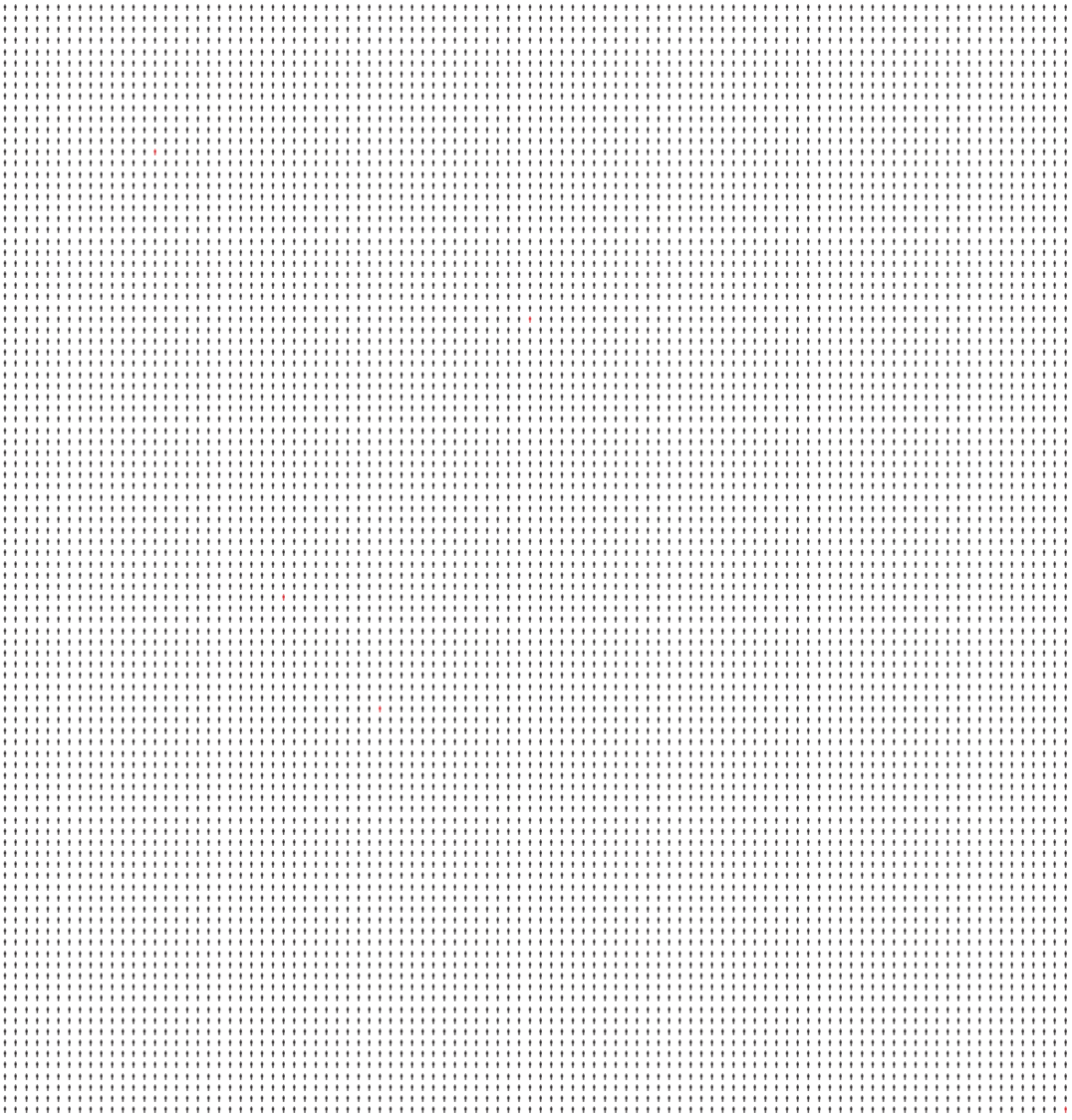
HEALTH TECHNOLOGY ASSESSMENT OF ORPHAN DRUGS

Tim Kanters

The example of Pompe disease



Health technology assessment of orphan drugs
The example of Pompe disease

Tim Andre Kanters

Layout and printing: Optima Grafische Communicatie, Rotterdam, the Netherlands
ISBN: 978-94-6169-992-3

Author: Tim Kanters
All rights reserved. No part of this thesis may be reproduced or transmitted in any form by any means without written permission from the author.

Health Technology Assessment Of Orphan Drugs
The example of Pompe disease

Health technology assessment van weesgeneesmiddelen
De ziekte van Pompe als voorbeeld

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

prof.dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

donderdag 8 december 2016 om 11.30 uur

door

Tim Andre Kanters
geboren te Utrecht

Erasmus University Rotterdam

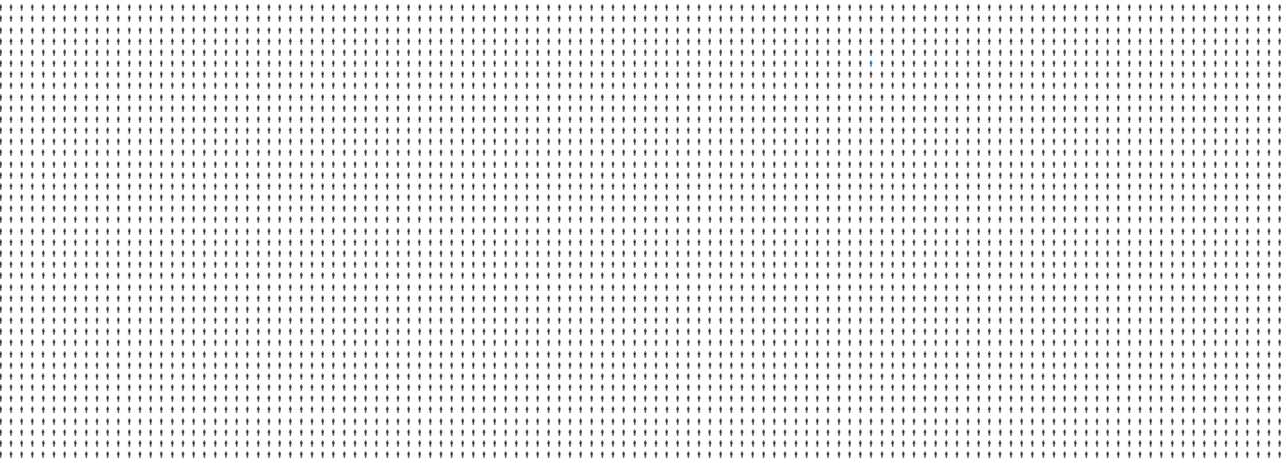
Erasmus

Promotiecommissie

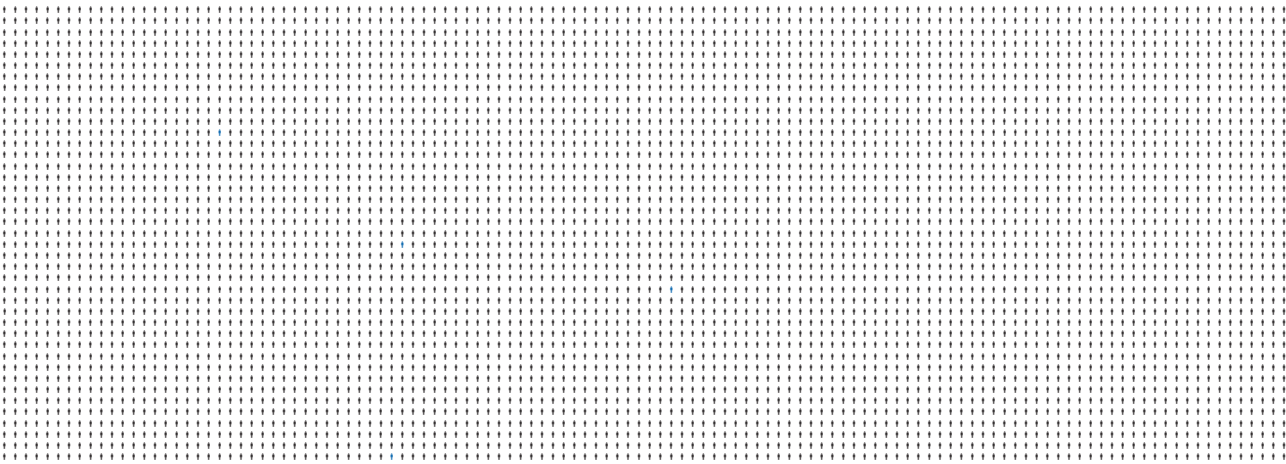
Promotoren:	Prof.dr. M.P.M.H. Rutten-van Mölken
	Prof.dr. A.T. van der Ploeg
Overige leden:	Prof.dr. A. Boer
	Prof.dr. J. Kievit
	Prof.dr. P.A. van Doorn
Copromotor:	Dr. L. Hakkaart-van Roijen

Contents

Chapter 1	Introduction	7
Chapter 2	Orphan drugs expenditure in the Netherlands in the period 2006-2012	21
Chapter 3	Burden of illness of Pompe disease in patients only receiving supportive care	31
Chapter 4	Comparison of EQ-5D and SF-6D utilities in Pompe disease	45
Chapter 5	The impact of informal care for patients with Pompe disease: An application of the CarerQol instrument	59
Chapter 6	A conceptual disease model for adult Pompe disease	73
Chapter 7	Cost-effectiveness of enzyme replacement therapy in adult Pompe disease	91
Chapter 8	Cost-effectiveness of enzyme replacement therapy with alglucosidase alfa in classic-infantile patients with Pompe disease	113
Chapter 9	Access to orphan drugs in western Europe: can more systematic policymaking really help to avoid different decisions about the same drug?	129
Chapter 10	Evaluation of orphan drugs in the Netherlands: can HTA offer guidance to healthcare policy?	137
Chapter 11	Discussion	157
	Summary	181
	Samenvatting	189
	PhD Portfolio	199
	List of publications	202
	About the author	204
	Dankwoord	207
	References	213



CHAPTER 1 Introduction



Orphan diseases and orphan drug legislation

In the European Union, about 30 to 40 million people suffer from a rare disease [1]. According to the definition used in the European Union, a disease is considered rare when less than 5 per 10,000 people suffer from the disease [2], although definitions of rarity differ between countries [3]. There are approximately 7,000 rare diseases [1]. Rare diseases are often genetic, chronic and progressive and many of them affect children. Increased understanding of underlying mechanisms enables medical science to identify subpopulations and new rare diseases. The term 'orphan disease' has been used to reflect the fact that historically pharmaceutical industry has not shown much interest in these rare diseases. This changed when specific legislation was passed which aimed to stimulate the development of treatments for rare diseases. Over the past decades, orphan drug legislation was implemented in various regions of the world, including the United States (1983), Japan (1993), Australia (1997), and the European Union (2000). Specific instruments aimed at stimulating orphan drug development vary between regions, but generally include a period of market exclusivity, tax exemptions, protocol assistance and an expedited review process [4, 5]. Table 1.1 describes orphan drug legislation in the United States and in the European Union. The number of developed orphan drugs increased drastically since legislation became effective. Only 10 orphan drugs were approved by the Food & Drug Administration (FDA) in the years before 1983 when the Orphan Drug Act was passed in the United States, whereas 352 products obtained FDA approval since then [6]. In the European Union, the European Medicines Agency (EMA) has approved 63 orphan drugs in 10 years after the passing of orphan drug legislation [1]. The number of orphan drugs is forecasted to further increase in the future, especially as large pharmaceutical companies have gained interest in the orphan drug market [7, 8]. The increasing availability of orphan drugs has improved lives of thousands of patients suffering from rare diseases worldwide. However, for the vast majority of orphan diseases, still no treatment is available yet.

Table 1.1 Orphan drug legislation in United States and European Union

	United States	European Union
Effective since	1983	2000
Definition of orphan disease	<200,000 patients in the US	<5 per 10,000 people and life threatening or chronically debilitating
Period of market exclusivity	7 years	10 years
Protocol assistance	Yes	Yes
Expedited review	Yes	Yes
Research grants	Yes	Yes
Tax exemptions	Yes	Not on EU level; individual countries can provide tax exemptions

Challenges for orphan drug research

Although many countries across the world have implemented specific legislation to stimulate the development of orphan drugs, the standards for regulatory approval of orphan drugs are the same as those for other drugs [9]. Substantial evidence of quality, safety and efficacy from adequate and well-controlled investigations, preferably randomized clinical trials (RCTs), needs to be provided. However, given the rarity of the diseases, this poses various additional challenges. The most prominent challenge is related to sample size and incorporating a sufficient number of patients to adequately power clinical trials [10-13]. Secondly, lack of knowledge on the natural course of the disease and potential treatment effects may complicate the identification and measurement of treatment effects [10, 11]. To illustrate this point, general practitioners might only encounter a specific rare disease only once or twice in their career and as a consequence might not recognize the disease [11]. This limits the development of knowledge of the disease, or entry of the patient into clinical studies. Thirdly, orphan disease are often chronic, progressive, severe and life-threatening diseases with high unmet medical needs. This could lead to ethical concerns about randomization and use of placebo [10, 14]. When a promising treatment finally comes available, it can be difficult to persuade patients (or their parents) to participate in a study with a placebo-arm, especially if it is known beforehand that patients die if left untreated [10]. This also conflicts with ethical norms of physicians and institutional review boards. As an example, the use of placebo was considered unethical in the pivotal clinical trials of enzyme replacement therapy in classic-infantile Pompe disease, because of the fatality due to the disease in young children and because earlier studies had demonstrated large treatment effects [15]. Furthermore, the heterogeneity of phenotypes may complicate the use of (historical) controls [10]. Finally, as commonly agreed endpoints, outcome measures, disease-specific instruments and biomarkers may be lacking because researchers have not shown much interest in the particular disease, some studies in orphan diseases may have to rely on surrogate endpoints [10, 13].

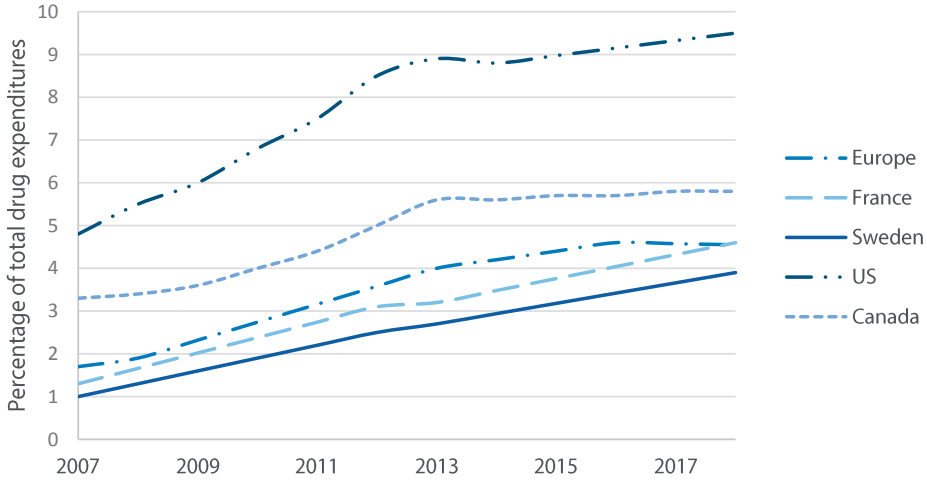
Because of all these challenges in designing clinical trials, most research in orphan drugs is performed using observational studies, sometimes after a RCT has been performed [10, 14]. Although observational studies do not have the scientific rigor of RCTs, they can be useful in evaluating treatment effectiveness if data for RCTs are not available [16]. International data collection can help to alleviate problems with small patient numbers [17]. Furthermore, timely collection of data, starting before treatments become available, is essential so that data on the comparator treatment are at hand once treatments become available. Especially, the collection of data of individual patients before starting treatment can be very helpful to determine treatment effects in that individual.

