with the exception of France, who generally has focused more on increasing access to orphan drugs rather than imposing limitations. There are generally two broad themes regarding which solutions countries have employed to handle orphan drug reimbursement: special arrangements uniquely for orphan drugs and general arrangements that can be used for orphan drugs as well as for other drugs.

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