Orphan drug expenditure

Because the standards for regulatory approval are not different from other drugs [9], research and development costs are often said to be relatively unaffected by either orphan drug legislation or the size of the study population. However, (research and development; R&D) costs do need to be retained from (very) few patients in orphan drugs. As a consequence, prices of orphan drugs are generally very high [18] with price and prevalence being inversely related [19]. Price setting of pharmaceutical products is undisclosed and a drug's price does not only reflect R&D costs but also the perceived value [20].

The high prices combined with the increasing number of orphan drugs available in the market have led to rising expenditures on orphan drugs, both in absolute numbers and in proportion of total pharmaceutical spending [21, 22]. Figure 1.1 depicts the rising expenditures on orphan drugs relative to total pharmaceutical spending in various regions. In the United States for instance, budget impact of orphan drugs rose from 4.8% of total pharmaceutical spending in 2007 to 8.9% in 2013 [23]. In Canada, orphan drug spending increased from 3.3% in 2007 to 5.6% in 2013 [24]. For both countries, these numbers were forecasted to further increase in the near future. In Europe, orphan drug spending is expected to rise from 4.0% in 2013 to 4.6% in 2018 [21]. Similar trends were forecasted in individual European countries, although variations were predicted in the magnitude of the increases [22, 25]. These studies all show increasing trends in orphan drug spending.

Figure 1.1 Orphan drug expenditures in various regions



Source: [21, 23-25]

Pompe disease

Pompe disease is an orphan disease. Pompe disease is a progressive muscle disorder and belongs to the group of lysosomal storage disorders. The disease is caused by a deficiency of the enzyme acid α-glucosidase [26]. As a result, glycogen is not broken down appropriately and accumulates in the lysosomes. Muscle tissue is particularly affected. In the Netherlands, the incidence of the disease is relatively high compared to other countries. The reason for this is not exactly known. It could be that the awareness of Pompe disease is higher in the Netherlands because of historical research on Pompe disease [27-29], or that there is a founder effect. What pleads against the latter explanation is that the disease is spread throughout the Netherlands. Research on neonatal dry blood screening cards on the three most frequent gene variations in the Netherlands predicted an incidence of 1 in 40.000 live births [30], which implied the birth of about four new cases per year in the Netherlands. The disease has a broad continuous clinical spectrum, ranging from a rapidly progressive infantile form to a more slowly progressive form affecting children and adults [31].

The most severe is the classic-infantile form of the disease. Infantile patients suffer from progressive thickening of the heart, respiratory and feeding problems and muscle weakness [32, 33]. Classic-infantile patients generally die within the first year of life (median age of death is 6.0 to 8.9 months [32, 33]). Main causes of death are heart failure and respiratory insufficiency.

Diagnosis in patients affected with less severe (late-onset) forms of the disease can be in the first to seventh decade of their lives [34-36]. These patients suffer from muscle weakness and respiratory problems [26]. Most of these patients become dependent on ambulatory and respiratory support; 15 years after diagnosis half of patients has become wheelchair dependent and approximately half of the patients has become dependent on ventilator use [35]. These proportions increased further with longer disease duration. Patients reported significantly worse quality of life than the general population on physical functioning, role functioning-physical, general health, vitality and social functioning domains of the SF-36 [37]. Finally, life expectancy for these patients is less than in the general Dutch population [38]. Death is often caused by respiratory failure [36].

Prior to the availability of enzyme replacement therapy (ERT), patients with Pompe disease received supportive care consisting of (a combination of) ambulatory support, respiratory support, physiotherapy and dietary treatment. This supportive care only partially relieved symptoms of the disease, but did not halt the progression of the disease. Prior to the availability of ERT, much attention was given to studies on the natural course

of the disease, in which supportive care was included. In 2002, the International Pompe Association (IPA) Survey, an international collaboration in which over 400 patients participated on a yearly basis, was initiated [34, 35]. In 2004, a standardized clinical follow-up program with a large set of follow-up parameters was implemented for all patients in the Netherlands. The protocols were approved by the Institutional Review Board of Erasmus Medical Center (Erasmus MC). To concentrate knowledge on the disease and improve quality of care, Erasmus MC was appointed as the national centre of expertise for Pompe disease. From then on, all hospitals in the Netherlands referred their patients to Erasmus MC. These studies have led to important insights in the natural course before ERT became available and could later be used as a benchmark to study the effects of ERT after the RCT [35, 37-39].

Erasmus MC has a long history when it comes to the development of ERT, starting with studies in cultured skeletal muscle cells of patients in 1984/1985 making use of an at that time recently recognized new receptor on the cell surface [40]. This receptor, i.e. the M6P/IGFII receptor, did not only appear to be involved in intracellular targeting of newly synthetized lysosomal enzymes (alpha-glucosidase) to the lysosomes, but also in the cellular uptake of exogenous alpha-glucosidase and transport to the lysosomes. Via this route exogenously administered alpha-glucosidase, which was purified in the lab, appeared able to clear stored glycogen in muscle cells [41]. From these experiments it also became evident that the natural sources from which the enzyme was purified (human urine and bovine testis) would never be sufficient to treat patients. Cloning of the alpha-glucosidase (GAA) gene by the investigators from Erasmus MC was the next step in opening the way to biotechnological production methods [42]. Before clinical implementation, the effect of the enzyme was first tested in vivo in a mouse model of Pompe disease developed by Erasmus MC [43]. After these studies, which had shown that the enzyme reached and corrected the target tissues muscle and heart, Erasmus MC performed the first clinical pilot trial worldwide with recombinant human alpha-glucosidase in four infants with the classic infantile form of Pompe disease [44]. The endpoint was survival. Three of these infants, who previously had prognosis of dying before the age of one year, are still alive and have recently become 18 years. This first clinical test at Erasmus MC was performed with a recombinant human alpha-glucosidase produced in milk of transgenic rabbits (Pharming BV Leiden). A product produced in cells (Chinese Hamster Ovary cells; CHO cells) was further developed by Genzyme/Sanofi and brought to the market. Various additional developmental procedures and clinical studies were performed during this process. In 2006, ERT for the treatment of Pompe disease was approved by regulatory authorities globally and became available for patients. The study that led to market authorization (AGLU1602) was performed in 18 infants with classic infantile Pompe disease [15]. The study period was one year and the primary endpoint

was survival. All patients survived over the treatment period. A follow-up study over three years showed a survival of 72% [45]. ERT also showed a remarkable increase in ventilator-free survival in infantile patients [15, 45]. The study provided proof of concept that an inheritable enzyme deficiency as observed in all patients with Pompe disease could be treated. With this achievement, Pompe disease became the first treatable inheritable muscle disorder.

At the time of registration in 2006, a placebo controlled study in 90 late onset patients had just started. This study ended in 2008. Erasmus MC participated with 22 patients. The primary endpoints of this study were distance walked during six minutes and respiratory function in sitting position [46]. Both endpoints of the study were met: ERT was associated with improvements in distance walked (an increase of 28 meters compared to placebo) and stabilization of pulmonary function (improvement of 3.4 percentage points in FVC compared to placebo). Treatment with ERT in these patients led to stabilization in lung function and improvements in muscle strength [46, 47]. ERT also has a positive effect on health related quality of life [48]. Survival increased as well because of ERT [49]. Although the majority of patients with Pompe disease benefit from treatment, ERT is not effective in every single patient [47], which stresses the importance of standardized follow-up of every single patient after implementation of ERT.

When ERT was implemented in the Netherlands after registration, several measures were taken to warrant that only those patients in need of therapy received it. Firstly, starting rules were defined, which implied that only symptomatic patients with impaired muscle function and/or reduced pulmonary function could receive therapy. Secondly, all patients were discussed within a team of experts with an independent chair (not employed by Erasmus MC), to decide on initiating treatment with ERT. Thirdly, patients could only receive treatment when they also committed to the standardized, regular follow-up program to assess the effectiveness of ERT. Via this protocol, a broad range of parameters were measured, such as six minute walk test, pulmonary function in sitting and supine position, muscle strength, muscle function, timed functional tests, level of antibodies and biomarkers, quality of life, level of handicap and fatigue. The results of these tests were regularly evaluated by the indication committee and published in international peer reviewed journals. The therapy was stopped if patients clearly did not benefit from therapy or had severe infusion associated reactions, which rarely occurred during the first years. As more evidence became available over time, these start and stopping rules can be increasingly better defined.

Start and stopping rules were also discussed by the recently founded European Pompe Consortium (EPOC) [50]. The consortium was installed in 2014. One of the reasons to

install the consortium was to harmonize guidelines for follow-up and treatment across Europe. Experts of the consortium concurred that treatment should only be started in symptomatic patients and treatment should be discontinued if patients do not respond to treatment. The full recommendations will be published shortly.

The development of ERT described above was costly. The costs of the therapy are based on a price per mg/kg body weight and the annual treatment costs per patient are approximately €420,000 for adults and up to €700,000 for classic-infantile patients [51]. Costs in children can be higher than in adults because of a more frequent dosing schedule (i.e. once weekly versus bi-weekly) and a higher dosage per kilogram (40 mg/kg versus 20 mg/kg). Although only the list price is publicly known, and the true price and exact composition of that price is not, there are several factors that cause ERT treatment to be expensive. Firstly, alternative treatments do not exist, which removes the incentive for price competition between drugs. As such, manufacturers can charge any price they deem to be accepted by reimbursement authorities. Secondly, according to the manufacturer, the price of medication in itself is high, because R&D costs are high and need to be retrieved from very few patients. According to the manufacturer, production costs of ERT are high because of a difficult and labour intensive production process, as the production of recombinant alglucosidase alfa is more complex than the production of a simple pill. Thirdly, patients need high dosages of medication. Finally, treatment is life-long and frequent; patients generally receive an infusion every other week, but many infantile patients receive weekly infusions. In 2010, 96 patients were treated with ERT (including 18 children) in the Netherlands. The associated yearly budget impact was approximately €44 million [51].

Reimbursement decisions

In publicly funded healthcare systems, resources like people, time, facilities and funding are scarce [52]. The budget is constrained. When reimbursing one treatment, fewer resources are available for other treatments, unless health insurance premiums or taxes to fund the rising healthcare expenditures are increased. Hence, choices must be made to use resources efficiently and are necessary to ensure the financial sustainability of the healthcare system. Health technology assessment (HTA) is being used in an increasing number of countries to substantiate these choices. HTA is a systematic approach of informing decision makers, using social, ethical and economic aspects next to clinical effects of an intervention [53]. An important component of an HTA study is an economic evaluation, in which costs and effects of two alternatives (in this case ERT with supportive therapy, and supportive therapy only) are compared and expressed in

an incremental cost-effectiveness ratio (ICER) of the costs per additional unit of effect. To enable a comparison of the cost-effectiveness across different types of interventions for different diseases, the cost per quality adjusted life year (QALY) is considered the most appropriate cost-effectiveness ratio to be calculated [52]. The ICER is compared to a cost-effectiveness threshold that reflects the societal willingness to pay for one QALY. Theoretically, the cost-effectiveness threshold should reflect the opportunity costs of healthcare spending, i.e. the value of the QALYs forgone by the best alternative use of resources. By comparing the ICER of a treatment with the threshold it can be assessed whether the health gains of a new intervention exceed the health effects of the interventions that are displaced elsewhere in the healthcare system to compensate for the additional costs of the new technology. In practice, there is no formal threshold in the Netherlands that is used as a strict decision criterion, such as in the UK, but decision makers do use the threshold as a reference to guide the discussion on cost-effectiveness. Decision makers currently experiment with threshold levels for the costs per QALY that vary with the severity of the disease, i.e. €20,000 per QALY for a severity between 0.1 and 0.4, €50,000 per QALY for a severity between 0.41 and 0.7, and €80,000 per QALY for a severity between 0.71 and 1 [54]. Disease severity is based on the notion of 'proportional shortfall', i.e. the proportion of normal quality adjusted life expectancy lost due to the condition and can be expressed on a scale from 0 to 1 [55]. Using the life expectancy and quality of life, severity for patients with adult Pompe disease is estimated to be 0.56 and for classic-infantile patients 1.00, as calculated with the proportional shortfall method.

Expensive orphan drugs have confronted decision makers with difficult choices regarding their coverage as part of the basic benefit package. Commonly, several criteria play a role in reimbursement decisions on novel therapies. Although criteria differ between countries, criteria such as effectiveness, added therapeutic value, cost-effectiveness and disease severity are most often used in reimbursement decisions [56, 57]. In the Netherlands, a set of four criteria (necessity, effectiveness, cost-effectiveness and feasibility) is used to inform reimbursement decisions [58]. Necessity can be divided into two parts: disease severity and whether the type of intervention justifies coverage by health insurance. With regard to effectiveness, only effective treatments should be included in the basic benefit package [59]. In determining whether a treatment is effective, the principles of evidence based medicine should be applied. In cost-effectiveness studies, additional costs and effects of a new treatment are compared to the current standard of care. Effects are often expressed in QALYs, which constitute a combination of length of life and quality of life. Feasibility is comprised of several aspects, such as ethical arguments, broader societal impact and budget impact of a treatment.

Reimbursement decisions in the Netherlands are formally made by the Minister of Health, based on an advisory report issued by the Dutch Health Care Institute (ZIN; formerly Health Care Insurance Board, CVZ). The advisory report summarizes the available evidence as evaluated in a two-step approach by ZIN consisting of 1) assessment and 2) appraisal [60]. In the first step, the clinical and pharmacoeconomic outcomes are assessed by the Scientific Advisory Council (WAR; formerly Committee Pharmaceutical Aid, CFH). The aim of this step is to review the evidence and the quality of the underlying studies. The WAR only assesses whether the evidence presented is correct; it does not judge the outcomes. The Appraisal Committee (ACP) performs the second step of the evaluation and provides a societal value judgment on the available evidence using the four reimbursement criteria. All four criteria are taken into account, but the relative weighting of the criteria is implicit.

Reimbursement of ERT in Pompe disease and other inpatient orphan drugs was arranged under a specific regulation for orphan drugs, the so-called policy rule for orphan drugs. This policy rule was installed in 2006 to ensure access to treatment for a pre-specified period of time [61]. The drugs were reimbursed under a coverage with evidence development (CED) scheme, subject to additional outcomes research during this period. Evidence on the effectiveness, cost-effectiveness and budget impact of the treatment were studied during the CED period. Based on the evidence gathered, CVZ would issue an advice on continuation of reimbursement after the CED period. ERT with alglucosidase alfa for the treatment of Pompe disease was the first newly registered orphan drug that was included in this regulation. An extensive standardized follow-up protocol was established by Erasmus MC in collaboration with CVZ, to answer to the requirements of the CED scheme. The evidence gathered during the CED period was reported in a reimbursement dossier, which was submitted to CVZ.

In the summer of 2012, continuation of reimbursement of ERT in Pompe disease was discussed by CVZ. The treatment was assessed and appraised similar to non-orphan drugs. Based on the evidence in the submitted dossier CVZ drafted a preliminary advice to the Minister to continue reimbursement only for classic-infantile patients [62]. According to CVZ, effectiveness in the adult population was insufficient and the ICER too high to justify reimbursement of ERT in adult patients. The preliminary advice to the Minister of Health was leaked to the press. A lively societal debate followed. In September 2012, ERT for Pompe disease was discussed by the ACP. The ACP rejected the preliminary advice by CVZ and advised to continue reimbursement of ERT in Pompe disease for all patients [51]. To improve cost-effectiveness of the treatment, the Ministry of Health engaged in negotiations with the manufacturer to reduce the price of the drug. After agreement

on an undisclosed discount on the price of ERT was reached, the Minister announced to prolong reimbursement of ERT in all patients with Pompe disease [63].

It has often been asked why the CED scheme included cost-effectiveness studies, because it is obvious upfront that many of the orphan drugs will not meet the commonly used cost-effectiveness threshold given their high prices. However, cost-effectiveness studies are still required to provide decision makers with information that can be used in possible price negotiations later on in the reimbursement process. Furthermore, these studies may provide valuable information on the breakdown of costs, the drivers of cost-effectiveness besides the price of the drug, potential differences between subgroups, and they enable comparisons of cost-effectiveness ratios among orphan drugs.

Aims and outline of the thesis

This thesis aims to provide insight in the various aspects that affect reimbursement decisions. As part of this thesis, HTA studies of Pompe disease were conducted. This thesis contributes to the decision making process regarding the reimbursement of orphan drugs. It can be divided into three parts.

Part 1: The burden of disease from different perspectives (chapter 2 to 6)
Part 2: Cost-effectiveness of ERT in Pompe disease (chapter 7 and 8)
Part 3: Use of HTA in policy making on orphan drugs (chapter 9 and 10)

In the first part of this thesis the burden of disease is investigated from multiple perspectives, including a financial and economic perspective, the perspective of the patient and the perspective of the informal caregiver. Chapter 2 investigates the budget impact of orphan drugs in the Netherlands. This chapter quantifies the costs of orphan drugs as a proportion of total pharmaceutical costs, as well as the development of costs associated with orphan drugs over time. Chapter 3 describes the burden of illness of Pompe disease of untreated adult patients using a societal perspective. The chapter presents both the burden to society in terms of costs related to healthcare consumption and productivity losses, as well as the burden for patients with respect to their impaired quality of life. Chapter 4 compares two generic instruments that can be used to quantify quality of life. The chapter describes how these instruments perform in this specific patient population and how they are associated with clinical indicators of pulmonary function and muscle strength. Chapter 5 describes yet another aspect of the overall burden of Pompe disease, namely the burden of providing informal care for these patients. In this chapter, the subjective and objective burden on caregivers for Pompe patients is studied, both in adult patients and paediatric patients. Chapter 6 provides a conceptual model that can

be used to operationalize and quantify the relationships between clinical aspects of the disease and patient's quality of life.

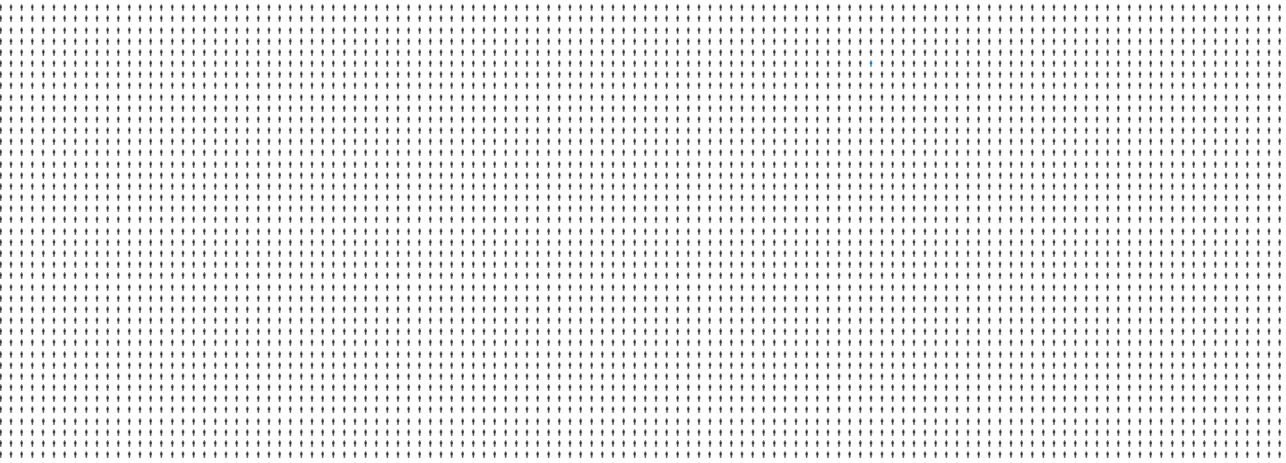
In the second part of this thesis (chapter 7 and chapter 8) two cost-effectiveness studies of ERT in Pompe disease are presented. Firstly, chapter 7 describes the cost-effectiveness of ERT in adult patients. The results from chapters 3 and 6 are used as input for the cost-effectiveness model. Chapter 8 describes the cost-effectiveness of ERT in classic-infantile onset patients.

Together, part one and two of this thesis provide a comprehensive evaluation of ERT in Pompe disease, informing various criteria used in reimbursement decisions, namely disease severity, effectiveness in terms of life years gained and QALYs, cost-effectiveness, budget impact and broader societal impact.

The third part of the thesis describes how HTA is actually used in reimbursement decisions on orphan drugs. Chapter 9 presents reimbursement decisions on ERT in Pompe disease in various European countries and describes international differences in reimbursement. Chapter 10 no longer focusses on ERT in Pompe disease only, but describes how HTA is being used in decision making on orphan drugs in general in the Netherlands. The chapter describes whether methodology used to assess common drugs is also applicable for orphan drugs and whether other criteria apply for orphan drugs than for common drugs in the appraisal phase.

Lastly, chapter 11 provides a general discussion on the various aspects related to HTA research in orphan drugs and contemplates on future directions for policy and research with respect to orphan drug legislation and reimbursement.

The research presented in chapters three to eight was made possible by a close collaboration with clinical experts of the Center for Lysosomal and Metabolic Diseases at Erasmus MC. Since 2004, they have built an extensive database with clinical and economic data on all Pompe patients treated at Erasmus MC. Patients that receive supportive treatment are also included in the database. The database resulted from prospective long-term standardized collection of a large amount of clinical data in committed patients who also repeatedly completed a number of questionnaires over a period of many years. This is rather unique in an orphan disease. Moreover, Erasmus MC coordinates and runs, in co-operation with the International Pompe Association (IPA), the IPA/Erasmus MC Pompe Survey. The Pompe Survey was initiated in 2002, and collects data from various countries. Data from the Pompe Survey were also available for these studies. This setting provided an excellent opportunity to conduct such comprehensive HTA studies as presented in this thesis.



CHAPTER 2

Orphan drugs expenditure in the Netherlands in the period 2006-2012

Kanters TA, Steenhoek A, Hakkaart L

Orphanet J Rare Dis (2014) 9:154

Abstract

Background: The relatively low budget impact of orphan drugs is often used as an argument in reimbursement decisions. However, overall, the budget impact of orphan drugs can still be substantial. In this study, we assess the uptake and budget impact of orphan drugs in the Netherlands.

Methods: We examined the number of orphan drugs, the number of patients and budget impact of orphan drugs in the Netherlands in the period 2006 to 2012, both for inpatient and outpatient orphan drugs. Budget impact was provided in absolute numbers and relative to total pharmaceutical spending.

Results: The number of orphan drugs and patients treated increased substantially over the period studied. Overall, budget impact increased substantially over a period of six years, both in absolute terms (326% increase) as well as relative to total pharmaceutical spending (278% increase). Growth rates decreased over time. In 2012, 17% of available drugs had an individual budget impact of more than €10 million per year.

Conclusions: Individual budget impact of orphan drugs is often limited, although exceptions exist. However, in total, the budget impact of orphan drugs is considerable and has grown substantially over the years. This could potentially influence reimbursement decisions for orphan drugs in the future.

Background

The introduction of orphan drug legislation in various jurisdictions has played an important role for the development of orphan drugs; since European legislation was passed in 2000, 73 drugs for orphan indications were licensed [1]. However, on a national level this also poses policy makers for difficult decisions concerning reimbursement, as illustrated by examples from the United Kingdom and the Netherlands [64, 65]. On the one hand, therapies are developed for diseases that, next to being rare, are life-threatening and chronically debilitating by definition [2]. On the other hand, orphan drug prices can be enormous, as pharmaceutical companies recoup their investments in research and development on the small patient population. The high prices of orphan drugs place decision makers for a difficult task; cost-effectiveness ratios for these drugs are often very high, implying that the money spent on orphan drugs might be spend more efficiently in other disease areas. However, there are also arguments in favor of granting reimbursement to orphan drugs. Ethical considerations, the lack of alternative treatments and severity of the disease all apply to the case of orphan drugs [66].

Budget impact is yet another criterion used in reimbursement decisions [67, 68]. For orphan drugs, the impact on the pharmaceutical budget is limited due to the small number of patients, let alone the impact on the entire healthcare budget. Although this proposition holds for individual orphan drugs, the combined budget impact of all available orphan drugs might be considerable, especially as the number of orphan drugs on the market is still increasing. Various studies in several European countries have shown the increasing share of pharmaceutical spending that is spent on orphan drugs [21, 22, 25, 69]. Moreover, these studies have shown that differences between countries exist. In this study we assess the uptake and overall budget impact of orphan drugs in the Netherlands. As such, the results of this study can be useful for Dutch policymakers, as well as for validating results from earlier studies in other countries and providing a benchmark for countries were these studies have not been performed yet.

Methods

In the Netherlands, outpatient and inpatients orphan drugs are financed differently. Firstly, outpatient drugs are financed through the common Drug Reimbursement System (GVS). Outpatient cancer orphan drugs were transferred to the specialist drugs list in 2013. Secondly, inpatient drugs were financed through a specific policy rule on orphan drugs (until 2012) and since 2012 through an "add-on" diagnosis treatment combination

(DBC). We examined the number of orphan drugs in the Netherlands, the number of patients using them and the orphan drugs' budget impact.

Outpatient drugs

For outpatient drugs we examined the Drug Information Project (GIP) database hosted by the Health Care Insurance Board (CVZ) [70]. The GIP database is publicly accessible and contains information on the use and costs of medicines and medical devices. With respect to medicines, the database contains detailed information on number of patients, usage and expenditures. Some orphan drugs were also prescribed for non-orphan indications. For these drugs, only data related to orphan indications were taken into account. Prices were calculated by dividing drug's budget impact by the number of defined daily doses multi-plied by 365.25 to get price of treatment per year.

Inpatient drugs

From 2006 to 2012, inpatient drugs were financed through a specific policy rule on orphan drugs. When applying for inclusion on the policy rule, pharmaceutical companies had to make predictions on the number of users, prices and budget impact of the drug. Furthermore, after a reimbursement period of four years, pharmaceutical companies had to submit an outcomes research report with, among other aspects, clinical outcomes, observed number of users and budget impact. The primary sources of information for the current study were the outcomes research reports and the policy rule applications. When outcomes research reports and policy rule applications were not available, data on an aggregated level from the Monitor Expensive Drugs were used [71].

Analyses

Budget impact was expressed in euros and as a percentage of total pharmaceutical spending. Total pharmaceutical spending in the Netherlands (orphan drugs and non-orphan drugs) was derived from the GIP database for outpatient drugs. Total pharmaceutical spending on inpatient drugs were derived from FarmInform [72]. Total pharmaceutical spending resulted from the summation of inpatient and outpatient drugs spending.

In addition to the analyses with regard to all orphan drugs combined, characteristics are provided for the five orphan drugs ranked highest with regard to the number of patients treated, the price of the orphan drug and the individual drug's budget impact.

For some inpatient drugs, data were not available for all years. In these cases, the last observation was used for later years, implying a conservative scenario. As a sensitivity analysis, the individual drugs' growth rate for the last known year was used for extrapolation instead.

Results

Table 2.1 shows the uptake of orphan drugs and evolution of orphan drug spending over time in the Netherlands. Considering uptake of orphan drugs, both the number of drugs and the number of patients almost quadrupled over the studied period. Both factors contributed to the increase in budget impact of orphan drugs over time, both for inpatient and outpatient drugs. For inpatient drugs, the number of patients was relatively stable for each drug. For outpatient drugs, the number of users increased substantially; with an average growth of 168 patients over the study period.

For inpatient drugs, prices were constant over the time period studied. The average annual treatment costs for inpatient drugs was €255,615 (SD = 223,306). The average annual treatment costs for outpatient drugs was €40,679 in 2012 (SD = 45,283). For outpatient drugs, some variation was observed over the study period, but for most drugs price changes were modest. For 39.3% of the inpatient drugs, prices decreased with more than 2%. In contrast, prices increased with more than 2% for 17.9% of drugs. On average, drug prices slightly decreased over time (−1.2%).

Table 2.1 further shows that over a period of seven years, the total expenditure on orphan drugs quadrupled. The growth rate was decreasing over time; from 60.1% in the period 2006 to 2007 to 7.9% in 2011–2012. The absolute growth in budget impact was largest for outpatient drugs. The relative growth in budget impact over seven years was largest for inpatient drugs.

Table 2.1 Uptake and budget impact of orphan drugs in the Netherlands

	2006	2007	2008	2009	2010	2011	2012
Number of orphan drugs							
Outpatient	9	15	18	22	25	30	32
Inpatient	2	7	8	9	11	11	11*
Total	11	22	26	31	36	41	43
Number of patients treated with orphan drugs							
Outpatient	2,149	3,457	4,410	6,024	7,621	8,250	9,226
Inpatient	40	146	215	469	531	536	536*
Total	2,189	3,603	4,625	6,493	8,152	8,786	9,762
Budget impact of orphan drugs (millions)							
Outpatient	€ 52.7	€ 68.7	€ 97.8	€ 118.1	€ 141.6	€ 156.2	€ 175.2
Inpatient	€ 8.5	€ 29.2	€ 60.7	€ 74.6	€ 84.3	€ 85.1	€ 85.1*
Total	€ 61.2	€ 97.9	€ 158.6	€ 192.7	€ 225.9	€ 241.4	€ 260.4

* For inpatient drugs, figures for 2012 were assumed equal to 2011

Figure 2.1 Budget impact of orphan drugs as a proportion of total drug spending

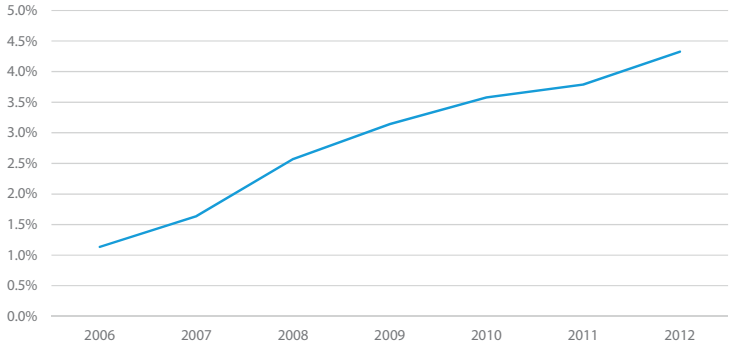


Figure 2.1 provides the development of budget impact of orphan drugs over time as a percentage of total pharmaceutical spending. The proportion of total pharmaceutical spending spent on orphan drugs almost quadrupled from 1.1% in 2006 to 4.2% 2012. The relative growth rate decreased over time. Total pharmaceutical spending increased with 12.6% in the period 2006–2012.

Table 2.2 shows the orphan drugs that were most often used in 2012. In 2012, a total of 1,485 patients received imatinib. The most-often used inpatient drug was trabectedin (Yondelis®, 240 patients). More than 60% of all orphan drug receiving patients in the Netherlands received one of the five most-used drugs, which are listed in Table 2.2. Lenalidomide (Revlimid®) was the drug with the biggest increase in the number of users over time; from 79 users in 2007 to 1,089 in 2012.

Yearly treatment costs exceeded €100,000 per patient for seven inpatient drugs (63.6%) and for two outpatient drugs (6.3%). The orphan drugs with the highest per patient prices are provided in Table 2.2. Velaglucerase alfa (VPRIV®) was the highest priced inpatient drug, with annual per patient costs of approximately €200,000 in 2012. Tafamidis (Vyndaqel®) was the only other inpatient drug with annual costs over €100,000. Yearly costs for three (five) drugs were lower than €2,000 (€3,000).

Table 2.2 also shows the orphan drugs with the highest budget impact in 2012. Seven out of 41 orphan drugs (17%) had an individual budget impact exceeding €10 million; the budget impact of 18 outpatient and nine inpatient drugs was more than €1 million in 2012. The drug with the largest budget impact in 2012 was alglucosidase alfa. Together, the five drugs with the largest budget impact accounted for 57.7% of the total budget impact of orphan drugs. Four drugs (one inpatient) had a cumulative budget impact of more than €100 million over the study period. Imanitib's cumulative budget impact exceeded €250 million.

Table 2.2 Orphan drugs with highest number of users, highest prices and highest budget impact (2012)

Rank	INN	Trade name	Setting	Patients
1	Imatinib	Glivec®	Outpatient	1,485
2	Lenalidomide	Revlimid®	Outpatient	1,089
3	Sildenafil	Revatio®	Outpatient	1,052
4	Thalidomide	Thalodomide Cellgene	Outpatient	1,030
5	Bosentan	Tracleer®	Outpatient	901
Rank	**INN**	**Trade name**	**Setting**	**Cost/Patient**
1	Galsulfase	Naglazyme®	Inpatient	€ 600,000
1	Idursulfase	Elaprase®	Inpatient	€ 600,000
3	Alglucosidase alfa	Myzoyme®	Inpatient	€ 474,857*
4	Eculizumab	Soliris®	Inpatient	€ 358,000
5	Aldurazyme	Laronidase®	Inpatient	€ 300,000
Rank	**INN**	**Trade name**	**Setting**	**Budget impact (millions)**	**Cumulative budget impact 2006-2012 (millions)**
1	Alglucosidase alfa	Myozyme®	Inpatient	€ 40.3	€ 203.4
2	Imatinib	Glivec®	Outpatient	€ 36.4	€ 251.2
3	Lenalidomide	Revlimid®	Outpatient	€ 36.2	€ 127.4
4	Bosentan	Tracleer®	Outpatient	€ 23.0	€ 132.4
5	Pegvisomant	Somavert®	Outpatient	€ 14.3	€ 72.5

Abbreviations: INN=International Nonproprietary Names

* Weighted average of infantile patients (€706,666/patient) and adult patients (€422,314/patient)

Sensitivity analysis

For missing data for inpatient drugs, we used the last observed budget impact. For drugs with a growing budget impact over time (majority of the 11 inpatient drugs) this might have led to an underestimation of the budget impact. Extrapolation of the last observed growth rates for individual drugs' resulted in an additional budget impact of €14 million in 2012. In this analysis, 4.6% of total pharmaceutical spending would be spent on orphan drugs in 2012. In contrast to the base case analysis, the growth rate would be constant over time.

Discussion

In this study, we showed that the budget impact of orphan drugs in the Netherlands increased substantially over time, both as a proportion of total drug spending as well as in absolute terms. The growth in budget impact was explained by the increasing number of orphan drugs available and the increasing number of patients receiving the drugs.

The proportion of total pharmaceutical spending on orphan drugs in the Netherlands for 2007 was 1.6%; similar to proportional spending in Spain (2.0%), Germany (2.1%) Italy (1.5%) and France (1.7%); and higher than in the UK (1.0%) [69]. For later years, budget impact in the Netherlands was higher than in Belgium (1.9% in 2008, compared to 2.6% in the Netherlands), Sweden and France (respectively 2.5% and 3.1% in 2012, compared to 4.2% in the Netherlands) [22, 25]. It should be noted that comparing our results to studies from other countries is difficult due to transferability issues: inter-country differences with respect to reimbursement decisions of (individual) orphan drugs and prices of orphan drugs exist [Kanters et al.: Factors affecting reimbursement decisions on 11 high-priced inpatient orphan drugs, submitted]. Furthermore, total pharmaceutical spending differs between countries, which could also affect the proportion spent on orphan drugs.

Two earlier studies have used a model to predict future proportion of pharmaceutical spending spent on orphan drugs [21, 25]. Schey et al. (2011) predicted the proportion of total pharmaceutical spending spent on orphan drugs to decrease from 2016 onwards [21]. An important element in their model was the assumption that orphan drug prices would decrease as a consequence of competition. Until now, the generic orphan drugs market did not expand, and it can be questioned whether the orphan drug market is attractive enough for generic companies to enter the field of rare diseases. More recently, Hutchings et al. (2014) forecasted that the proportion of total drug spending on orphan drugs in Sweden and France would increase until 2018, after which a steady state would be reached [25]. More research is needed to establish whether the steady state would actually be achieved and how these figures apply to other countries.

Our results show similarities with other studies over time increasing budget impact relative to total pharmaceutical spending but with decreasing growth rates [21, 25]. Over time, growth rates were decreasing. This might be explained by saturation of the target population; most eligible patients receive the available drug. Saturation might be especially high for these orphan drugs as alternative treatments are often non-existent.

Limitations

The time period in this study was limited to a period of seven years. Even in this relatively short time period, we observed a substantial growth in orphan drugs spending. A longer study period would be needed to investigate whether the growth rates continue to decrease, and if so whether a negative growth rate, i.e. a decreasing budget impact, will be observed in the future. Due to a change in financing outpatient cancer drugs since 2013, the analyses could not be extended to 2013. Remarkably, when a subsample of outpatient drugs that were available for 2013 (n = 26) was analyzed, a decrease (−6.0%)

of the number of patients treated was found. Despite the decrease in the number of patients treated, an increase in the total budget impact is observed. The growth rate of the budget impact relative to the previous year was modest (4.8%). Two new outpatient orphan drugs entered the Dutch market in 2013.

To predict the future budget impact of orphan drugs in the Netherlands, detailed information is needed on availability of individual orphan drugs in the Netherlands, number of patients using these drugs, and prices of orphan drugs in the Netherlands, also in relation to generic competition for orphan drugs. This information is yet unavailable for the Netherlands. Further research on these aspects is needed before a prediction of the future budget impact of orphan drugs in the Netherlands can be made.

Implications

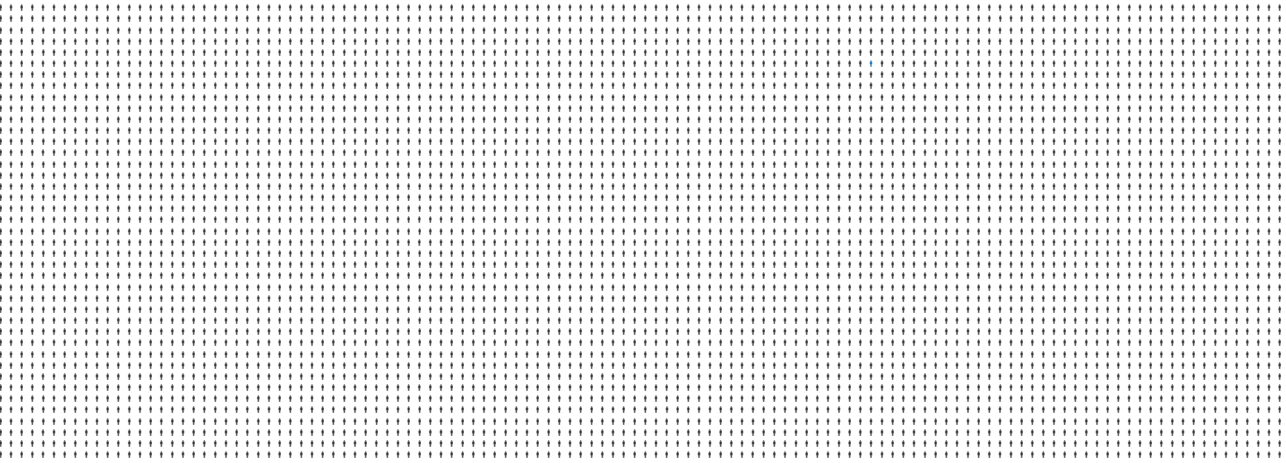
The combined budget impact of orphan drugs is substantial and increasing. Budget impact for individual orphan drugs might be limited (although 17% of orphan drugs had an individual budget impact exceeding €10 million). However, policy makers should acknowledge the increasing budget impact of all orphan drugs. The small budget impact might therefore not be a valid argument in discussions on reimbursement of orphan drugs, especially as the number of orphan drugs continues to grow and hence so will their budget impact.

Conclusions

The number of available orphan drugs and the number of patients receiving these orphan drugs have substantially increased over the last years in the Netherlands. Accordingly, the budget impact associated with these orphan drugs has increased, both in absolute terms as well as compared to the total pharmaceutical spending.

Acknowledgements

This study was financially supported by the Netherlands Organization for Health Research and Development (ZonMw; grant number 152002045). The authors would like to thank Hans Piepenbrink for his help in collecting the data.



CHAPTER 3

Burden of illness of Pompe disease in patients only receiving supportive care

Kanters TA, Hagemans MLC, Van der Beek NAME,
Rutten FFH, Van der Ploeg AT, Hakkaart L

J Inherit Metab Dis (2011) 34:1045-1052

Abstract

Background: Pompe disease is an orphan disease for which enzyme replacement therapy (ERT) recently became available. This study aims to estimate all relevant aspects of burden of illness - societal costs, use of home care and informal care, productivity losses, and losses in health-related quality of life (HRQoL) - for adult Pompe patients only receiving supportive care.

Methods: We collected data on all relevant aspects of burden of illness via a questionnaire. We applied a societal perspective in calculating costs. The EQ-5D was used to estimate HRQoL.

Results: Eighty adult patients (87% of the total Dutch adult Pompe population) completed a questionnaire. Disease severity ranged from mild to severe. Total annual costs were estimated at €22,475 (range €0 – €169,539) per adult Pompe patient. Patients on average received 8 hours of home care and 19 hours of informal care per week. Eighty-five percent of the patients received informal care from one or more caregivers; 40% had stopped working due to their disease; another 20% had reduced their working hours. HRQoL for Pompe patients who only received supportive care was estimated at 0.72, 17% lower than the Dutch population at large.

Conclusions: Adult Pompe disease is associated with a considerable burden of illness at both the societal and patient levels. The disease leads to substantial costs and dependency on medical devices, home care, and informal care, and has a high impact on the patient's social network. In addition, patients are limited in their ability to work and have significantly reduced HRQoL.

Introduction

Pompe disease (glycogen storage disease type II; acid maltase deficiency) is a neuromuscular and lysosomal storage disorder caused by deficiency of the enzyme acid alpha-glucosidase, which is required for the degradation of lysosomal glycogen [73]. Storage of glycogen occurs mainly in skeletal muscles and leads to loss of muscle function. The disease presents as a broad clinical spectrum. The severe classic infantile form is rapidly progressive and leads to death within the first year of life [26, 32, 33]. The majority of patients have a more slowly progressive or "late-onset" form of the disease. First symptoms may present from infancy to the sixth decade of life. The vast majority of patients are adults. Muscle weakness affects both mobility and respiratory function, and most patients eventually become wheelchair-bound or ventilator-dependent [26, 34, 74].

Pompe disease is an orphan disease, which is defined in Europe as a disease that affects fewer than 5 per 10,000 people and in the U.S. as a disease that affects fewer than 200,000 people. Pompe disease occurs with an estimated frequency of approximately 1 in 40,000 births in the Netherlands [30]. Similar or lower frequencies have been reported for other countries [75, 76]. Our study focuses on adult Pompe disease patients, who make up about 80% of the known Dutch patient population.

In 2006 the commercial availability of enzyme replacement therapy (ERT) made Pompe disease the first inheritable muscle disorder for which therapy is available [15, 46, 77]. For a few other lysosomal storage disorders (Gaucher disease, Fabry disease, mucopolysaccharidosis I, II, and VI), similar therapies became available at earlier stages [78-82]. Costs of ERT in Pompe disease are considerable, especially in adults, averaging about €300,000 per patient annually. In the Netherlands ERT for Pompe disease is conditionally reimbursed for a period of 3–4 years. Traditional cost-effectiveness analysis is considered inappropriate for orphan diseases because of their low frequencies and relatively high developmental costs of treatment [83]. Cost-effectiveness is, however, a topic that should be addressed given the conditions of reimbursement of ERT.

Most cost of illness studies, often performed from a societal perspective, fail to account for the entire burden of an illness. Patients might need medical devices; they might need home care and informal care (which can potentially also affect patients' families' lives); patients' capacity to work could be limited; and any disease can affect patients' health-related quality of life (HRQoL). A burden of illness (BOI) study, which compiles all these aspects, has heretofore been unavailable for adult Pompe disease patients, although BOI of adults with Pompe disease is expected to be substantial. Hence, the aim of this study

is to assess the burden of Pompe disease with respect to all aspects: societal costs, the use of home care and informal care, productivity losses, and losses in HRQoL. Following Hagemans et al. (2004), quality of life is expected to be lower for more severely affected patients, i.e., patients using ambulatory or respiratory devices [37]. These patients are also expected to incur higher annual costs.

Methods

Study population

The Center for Lysosomal and Metabolic Diseases at Erasmus Medical Center serves as the national referral center for patients with Pompe disease. From January 2005 to October 2009, 92 adults with Pompe disease were seen at Erasmus MC. This study focuses on patients that only receive supportive care, i.e., costs of ERT are not assessed in this study. Patients who completed one or more health economic questionnaire(s) while only receiving supportive care from January 2005 to October 2009 were included in the sample.

Data collection

As part of a long-term follow-up study on the natural course of the disease, effects of ERT, and health economic aspects, patients were asked to complete a health economic questionnaire every 6 months. All relevant aspects of BOI - medical consumption (e.g., hospital admissions and day visits, ambulatory care, medications, tests, use of medical devices), use of informal care and home care, productivity losses due to absence from work, reduced efficiency, and HRQoL - were considered in the questionnaire. The part of the questionnaire measuring healthcare utilization contained the most relevant medical services for patients with Pompe disease. No distinction was made between costs related to Pompe disease and those not specifically related to Pompe disease. A similar approach was taken for the assessment of productivity losses. Data collection started in 2005 and is ongoing for both patients receiving supportive care only and patients receiving ERT. The study was approved by the Central Committee on Research Involving Human Subjects in the Netherlands, and participants provided written informed consent.

Medical costs

Costs were calculated following the Dutch guidelines for costing studies [84]. Individual costs were obtained by multiplying volumes of components at individual patient levels with relevant unit costs from the costing manual [84]. We adopted the societal perspective, i.e., all relevant costs were included in the analyses regardless of who incurred these

costs [85]. Home care was valued with wage rates from the Dutch costing manual [84]. Medication prices were obtained from the Dutch Pharmacotherapeutic Compass [86]. Market prices were used as unit prices for medical equipment, medical devices, and home adjustments. Unit costs are given in Table 3.1. Semi-annual costs were calculated for each patient by taking the average costs of all observations during the period when the patient did not receive ERT. Semi-annual costs were then doubled to obtain yearly costs per patient. Consumer price indices were used to estimate all costs in 2009 euro values.

Nonmedical costs

Informal care

Informal care was valued using the shadow price method, which uses professionals' wage rates to valuate informal caregivers' time.

Productivity losses

Patients might be forced to reduce their working hours or stop working altogether due to disability. The disease might also lead to absences from work. All these aspects were included in the analyses. Costs associated with productivity losses were computed using the friction cost method as recommended in the Dutch guidelines for costing studies [84]. In this approach, societal production losses are limited to short-term productivity losses. For absences longer than 22 weeks, an absent employee is assumed to be replaced by a previously unemployed person. The period required to hire and train the

Table 3.1 Medical cost components and associated unit costs (2009 prices)

Cost component	Cost per unit *	Source
Hospital care	€ 394 **	[84]
Intensive care	€ 1,847	[84]
Nursing home	€ 226	[84]
Ambulatory care		
Hospital day visits	€ 69 **	[84]
GP visits	€ 22	[84]
Physiotherapy	€ 25	[84]
Other paramedical	€ 14 - € 91	[84]
Home care per hour	€ 29 - € 65	[84]
Medication		[86]
Other medical costs		
Tests & Procedures	€ 54 - € 181	[84]
Respiratory support per day	€ 5	[87]
Medical devices	€ 18 - € 1,500	Market prices

* Costs per unit are based on average unit costs for medical procedures, consultations and admissions [84];
** Weighted average of academic and general hospital costs

new employee is called the friction period, which is the only time associated with productivity costs [88]. For (international) comparison, we also applied the human capital approach, which assumes that productivity losses are generated until retirement [89]. Wage rates, corrected for age and gender, were obtained from the costing manual [84].

Health-related quality of life

HRQoL was assessed using the EQ-5D instrument, which consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each having three levels (no limitations, some limitations, and severe limitations). When combined with health states "unconscious" and "death" the instrument describes 245 distinct health states. Each health state is associated with a utility using a scoring formula [85]. Utility scores were estimated using the Dutch tariff [90]. As such, utilities derived from health states can be regarded as a valuation of that specific health state by the Dutch general population. Utilities typically range from zero (death) to 1 (perfect health). Some health states correspond to negative utilities, implying that these health states are regarded as being worse than death [90].

Statistical methods

Respiratory support and ambulatory support were used as indicators of disease severity [34, 37, 74]. Changes in use of such support over time were examined with McNemar's test. Year of diagnosis was used to determine disease duration. In comparing utilities and costs, patients were categorized on the basis of their last observation. Differences in utilities and total costs between users and nonusers of ambulatory and respiratory support were examined with Mann-Whitney tests. To examine differences in utilities due to disease duration, patients were divided into three groups. Differences in utilities between these groups were examined using Kruskal-Wallis tests. The level of significance for statistical tests was set at 5%. To examine the relation between costs and HRQoL, a Spearman's correlation was computed. Statistical analyses were performed using Microsoft Excel 2003 (Microsoft, 2003) and SPSS version 15.0 (SPSS, 2006).

Results

Patient population

Eighty adult Pompe patients (87% of the Dutch Pompe population) completed at least one health economic questionnaire while only receiving supportive care. In total, 161 questionnaires were completed. Patient characteristics are presented in Table 3.2. The average baseline age of the population was 51 years; half of the population was male. The average disease duration at baseline was 9 years. The number of patients using respi-

Table 3.2 Characteristics of the study population

	First questionnaire	Last questionnaire
Number of patients *	80	80
Demographic characteristics		
Age (years; SD, min-max)	51.0 (± 12.2; 25-76)	51.9 (± 12.2; 25-76)
Gender (number, % male)	41 (51%)	41 (51%)
Clinical characteristics		
Duration since diagnosis		
(years; SD, min-max)	9.3 (± 9.4; 0-30)	10.2 (± 9.3; 0-30)
Ambulatory support (%)	48.8%	55.0%
Respiratory support (%)	30.0%	32.1%

* For patients that completed only one questionnaire, it was used both as first and last observation

ratory support and ambulatory support increased during the study, but not significantly (McNemar's $p = 1.000$ and $p = 0.125$, respectively, Table 3.2). Background information on ambulatory and respiratory support for the 12 patients who did not participate in the study showed no significant differences compared to participating patients.

Medical costs

Table 3.3 shows the volumes of medical consumption for adult Pompe patients only receiving supportive care. Patients annually made five outpatient hospital visits on average, primarily to the neurologist (28%). Three patients lived permanently in a nursing home due to Pompe disease. On average, patients made two visits to the general practitioner. Physiotherapy was the most frequently used type of paramedical care, averaging 18 visits per patient annually, but its use varied widely among patients. Half the population used medication, taking four different medicines on average. Most patients (70%) reported using medical devices, of which the majority (75%) used more than one device (on average three devices per patient). Most frequently used devices were wheelchairs and other ambulatory support equipment. Thirty-three percent of the patients used respiratory support. Patients' average need for home care was 8 hours/week.

Table 3.3 also shows the distribution of costs of different medical components. Annual medical costs per patient were estimated at €13,679 (range €0 – €167,935). Home care, associated with an annual cost of €7,011 (range €0 – €85,987), was the largest medical cost component (51%). Nursing home admissions - relevant for three patients - accounted for 19% of medical costs. Respiratory support was calculated by multiplying daily costs by 365 days and the percentage of patients using the support. Respiratory support accounted for average annual costs of €574 per patient. Volumes are also presented in Table 3.3.

Table 3.3 Average medical consumption and average costs per patient for adult Pompe patients only receiving supportive care

	Respondents using service, n (%)	Average units used per patient, n (SD)	Average annual costs per patient (n = 80)	Range of costs
Hospital care			€ 313	€ 0 - € 6,303
Patients hospitalized	12 (15)			
Number of hospitalizations (if hospitalized)		2 (1.2)		
Duration per hospitalization (nights)		4 (4.4)		
Intensive care			€ 808	€ 0 - € 18,467
Patients hospitalized	7 (9)			
Number of hospitalizations (if hospitalized)		2 (1.1)		
Duration (nights; if hospitalized)		5 (3.3)		
Nursing home	3 (4)		€ 2,571	€ 0 - € 82,454
Ambulatory care				
Hospital day visits	71 (89)	5 (6.1)	€ 372	
GP visits	46 (58)	2 (1.9)	€ 36	
Physiotherapy	32 (40)	18 (39.2)	€ 473	
Other paramedical	27 (34)	4 (9.7)	€ 162	
Total costs			€ 1,043	€ 0 - € 7,217
Home care	31 (39)		€ 7,011	€ 0 - € 85,987
Home care (hours/week)		8 (18.4)		
Medication			€ 198	€ 0 - € 1,257
Patients on medication	42 (53)			
Number of medicines (if on medication)		4 (3.8)		
Other medical costs				
Tests & Procedures	71 (89)	7 (4.3)	€ 750	
Respiratory support	26 (33)		€ 574	
Medical devices	56 (70)		€ 411	
Number of devices (if using devices)		3 (2.0)		
Total costs			€ 1,735	€ 0 - € 5,020
Overall			€ 13,679	€ 0 - € 167,935

Nonmedical costs

Table 3.4 shows the indirect (nonmedical) costs associated with Pompe disease for patients only receiving supportive care and how these indirect costs relate to medical cost components.

Table 3.4 Estimated annual costs of Pompe disease per adult patient

Cost category	Average per patient cost	Ranges of per patient costs
Hospital days	€ 313	€ 0 - € 6,303
Intensive care	€ 808	€ 0 - € 18,467
Nursing home	€ 2,571	€ 0 - € 82,454
Ambulatory care	€ 1,043	€ 0 - € 7,217
Home care	€ 7,011	€ 0 - € 85,987
Medication	€ 198	€ 0 - € 1,257
Other medical costs *	€ 1,735	€ 0 - € 5,020
Total medical costs	€ 13,679	€ 0 - € 167,935
Informal care	€ 5,741	€ 0 - € 36,037
Transportation	€ 158	€ 0 - € 1,918
Productivity losses	€ 2,633	€ 0 - € 38,176
Other non-medical costs	€ 263	€ 0 - € 7,032
Total non-medical costs	€ 8,796	€ 0 - € 46,992
Overall	€ 22,475	€ 0 - € 169,539

* Including tests, procedures, respiratory support, medical devices

Informal care

Patients on average received 19 hours/week of informal care, totaling €5,741 annually (range €0 – €36,037). Informal care mostly comprised household activities such as cleaning and grocery shopping (44%). Eighty-five percent of the patients received informal care, in most cases from more than one caregiver. Caregivers were most often the patient's spouse (76%), followed by children (34%), friends (18%), and parents (16%).

Productivity losses

Thirty-nine percent of the patients (n = 31) were employed, 52% of whom indicated they were working fewer hours than they would have without the disease (average: 14 hours fewer). In addition, 32% were absent from work due to illness for an average of 12 work days. Thirty-two patients (40%) indicated they stopped working due to Pompe disease; 11 of them had been declared unfit for work. Using the friction cost method, productivity losses were estimated at €2,633 (range €0 – €38,176) per patient per year.

Using the human capital approach to assess productivity losses, average annual costs accumulated to €40,590 (± 45,574), 51% of which were due to productivity losses. Total productivity losses until retirement would accumulate to over €200,000 per patient.

Total costs for adult Pompe patients only receiving supportive care accumulated to €22,475 per year (range €0 – €169,539). Medical costs accounted for 61% of total annual

costs. The largest cost components were home care (31%), informal care (26%), and productivity losses (12%).

Health-related quality of life

Seventy-two patients (78% of the Dutch adult Pompe population only receiving supportive care) completed the EQ-5D. Table 3.5 shows the HRQoL of patients with Pompe disease subdivided by disease duration, ambulatory support, and respiratory support. The average utility for Pompe patients was 0.72, whereas the mean utility for a representative sample of the Dutch population has been estimated at 0.87 [91]. The utility decrement as a consequence of Pompe disease of 0.15 was significant. Adult Pompe patients had a 17% lower utility than an average Dutch person. The decrement resulted mainly from mild limitations in the domains of mobility, usual activities, and pain. Severe limitations were only observed in a limited number of cases.

Disease severity was determined on the basis of the use of ambulatory and respiratory support. Patients using ambulatory and respiratory support reported lower HRQoL compared to patients without such devices, but the differences were not significant. In contrast, total costs were significantly higher for patients using ambulatory and/or respiratory devices. Longer disease duration resulted in higher annual costs. The association between disease duration and total annual costs or utilities was not significant. As expected, total annual costs per patient were significantly negatively correlated with HRQoL (rho = −0.534).

Table 3.5 Health-related quality of life and total costs for adult Pompe patients only receiving supportive care

	Number (%)	EQ-5D utility score (SD)	Number (%)	Total costs
Overall (SD, min-max)	72	0.72 (0.18, 0.17-1.00)	80	€ 22,475
Disease duration				
≤5 years	31 (43)	0.74 (0.15)	33 (42)	€ 13,922
6-15 years	18 (25)	0.70 (0.16)	19 (24)	€ 26,290
>15 years	22 (31)	0.69 (0.23)	27 (34)	€ 30,736
Ambulatory support	37 (51)	0.67 (0.21)	44 (55)	€ 33,246
Respiratory support	20 (28)	0.61 (0.26)	25 (32)	€ 41,485

Discussion

This is the first burden of illness study of adults with Pompe disease. The study shows that the disease poses a substantial burden on patients, their families, and society in terms of costs of illness, use of medical devices, home care and informal care, productivity losses, and HRQoL. Costs due to Pompe disease for patients that only receive supportive care amount to an average of €22,475 per patient annually, ranging from €0 to €169,539. Besides costs to society, patients' daily lives are substantially affected. Indicative is the large number of hours of support patients require from professionals and their social environment. Home care is used on average 8 hours/week per patient and accounts for 31% of total annual costs. In addition, patients require 19 hours/week of informal care, accounting for 26% of annual costs. Eighty-five percent of the patients receive informal care from one or more caregivers, indicating that the disease also has an important impact on the patient's social network. Most patients (70%) use medical devices; the majority (75%) of those patients use more than one device. The impact on productivity is considerable. Forty percent of the adult Pompe patients had stopped working due to their disease; another 20% had reduced the number of working hours. Six patients (19% of working patients) indicated they would have applied for a job at a higher functional level if they had not been affected by the disease. The study also shows that HRQoL for patients is estimated at 0.72, an average 17% lower than the Dutch population at large. Lower utilities were associated with higher patient costs.

The highest costs were incurred by patients living in nursing homes with utilities below 0.4 and involved severely affected patients who were both ventilator- and wheelchair-dependent. Only one 20-year-old male patient had zero costs and a utility of 1.

There were no data available on medical costs associated with MRI and DNA testing and home mechanical ventilation. Consequently, medical costs could have been underestimated. In addition, 58% of the working patients indicated they would be more efficient (on average 32%) absent their disease. For some of the patients who had stopped working, corresponding productivity losses could not be estimated due to lack of data; productivity losses are thus underestimated.

As recommended by the Dutch guidelines for costing studies [84], we applied the friction cost method as the primary approach to assess productivity costs in Pompe patients. Average productivity costs using this method are €2,633 (range €0 – €38,176) per patient per year, but would have been substantially higher (€40,590 per patient per year; range €0 – €224,205) had we used the human capital approach. As Pompe disease is a chronic condition, the large difference between the estimates is caused by absence

from work due to the disease for a period longer than 22 weeks, which is not associated with costs using the friction cost method. Koopmanschap et al. (1995) argue that the friction cost method is the most realistic approach to value productivity losses in terms of societal costs since a person unable to work for a period of more than 22 weeks will be replaced [88].

Due to the relatively small number of patients, the uncertainty surrounding the estimates is large, as revealed by the broad ranges of costs and HRQoL estimates. Excluding the three patients permanently living in a nursing home reduced the average annual costs per patient by €3,435 (standard deviation 23%). The impact of the three patients on total costs and standard errors reflects the major problem of dealing with a small patient population in a rare illness such as Pompe disease. This study used information over a period of almost 5 years instead of 1 to increase the number of observations. Such an approach - averaging all observations per patient to enlarge the study population - can be used as a tool to investigate the burden of illness in other rare diseases. For adult Pompe patients only receiving supportive care, costs associated with informal care and productivity losses account for 26 and 12% of total annual costs of €22,475, respectively. In comparison, total medical and nonmedical annual costs for Dutch patients with multiple sclerosis have been estimated at €17,450 (2009 prices), with productivity losses estimated at 4–5% and informal care about 21% [92] of the total. For patients suffering from rheumatoid arthritis, informal care and productivity losses have been estimated at 25 and 18% of total annual costs, respectively [93]. For the Netherlands no cost of illness study was available for a neuromuscular disorder similar to Pompe disease. For the U.S., total annual medical costs for children and young adults with muscular dystrophy were estimated at €18,250 (conversion rate $1 = €0.822; 2009 prices). Costs of informal care and productivity losses were not provided in this study [94]. Transferability of cost of illness estimates is generally limited due to specifics of national healthcare systems [95]. To increase transparency of the results, volumes and unit costs are also presented in Tables 3.1 and 3.3.

For adult Pompe patients who only receive supportive care, HRQoL is 0.72. By comparison, hearing complaints have been associated with an HRQoL of 0.86 [96], and multiple sclerosis with an HRQoL of 0.61 [92]. These figures represent average levels of HRQoL. Large variations in disease severity, however, make HRQoL comparisons between different diseases difficult.

Here we have focused on adult Pompe patients who only receive supportive care. Future studies will similarly examine the burden of illness for adult Pompe patients receiving enzyme therapy to evaluate the cost-effectiveness of enzyme replacement therapy.

Acknowledgements

This study was financially supported by the Dutch organization for health research and healthcare innovation (ZON-MW; grant no. 152001005). The authors would like to thank Ewout Steyerberg and Willem Jan Meerding for their efforts in setting up the health economic questionnaires. The authors would also like to thank Ken Redekop, Judy Kempf, and Jaap de Boer for their comments on earlier versions of this paper.

CHAPTER 4

Comparison of EQ-5D and SF-6D utilities in Pompe disease

Kanters TA, Redekop WK, Kruijshaar ME, Van der Ploeg AT, Rutten-van Mölken MPMH, Hakkaart L

Qual Life Res (2015) 24:837-844

Abstract

Purpose: Comparative studies between Euroqol-5D (EQ-5D) and ShortForm 6D (SF-6D) utilities have been performed for a number of diseases, but not yet for orphan diseases. Pompe disease is an orphan disease with a prevalence of <5 per 10,000, characterized by impaired ambulatory and pulmonary functioning. We compared the psychometric properties of EQ-5D and SF-6D in patients with this disease and assessed their convergent validity, discriminative ability and sensitivity to change.

Methods: EQ-5D utilities and SF-6D utilities were computed using the UK value set. Dimensions and utilities of the two instruments were compared by correlation coefficients and descriptive statistics. We assessed whether EQ-5D and SF-6D were able to discriminate between different levels of severity and examined sensitivity to change for patients with multiple observations.

Results: Correlations between theoretically related dimensions of the EQ-5D and SF-6D were highly significant and were moderate to strong (range rho = 0.409–0.564). Utility values derived from the two instruments were similar (mean EQ-5D = 0.670; mean SF-6D = 0.699) and correlated strongly (rho = 0.591). Discriminative properties were somewhat better for EQ-5D; mean changes and effect sizes were better for SF-6D.

Conclusions: Overall, we conclude that both instruments appear to be equally appropriate with respect to assessing utilities in Pompe disease, but neither of them performed excellently. The descriptive system of the SF-6D describes health states for Pompe disease more accurately. EQ-5D showed better discriminative properties. The SF-6D performed better with respect to sensitivity to change.

Introduction

In the European Union, a disease is labelled orphan disease when the disease has a prevalence of <5 per 10,000 people and the disease is life-threatening or seriously debilitating [2]. In the USA, a disease which affects less than 200,000 US citizens is marked as an orphan disease [97]. The number of orphan drugs, i.e. drugs used to treat orphan diseases, has increased considerably over the last decades and so has the impact of these, often expensive, drugs on national healthcare budgets [21]. To control costs to the healthcare system, policymakers increasingly use health technology assessment for new therapies, including those for orphan diseases [83].

In the Netherlands, a "coverage with evidence development" system was in place for intramural orphan drugs, providing 4 years of conditional coverage while additional studies on effectiveness and cost-effectiveness of the orphan drug were performed. The first orphan treatment assessed under this scheme was enzyme replacement therapy for the treatment of Pompe disease. Pompe disease (acid maltase deficiency) is a rare inherited metabolic myopathy with a broad clinical spectrum [26]. The prevalence of Pompe disease in the Dutch population is estimated at 1:40,000 [30]. This paper focuses on the adult Pompe population (~80% of all Dutch patients with Pompe disease), in which the disease follows a slowly progressive disease course and typically affects ambulatory and pulmonary function [98-100]. In many cases, the disease leads to dependency on a wheelchair and/or mechanical ventilation [101]. Adult patients have also been shown to experience a reduced quality of life [37, 102] and survival [38].

For patients, the most relevant outcome parameter is improvement in health-related quality of life. Health-related quality of life is often expressed in utilities. Previous studies have shown that the choice of the utility measure can result in different cost-effectiveness ratios [103-105]. To allow an evaluation of cost-effectiveness for treatment(s) for Pompe disease, the choice of the appropriate utility instrument is therefore pivotal.

The two most widely used utility instruments in Europe are the EQ-5D [106] and the SF-6D [107]. The SF-6D can be derived from the SF-36 instrument. The EQ-5D and the SF-6D differ in their descriptive systems and different valuation methods were used to estimate their sets of utility scores [107, 108]. Consequently, completion of both instruments by the same patient may result in different utilities. The EQ-5D and the SF-6D have been compared for several diseases, and most studies found a high level of agreement between the two instruments [103, 109-111]. Both EQ-5D and SF-6D utilities decrease when disease severity increases [103, 109, 110, 112, 113]. SF-6D utilities appear to be somewhat lower than EQ-5D utilities for mildly impaired health states, whereas they

appear to be somewhat higher for the severely impaired health states [111-113]. The EQ-5D and the SF-6D have never been compared in Pompe disease.

The aim of this paper is to assess the measurement properties of the two instruments and to compare utilities of the EQ-5D and the SF-6D in adult Pompe patients. We will assess validity by examining the correlations between EQ-5D and SF-6D dimensions that theoretically should and should not be related (convergent validity and divergent validity, respectively). We also assess the ability of the EQ-5D and the SF-6D to discriminate between subgroups of patients with different disease severities. Finally, we determine the sensitivity to change of the two instruments over time (responsiveness).

Methods

Patients and setting

All patients with Pompe disease in the Netherlands are followed at the Erasmus Medical Center in Rotterdam. Between January 2005 and August 2011, 110 Dutch adult patients diagnosed with Pompe disease were monitored at Erasmus MC and asked to complete the EQ-5D every 3–6 months as part of a long-term follow-up study on the natural course and effects of treatment and health economic aspects. In addition, patients were asked to complete the SF-36 as part of an annual international Pompe survey. A description of the Pompe survey can be found in [38]. Only Dutch patients were included in the current study. Both the quality of life and the follow-up studies were approved by the Central Committee on Research Involving Human Subjects in the Netherlands. All participants provided written informed consent.

Measurements

The EQ-5D consists of five health dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) each dimension with three levels (no problems, some problems and major problems) [106]. Consequently, the instrument provides 243 distinct health states. Each of these health states can be assigned a particular utility using a scoring algorithm. Utilities typically range from 0 (indicating death) to 1 (perfect health), but negative utilities do occur, representing health states regarded as worse than death. The UK set of EQ-5D utility weights was determined in a time trade-off study by the Measurement and Valuation of Health group in York, with utilities ranging from -0.592 to 1 [108].

The SF-6D is a preference-based instrument derived from the Short Form 36 and consists of six dimensions (physical functioning, role limitations, social functioning, pain, mental health and vitality) [107]. Each of the dimensions can be rated using four to six levels. The

SF-6D comprises 18,000 possible health states. Each of these health states can be assigned a utility by using a scoring algorithm, which was developed using standard gamble methods by the Sheffield Health Economics Group. SF-6D utilities range from 0.291 to 1 [107].

To a large extent, the dimensions of the two instruments theoretically address similar aspects of health [109]. The "mobility" and "self-care" dimensions of the EQ-5D are theoretically related to the "physical functioning" dimension of the SF-6D. The dimensions "role limitations" and "social functioning" of the SF-6D can be linked to the "usual activities" dimension of the EQ-5D. A dimension "pain" is measured in both instruments. "Mental health" (SF-6D) and "anxiety/depression" (EQ-5D) are also theoretically related. Only the "vitality" dimension in the SF-6D is not theoretically similar to one of the EQ-5D dimensions.

In addition to patients completing the EQ-5D and the SF-36, pulmonary function and muscle strength were measured, since these are two important features of Pompe disease. Forced vital capacity (FVC) was measured in a sitting position to determine pulmonary function. Results were expressed as a percentage of the predicted normal reference value derived from published data [114]. As a sensitivity analysis, the analyses were repeated with FVC measured in supine position. Neurological examinations comprised measurement of skeletal muscle strength by manual muscle testing using the Medical Research Council (MRC) grading scale (0–5) [115]. MRC scores were summed for designated muscle groups and expressed as a percentage of the highest attainable score [47].

Statistical analyses

We compared the descriptive statistics and frequency distributions of EQ-5D and SF-6D dimensions and utility scores. Normal distributions for EQ-5D and SF-6D utilities were tested using Shapiro–Wilk tests. Spearman's rank correlations were calculated to assess the levels of agreement between the theoretically related and unrelated dimensions of the EQ-5D and the SF-6D, and between EQ-5D and SF-6D utilities. A correlation coefficient below 0.1 was considered very weak; 0.1–0.3 weak; 0.3–0.5 moderate; and a correlation coefficient above 0.5 was considered strong [116]. Differences in utilities between the instruments were tested using a Wilcoxon signed-rank test.

Four different external criteria of disease severity were used to assess whether the EQ-5D and SF-6D were able to discriminate between patients with a different disease severity: (1) pulmonary function measured by percentage predicted FVC; (2) muscle strength measured by MRC; (3) use of wheelchair, yes or no; and (4) use of respiratory support, yes or no. The differences in utilities with respect to wheelchair use and use of respiratory support were tested using Mann–Whitney tests. The relationships between utilities and pulmonary function and muscle strength were assessed with correlations and graphically presented in a scatterplot.

Sensitivity to change between the patient's first and the last measurement was assessed by comparing the mean changes and the effect sizes (Cohen's D) of utilities with respect to pulmonary function and muscle strength. Effect sizes were computed by dividing the mean change by the standard deviation of the first observation [117]. Patients were divided into two groups. One group included patients whose pulmonary function (measured by percentage predicted FVC) worsened, and the other group included patients whose pulmonary function increased over time. This was done similarly for the MRC muscle strength score. Patients with clinical scores that did not change over time were not included in the analyses examining sensitivity to change.

The analyses for convergent validity and discriminative ability were assessed on baseline observations, i.e. the first time that a patient completed both the EQ-5D and the SF-6D. Comparative analyses between the EQ-5D and the SF-6D were performed only for those patients who had responded to both instruments within a period of 28 days. Statistical analyses were performed using Stata version 12.0 (Statacorp, 2009).

Results

Eighty (73% of the total Dutch adult Pompe population) patients completed both the EQ-5D and the SF-6D. Their average age at baseline was 49.4 years, and 54% were female. Their average disease duration since diagnosis was 8.7 years. There was no significant difference in gender ($p = 0.110$), age ($p = 0.578$) or disease duration ($p = 0.982$) between responders and non-responders.

Tables 4.1 and 4.2 show the frequency distributions of the scores for each dimension of the two instruments at first measurement. The results for both instruments showed that patients most often reported none to moderate problems. Patients particularly seem to suffer from problems with respect to physical functioning, role limitations and vitality. The most severe levels of problems were not often reported on any of the dimensions.

Table 4.3 provides the degree of association between the various dimensions of the two instruments. The correlations between theoretically related dimensions (in bold) were all highly significant and moderate to strong.

Table 4.4 shows utility scores of both instruments. EQ-5D utilities were not normally distributed ($p < 0.001$), whereas SF-6D utilities followed a normal distribution ($p = 0.084$). Dispersion of EQ-5D utilities was larger than for SF-6D utilities, also reflected by the larger standard deviation (Table 4.4). There was no significant difference between

utilities derived from the EQ-5D and the utilities derived from the SF-6D ($p = 0.542$). The correlation between the utilities of the two instruments was significant ($p < 0.001$) and strong (rho = 0.591). The maximum utility score of 1 was reported in 6% of the EQ-5D observations. The maximum utility score was not observed for the SF-6D. The lowest possible score was not reported for either instrument.

Table 4.1 Frequency distribution of SF-6D scores by dimension

Score	Physical functioning	Role limitations	Social functioning	Pain	Mental health	Vitality
1	1 (1%)	30 (38%)	31 (39%)	18 (23%)	22 (28%)	3 (4%)
2	7 (9%)	28 (35%)	23 (29%)	15 (19%)	22 (28%)	21 (26%)
3	25 (31%)	2 (3%)	20 (25%)	34 (43%)	29 (36%)	34 (43%)
4	28 (35%)	20 (25%)	5 (6%)	10 (13%)	7 (9%)	19 (24%)
5	15 (19%)	-	1 (1%)	3 (4%)	0 (0%)	3 (4%)
6	4 (5%)	-	-	0 (0%)	-	-

Table 4.2 Frequency distribution of EQ-5D scores by dimension

Score	Mobility	Self-care	Usual activities	Pain/ Discomfort	Anxiety/ Depression
1	17 (21%)	57 (71%)	23 (29%)	27 (34%)	62 (78%)
2	61 (76%)	17 (21%)	54 (68%)	52 (65%)	18 (23%)
3	2 (3%)	6 (8%)	3 (4%)	1 (1%)	0 (0%)

Table 4.3 Spearman's rank correlations between EQ-5D and SF-6D dimensions

SF-6D	EQ-5D				
	Mobility	Self-care	Usual activities	Pain/ discomfort	Anxiety/ depression
Physical functioning	**0.524****	**0.564****	0.323**	-0.040	0.005
Role limitations	0.311**	0.415**	**0.409****	0.154	0.473**
Social functioning	0.382**	0.047	**0.433****	0.121	0.491**
Pain	0.161	0.113	0.316**	**0.545****	0.287**
Mental health	0.064	0.020	0.243*	0.119	**0.517****
Vitality	0.231*	-0.059	0.337**	0.147	0.328**

Note: Theoretically related dimensions are indicated in bold
* Indicates significance at 0.05 level; ** Indicates significance at 0.01 level

Table 4.4 Descriptive statistics for EQ-5D and SF-6D utilities

	EQ-5D utility	SF-6D utility
Mean (standard deviation)	0.670 (0.201)	0.699 (0.092)
Median (range)	0.691 (-0.043 – 1.000)	0.687 (0.497 – 0.894)
Correlation (Spearman)	0.591	

Figure 4.1a Scatterplot of EQ-5D utilities versus pulmonary function (% predicted FVC)

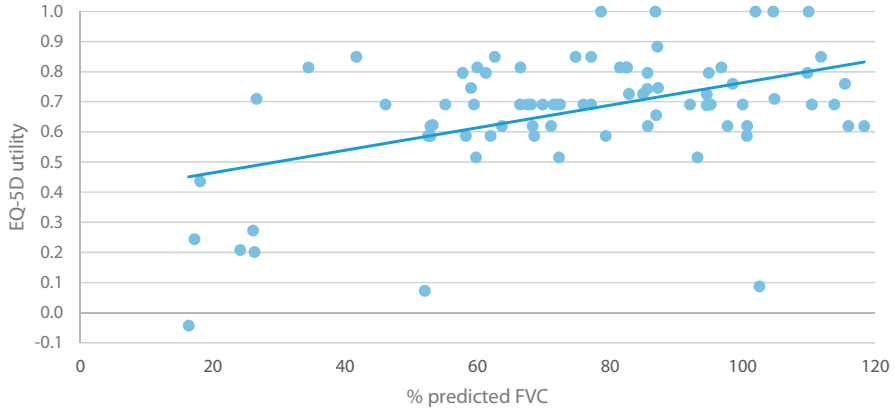


Figure 4.1b Scatterplot of SF-6D utilities versus pulmonary function (% predicted FVC)

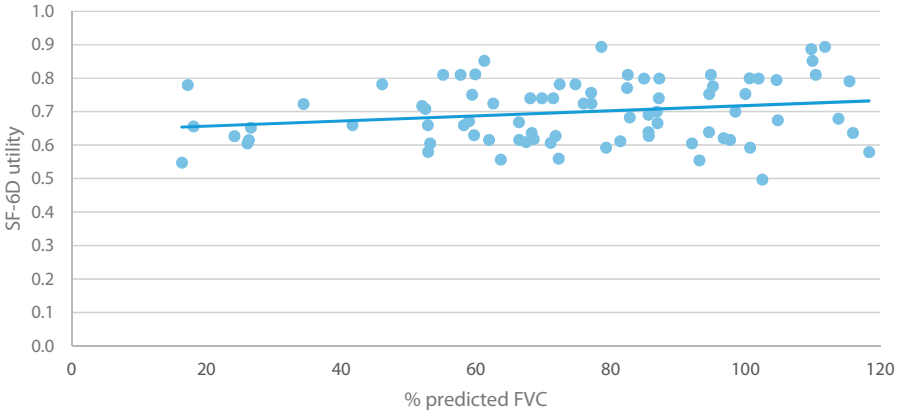


Table 4.5 and Figures 4.1 and 4.2 show the ability of the EQ-5D and the SF-6D to distinguish between patients with different levels of disease severity. Utilities were higher in patients not requiring a wheelchair or ventilation, but the differences in utilities were only statistically significant with respect to wheelchair use (Table 4.5). The differences between EQ-5D and SF-6D utilities were not significant. Figures 4.1 and 4.2 provide the scatterplots in which utilities of patients are compared with their pulmonary function and muscle strength. Although there was a positive relationship between pulmonary function and both utility measures, the correlations were weak for both instruments and only significant for EQ-5D utilities (EQ-5D rho = 0.325, $p = 0.003$, Figure 4.1a; SF-6D rho = 0.196, $p = 0.082$, Figure 4.1b). Similarly, correlations with muscle strength were weak and again significant only for EQ-5D utilities (rho = 0.275; $p = 0.013$, Figure 4.2a) and not for SF-6D utilities (rho = 0.212; $p = 0.059$, Figure 4.2b).

Figure 4.2a Scatterplot of EQ-5D utilities versus muscle strength (MRC)

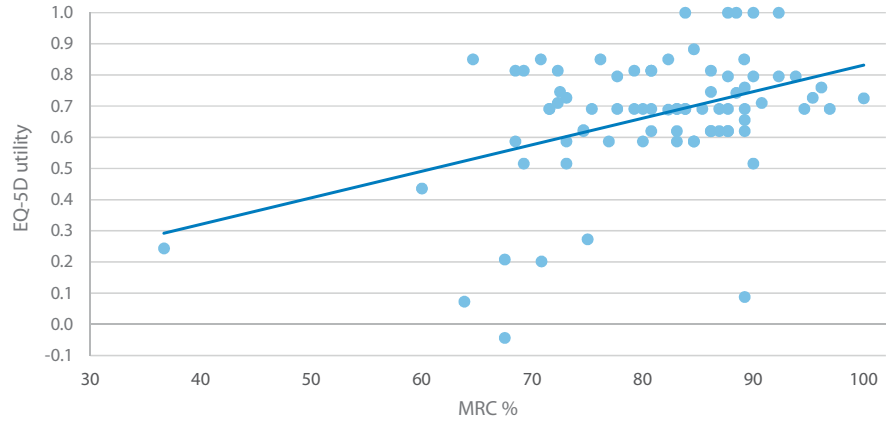


Figure 4.2b Scatterplot of SF-6D utilities versus muscle strength (MRC)

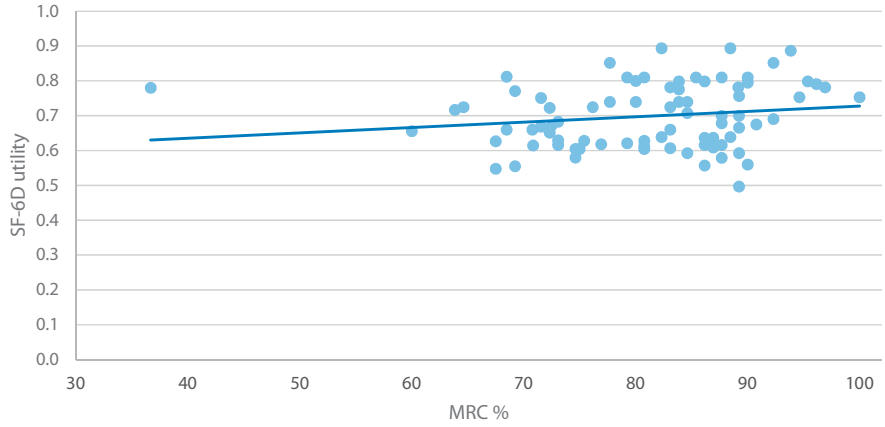


Table 4.6 shows the mean changes and effect sizes of EQ-5D utilities and SF-6D utilities over time for 70 patients with multiple observations. On average, patients completed 3.9 sets of questionnaires (range 1–9). The average time between the first and last observation was 2.8 years (range 0.5–6.3 years). Mean changes and effect sizes of utilities had the same direction as the changes observed in clinical outcome measures, except for the EQ-5D for patients with declining health. Overall, absolute differences in mean changes for EQ-5D and SF-6D utilities were small. Effect sizes for SF-6D utilities were larger with respect to muscle strength than for pulmonary function.

Table 4.6 Mean changes and effect sizes of EQ-5D and SF-6D

	Mean Change					Effect Size	
	n	%pred. FVC	MRC*	EQ-5D	SF-6D	EQ-5D	SF-6D
Decreased pulmonary function	35	-7.206		0.026	-0.003	0.152	-0.039
Increased pulmonary function	35	5.967		0.054	0.020	0.255	0.198
Decreased muscle strength	25		-4.544	0.020	-0.019	0.179	-0.240
Increased muscle strength	41		4.392	0.055	0.026	0.239	0.286

Abbreviations: pred. = predicted; FVC = Forced Vital Capacity; MRC = Medical Research Council
* MRC scores did not change for four patients, and these patients were not included in the analyses with respect to MRC

Table 4.5 Discriminative properties of EQ-5D and SF-6D utilities

	n	EQ-5D	p-value*	SF-6D	p-value*
Overall average	80	0.670		0.699	
Wheelchair			0.014		0.046
Yes	24	0.533		0.666	
No	56	0.729		0.713	
Ventilation			0.332		0.458
Yes	18	0.593		0.688	
No	61	0.693		0.704	

* Differences between categories were tested using Mann-Whitney tests

Discussion

This study showed that for the Dutch adult Pompe population utilities obtained using the EQ-5D were similar to SF-6D utilities. Theoretically related dimensions showed moderate to strong and highly significant correlations. Discriminative properties of both instruments were as expected, i.e. more severely affected patients reported lower utilities than those less severely affected, although the differences were more pronounced for EQ-5D utilities. However, statistically significant differences were only observed with respect to wheelchair usage, and correlations between utilities and clinical measures were rather weak. Sensitivity to change, assessed by comparing mean changes and effect sizes of utilities with respect to change of pulmonary function and muscle strength over time, had the expected sign for SF-6D utilities, but were always positive for EQ-5D utilities.

Pulmonary function was measured in sitting position. Results for percentage predicted FVC measured in supine position (with n = 69) were similar with respect to discriminative power and responsiveness to change, except that in this case the two measured

performed even more similar to each other. The correlations with the percentage predicted supine FVC were not only insignificant for SF-6D but also not for the EQ-5D utilities. Decreasing supine percentage predicted FVC was not reflected in a negative change in EQ-5D nor in SF-6D utilities.

The vitality dimension of the SF-6D has no counterpart in the EQ-5D. Hagemans et al. (2004) found that Pompe disease has an important impact on a patient's vitality [37]. This outcome was supported by the responses of the patients on the vitality dimension of the SF-6D. The SF-6D might therefore describe health states in Pompe disease better than the EQ-5D, although this hypothesis was not specifically tested in the current study.

Furthermore, the number of severity levels of the EQ-5D is limited. The response distribution for the dimension "mobility" makes this problem particularly apparent for Pompe disease. Wheelchair-dependent patients (30% of the sample) can only report "some problems in walking about" on the mobility dimension, as the most severe level ("Confined to bed") does not describe their situation adequately. This limitation of the EQ-5D for wheelchair-dependent patients has already been described elsewhere [118]. The recently developed 5-level version of the EQ-5D might alleviate these problems [119]. Despite the smaller number of levels compared to the SF-6D, EQ-5D utilities showed better discriminative properties. This might be explained by the fact that multiple dimensions are used to calculate utilities; i.e. patients using wheelchairs can have lower utilities by reporting problems on other dimensions of the EQ-5D.

Differences between severity levels and correlations between utilities and clinical parameters were not always significant for Pompe patients, especially for SF-6D utilities. The SF-6D in particular was insensitive for respiratory problems, i.e. utility differences in ventilation use were not significant and utilities were not significantly correlated to pulmonary function. While SF-6D and EQ-5D utilities discriminate well between different disease severities for various diseases (among others COPD) [103, 109, 110, 112, 113], their insensitivity to record respiratory problems has been reported for other diseases as well [120, 121], and may be due to the absence of a respiratory dimension in the instruments. The absence of a significant difference in utilities between patients with and without ventilation might be explained by the large variation in the extent to which this device is used, e.g. some patients only use their mechanical ventilation at night. The analyses preformed did not differentiate between type, i.e. invasive versus non-invasive, and number of hours of ventilation.

Effect sizes for EQ-5D utilities were not credible for patients with declining health. The mean changes and effect sizes for the EQ-5D and the SF-6D utilities might have been

small due to the relatively short follow-up period (i.e. 2.8 years; range 0.5–6.3 years) compared to the slowly progressive course of the disease, but due to the small number of patients, no minimum follow-up time was set. When an arbitrary minimum follow-up period of 2.0 years was used instead, absolute values of the mean changes and effect sizes increased, especially for utilities.

Limitations

A Dutch value set to compute utilities for the SF-6D is currently not available. Therefore, UK value sets were used for the computation of both EQ-5D and SF-6D utilities to enhance comparability of the results. The decrements in the Dutch EQ-5D value set are lower than in the UK value set; hence, corresponding utilities are higher if the Dutch value set is used [90].

Hagemans et al. (2004) hypothesized that coping plays a role in Pompe disease [37]. If one wants to include coping in the assessment, it may be better to use patient preferences to calculate utilities. However, in this study, we used preferences from the general population, as recommended in several pharmacoeconomic guidelines (e.g. UK, the Netherlands).

Studies of orphan diseases are inherently limited because of the small numbers of patients. The small study population might explain the non-significant results for the discriminative analyses. Our study included the majority of the Dutch adult patients. Although the absolute number of patients is limited in our study, the number of patients is relatively large compared to other studies on orphan diseases. The study seems representative for the adult Dutch Pompe population, since there were no significant differences between responders and non-responders. The transferability of our findings to other countries needs to be studied further. Hagemans et al. showed that physical quality of life scores for Pompe patients were similar between countries; differences did exist with respect to mental quality of life scores [37]. Pooling of international data might lead to more robust analyses and statistical differences. For now, these data are not available.

Future research

The EQ-5D and the SF-6D are generic preference-based instruments that aim to capture the loss of health-related quality of life in terms of utilities, for the purpose of QALY calculations. Disease-specific preference-based measures are considered a valid alternative to the measurement of utilities, when performance of generic instruments is shown to lack sensitivity. Using a disease-specific preference-based instrument has the advantage of increased sensitivity to disease-specific improvements, but has the obvious loss of

comparability in outcomes: the EQ-5D and the SF-6D have many reference populations that can help understand and interpret the effect size. If a disease-specific measure becomes available in the future, it might become clear whether the inability to discriminate between utilities for patients with and without ventilation and the relatively small changes over time stem from the small patient numbers or from the generic measures used. For these effects to be adequately captured, a disease-specific measure should at least have items on respiratory functioning, which is not included in the EQ-5D and the SF-6D. Future research could also focus on whether using the 5-level version of the EQ-5D might be more appropriate in patients with Pompe disease.

Overall, we conclude that the EQ-5D and the SF-6D are equally appropriate to assess health-related quality of life in Pompe disease, but neither of them performed excellently. No large statistical differences between EQ-5D and SF-6D utilities were found for patients with Pompe disease. The SF-6D seemed to be more accurate in describing health states for patients with Pompe disease, especially because the SF-6D comprises a vitality dimension. Discriminative properties were better for the EQ-5D. The SF-6D performed better with respect to mean changes and effect sizes.

Acknowledgements

This study was financially supported by the Netherlands Organization for Health Research and Development (ZonMw; grant no. 152001005). The authors would like to thank MLC Hagemans for comments on earlier versions of the manuscript.

CHAPTER 5

The impact of informal care for patients with Pompe disease: An application of the CarerQol instrument

Kanters TA, Van der Ploeg AT, Brouwer WBF, Hakkaart L

Mol Genet Metab (2013) 110:281-286

Abstract

Background: Patients with Pompe disease, a rare progressive neuromuscular disorder, receive a considerable amount of informal care. In this study, we examined the impact of providing informal care to patients with Pompe disease.

Methods: Caregivers were administered various instruments, which measured the (impact of) informal care in the context of Pompe disease. Patients' quality of life and use of a wheelchair and respiratory support were used to investigate the impact of disease severity on the burden and well-being of caregivers.

Results: Of all Dutch patients with Pompe disease, 88 indicated to receive informal care, of which 67 (76%; 67 caregivers) participated in this study. On average, caregivers provided 17.7 hours of informal care per week. Higher disease burden was associated with more hours of informal care. Caregivers experienced burden due to caregiving. Half of the informal caregivers reported mental health problems and problems with daily activities due to providing informal care. Physical health problems occurred in 40% of informal caregivers. Caregiver burden was higher for patients with a lower quality of life and for wheelchair dependent patients. Burden was not associated with respiratory support. Caregivers reported deriving personal fulfillment from caregiving and, on average, would become unhappier if someone else were to take over their care activities.

Conclusions: The provision of informal care causes burden to caregivers. However, caregivers also value caring for their loved ones themselves. The study may help physicians and policy makers to design measures to support informal caregivers.

Introduction

Informal care is care provided by someone from the patient's social environment, often unpaid and not in a professional capacity [122]. Attention for informal care is growing. This is due to the growing awareness of the impact of informal care on patients (who often prefer informal care to formal care) and caregivers (both negative and positive) [122]. In addition, the awareness of the importance of informal care as part of the total care provided to many groups of (chronic) patients has increased. Demographic and cultural changes may reduce the ability and willingness to provide informal care. Simultaneously, the demand for informal care is likely to increase in the future, due to a shortage of employees in the healthcare sector, the aging population and the substitution of formal care to informal care. This stresses the need to support informal caregivers in their important task.

As has been shown for a number of diseases, providing informal care affects informal caregivers in several respects [123-126]. An overall outcome measure capturing the impact of caregiving is well-being. Typically, two types of effects on well-being are observed in informal caregivers: the family effect and the caregiving effect [127]. The "family effect" is not directly related to caregiving, but to the fact that somebody in the direct environment of the caregiver is ill. Illness commonly results in reductions in well-being in the ill person's social environment. The "caregiving effect" ensues from the activity of providing informal care. While this impact is generally expected to be negative due to the burden informal care can impose, given the circumstances, providing informal care can also offer caregivers fulfillment. The burden of informal care can be substantial, and it not only affects well-being directly, it can also have adverse impacts on the health of caregivers [128]. It has been shown that providing informal care in some instances can even increase mortality risks for the caregiver [129]. Moreover, providing informal care can lead to personal and societal costs [130].

This study focuses on informal care in Pompe disease. Pompe disease (acid maltase deficiency) is a genetic orphan disease with a birth prevalence of 1:40,000 [30]. The disease presents as a progressive muscle disorder with a broad continuous clinical spectrum. The severe, infantile form of the disease is associated with muscle weakness, respiratory insufficiency and heart malfunctioning and results in death before reaching the first year of life [131]. The majority of patients are affected with slower progressive forms of the disease. In these patients, symptoms may present at any time from infancy to late adulthood and progressive muscle weakness may eventually affect both respiratory functioning and motor functioning. Ultimately, patients may become dependent on artificial ventilation and/or a wheelchair [26, 36]. Pompe disease also affects survival of adult patients [38].

We previously reported that patients with Pompe disease experience a reduced health-related quality of life and receive a substantial amount of informal care and home care [37, 102]. This study identifies and measures the effects of providing informal care to Pompe patients, in order to establish the degree of burden felt by these caregivers. This may help, where necessary, to design policies to support caregivers in their tasks, to enable caregivers to remain active in care provision. To this end, this paper examines the volume of care provided by caregivers and the burden of care experienced by caregivers and how this is related to patient's disease severity in the context of Pompe disease. These are aspects that have previously not been studied.

Methods

Study population

All patients with Pompe disease receiving care at the Center for Lysosomal and Metabolic Diseases of the Erasmus University Medical Center in Rotterdam were asked whether they received informal care. As all patients in the Netherlands (infants, older children and adults) are referred to this center, the population is representative for the entire Dutch Pompe population. Then, specific questionnaires assessing the burden of caregiving were provided to those patients indicating that they received informal care. These patients were asked to give the questionnaire to their informal caregiver. Per patient only one caregiver was allowed to participate in this study. No distinction was made between patients receiving enzyme replacement therapy or supportive treatment only. Data were collected from July 2009 till December 2011. All patients provided written informed consent.

Instruments

The CarerQol, the CarerQol-VAS, the self-rated burden scale, and the EuroQol-5D were used as instruments in this study. We applied the CarerQol to measure care-related quality of life of informal caregivers of Pompe patients. The CarerQol consists of 7 dimensions (the CarerQol-7D) and a valuation component (the CarerQol-VAS). The CarerQol-7D consists of 7 main domains of subjective burden (fulfillment, relational problems, mental health problems, problems with daily activities, financial problems, support, and physical health problems) each with three levels (no, some, a lot) [132-134]. The CarerQol-VAS assesses the overall well-being of the caregiver on a 0–10 scale, ranging from "completely unhappy" (0) to "completely happy" (10). Previous studies in different populations have shown that the CarerQol has excellent feasibility, good reliability, and moderate to good clinical and construct validity [132-134].

We also assessed whether caregivers derived happiness from providing informal care. This was computed by taking the difference between the current level of happiness of the caregiver (measured by the CarerQol-VAS) and the caregiver's hypothetical level of happiness (measured by a similar VAS) if all informal care activities were to be passed on to another, self-selected person [122]. In addition to the CarerQol, the subjective burden of caregiving was assessed with the self-rated burden scale [135]. The self-rated burden scale uses a Visual Analogue Scale (VAS) which ranges from 0 (not at all straining) to 10 (much too straining). In addition, we assessed the volume and type of informal care the caregiver provided.

To investigate whether disease severity impacted on the degree to which caregiver well-being was affected, we measured the patients' health-related quality of life using the Euroqol-5D (EQ-5D) and their use of wheelchair and mechanical ventilation. The EQ-5D is a widely used and validated instrument, which consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each with three levels (no limitations, some limitations, and severe limitations) [106]. The instrument describes 245 distinct health states and a utility value can be attached to each health state. Utilities reflect health-related quality of life on a scale from 0 (dead) to 1 (perfect health). Some health states correspond to negative utilities, implying a health state worse than dead. In this study, the Dutch tariff was used to compute utility values [90]. For children, a proxy version of the EQ-5D was completed. The EQ-5D was only completed by the patients and not by informal caregivers.

Statistical analyses

Several statistical tests were performed to identify factors associated with caregivers' experiences. Firstly, statistical differences between caregivers for adult patients and caregivers for patients below the age of 18 were tested using Mann–Whitney tests. Secondly, Spearman correlations were computed to test the relationships between measures of caregivers' burden and patients' quality of life. Thirdly, the relationship between caregivers' burden and disease severity was assessed using Mann–Whitney tests. Disease severity was based on the use of a wheelchair and respiratory support. Linear regression analyses were performed to examine the combined effect of disease severity and patient characteristics on caregiver's burden (as measured with the self-rated burden scale) and caregiver well-being (as measured with CarerQol-VAS).

For all statistical tests, a level of significance of 5% was used, unless otherwise stated. Statistical analyses were performed using Stata 11 (Statacorp, 2009).

Results

Response

Of the entire Dutch Pompe population of 120 patients, 88 (73%) were recipients of informal care. For these care-receiving patients, 67 informal caregivers (response rate 76%) completed the questionnaire in the period between July 2009 and December 2011. The response rate for caregivers of adult patients (73%) was slightly lower than for caregivers of patients below the age of 18 (86%). Table 5.1 provides patient and caregiver characteristics of the study population. In the study population (n = 67), 27% of the patients were under the age of 18. For adult patients, caregivers were most often the partners of the patients (92%). Parents made up the majority of caregivers providing informal care to patients under the age of 18 (94%). A grandparent completed the questionnaire for one pediatric patient. Table 5.2 shows that, on average, informal caregivers provided 17.7 hours per week of informal care. This number varied substantially between informal caregivers (SD 27.5). Adult patients received fewer hours of care (12.8 hours/week) than patients below the age of 18 (31.0 hours/week), but the difference was not significant ($p = 0.952$; which may be related to the modest size of the group of young patients). On the whole, most of the informal care time was spent on household activities and personal care. Adult patients mainly received support in performing household activities (48% of time) and less in the area of personal care (18%). In contrast, pediatric patients demanded more informal care in the area of personal care (32% of time) and social activities (36%), while less time was spent on household activities (11%). Virtually no time was spent on nursing activities (see Table 5.2 for the descriptions of the several types of care). Informal care in general was provided at the expense of the informal caregiver's leisure time or work time.

Figure 5.1 shows the distribution of responses on the 7 domains of the CarerQol-7D. Almost all (97%) informal caregivers obtained at least some "fulfillment" from providing care; almost 60% derived a "lot of fulfillment." The majority of caregivers did not experience financial or relational problems due to caregiving. Half of the informal caregivers reported mental health problems and problems with daily activities due to providing informal care. Physical health problems occurred in 40% of informal caregivers. Most of the caregivers indicated that they received support from others in performing their caregiving tasks.

Table 5.3 shows that informal caregivers of patients with Pompe disease experienced a burden of 3.2, as measured by the self-rated burden scale. The reported burden varied widely, from 0.0 to 8.9. The burden of caregiving for patients below the age of 18 was higher than the burden of caregiving for adults (4.1 versus 2.9 respectively). However, this difference was only statistically significant at the 10% confidence level ($p = 0.075$).

Table 5.1 Patient and caregiver characteristics

	n (% of sample)	Mean (range)
Number of patients	67 (100)	
Patient < 18 years	18 (27)	
Gender patient (female)	33 (49)	
Disease duration in years		10.8 (0.0 to 31.7)
Quality of life patient (EQ-5D utility) ***		0.70 (-0.13 to 1.00)
Patients using a wheelchair *	21 (32)	
Patients using respiratory support *	17 (26)	
Gender caregiver (female) **	39 (60)	
Relation caregiver to patient *		
- Partner	45 (68)	
- Parent	19 (29)	
- Other	2 (3)	

* Not available for one patient/caregiver; ** Not available for two caregivers; *** Not available for three patients

Table 5.2 Hours of informal care provided by type of care for Pompe patients

Total hours per week of informal care provided by respondent *	17.7
Type of informal care task (percentage of total hours)	
- Personal care (e.g. dressing, bathing, eating, using the toilet etc.)	27%
- Household activities (e.g. cleaning, cooking, doing groceries etc.)	33%
- Nursing (e.g. help with injections, wound care, changing catheters etc.)	1%
- Mobility outdoor (e.g. support during walking, visit to doctors etc.)	19%
- Logistic activities (e.g. help with contact doctors, financial affairs, insurances, etc.)	5%
- Social activities (e.g. talking, company etc.)	15%
Alternative spending of time (hypothetical)	
- Work	34%
- Household	23%
- Leisure	43%

* Three caregivers indicated that they provided 168 hours of informal care per week, which was not considered to be realistic. For these responses, a maximum volume of care provision was set as done in previous studies [136]. Here, we used a maximum of 126 hours per week (18 hours per day)

The well-being of the caregiver, as measured by the CarerQol-VAS, was estimated at 7.2 (range 2.0 to 10.0), where 0 represents "completely unhappy" and 10 represents "completely happy." In comparison, the Dutch level of happiness has been estimated at 7.6 [137]. Burden was significantly correlated with the hours of informal care provided (rho = 0.511; $p < 0.001$), and negatively correlated with the well-being of the caregiver (rho = −0.617; $p < 0.001$). There was no significant correlation between the well-being of the caregiver and the volume of care provided ($p = 0.154$).

Figure 5.1 Responses on the domains of the CarerQol

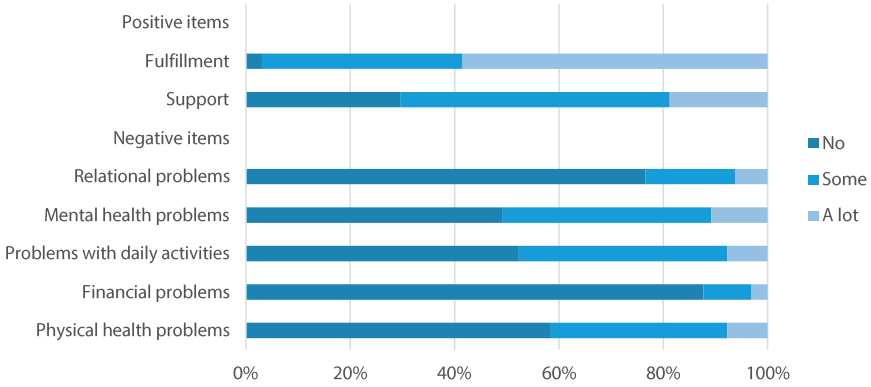


Table 5.3 Burden of caregiving

	Overall		Adult	Child	
	Mean	SD	Mean	Mean	p-value
Burden of caregiving (0 = not straining at all; 10 = much too straining)	3.2	2.6	2.9	4.1	0.07
Well-being caregiver (0 = completely unhappy; 10 = completely happy)	7.2	1.8	7.5	6.5	0.13
Happiness derived from providing care	1.7	3.5	2.3	0.1	0.03

On average, caregivers' well-being would decrease if their caregiving tasks were to be taken over completely by another person. However, there were large variations between caregivers; 27% of caregivers expected their personal well-being to increase if their care tasks were to be taken over by someone else. This group of caregivers reported a higher volume of care provided and a higher burden than caregivers who derive happiness from providing care. A further 25% of informal caregivers reported the same well-being with and without care tasks. Caregivers for patients below the age of 18 derived no well-being from providing informal care (happiness derived from providing care of 0.1), whereas caregivers for adult patients did (happiness derived from providing care of 2.3). The difference between caregivers for patients below the age of 18 and caregivers for adult patients was statistically significant ($p = 0.03$).

Differences in findings with respect to disease severity

The volume of care provided burden was significantly correlated to the patient's health-related quality of life (rho = −0.465; $p < 0.001$), as was the caregiver's burden (rho = −0.430; $p < 0.001$). Both increased significantly as the patient's quality of life worsened. Patients with the lowest quality of life (lowest quartile) received 35.1 hours of care per week; the burden for caregivers of these patients was 5.3. Patients with the highest qual-

Table 5.4 Informal caregiving with respect to patient's disease severity

	Wheelchair use			Respiratory support		
	Yes	No	p-value	Yes	No	p-value
Total hours per week	25.6	14.0	<0.001	19.2	17.2	0.041
Burden of caregiving	5.1	2.4	<0.001	4.1	3.0	0.101
Well-being caregiver	6.4	7.5	0.024	6.9	7.3	0.491
Happiness derived from providing care	1.3	1.7	0.518	2.0	1.4	0.909

ity of life (highest quartile) received 3.9 hours per week, while the burden for caregivers of these patients was 2.3. The caregiver's well-being was positively correlated to the patient's health (rho = 0.299; $p = 0.019$). The happiness derived from providing care was not significantly related to the patient's quality of life ($p = 0.281$).

Patients using a wheelchair received significantly more hours of informal care compared to patients who were not dependent on a wheelchair (Table 5.4). The caregiver burden was significantly higher for patients who needed a wheelchair. Well-being of caregivers was significantly higher for patients who did not use a wheelchair. Patients requiring respiratory support also received a significantly large volume of care, but burden for and well-being of their caregivers did not differ significantly from those not receiving respiratory support. The happiness derived from providing care did not differ significantly by patient's disease severity.

Multivariate regression analyses showed that caregiver burden was explained by the patient's quality of life ($p = 0.012$) and whether the patient needed a wheelchair ($p = 0.020$). Respiratory support did not influence burden in this regression model ($p = 0.285$), neither did gender of the caregiver ($p = 0.106$) nor whether the patient was a child or adult ($p = 0.229$). Regression analyses with caregiver well-being as dependent variable showed no significant results (quality of life $p = 0.143$; wheelchair $p = 0.282$; respiratory support $p = 0.534$; caregiver's gender $p = 0.425$). Whether the patient was a child or adult was only significant at the 10% level ($p = 0.067$).

Discussion

This study shows that the informal care related to Pompe disease importantly impacts the caregivers. Over 40% of caregivers experienced mental health problems and physical problems, indicating that providing informal care has substantial impact on the health of caregivers. The amount of time spent on informal care is substantial. The caregiver burden, on average, was relatively mild. For instance, caregiver's happiness was esti-

mated at 7.2, slightly below the average Dutch level of happiness [137]. Such averages can mask important differences between subgroups (e.g. adult patients versus pediatric patients). For instance, the burden of the caregivers of patients with Pompe disease was 3.2, but caregivers of child patients experienced a much heavier burden (4.1) than those of adult patients (2.9). A large majority of informal caregivers obtained fulfillment from their caregiving tasks. On average, well-being of informal caregivers would decrease if their caregiving tasks were to be fully taken over by another person. However, nearly one third of caregivers did not derive happiness from providing care, implying that these caregivers would prefer to have their care tasks taken over by another person.

Disease severity and caregiver burden

Both the volume of care provided and the caregiver burden increased significantly with decreases in quality of life of the Pompe patient. Moreover, the volume of care and caregiver burden were positively correlated. Caregivers' well-being was positively associated with patients' quality of life. This may be explained by both the family effect (i.e. effects of caring about someone who is ill) and the caregiving effect (i.e. effects of caring for an ill person) [127].

The volume of care provided and caregiver burden were higher and the well-being lower for caregivers of patients using a wheelchair as compared to patients who were independent of supportive devices. In contrast, no significant differences were found in terms of volume of care provided, caregiver burden and caregiver well-being between caregivers of patients using respiratory devices and those caring for patients who did not use a ventilator. The insignificance may be due to a lack of statistical power, or to the fact that the intensity of respiratory support is highly variable between patients; some patients only use respiratory support at night while others require it continuously. The difference in outcomes between patients using a wheelchair and respiratory devices is noteworthy and might be explained by the difference in intensity of care required by these patients. In particular, care for patients using a wheelchair may be physically more burdensome to caregivers (for instance due to activities such as lifting and carrying patients) than care for patients requiring respiratory devices.

This study showed that caregivers for adult patients derive more well-being from providing care to the patient than caregivers of pediatric patients do. While this study cannot conclusively ascertain answers to why this was observed, some possible reasons can be provided. First, younger patients may have more severe symptoms, making the provision of informal care more burdensome. Second, caregivers of adult patients may self-select. Those caregivers who consider taking care of patients to be unfulfilling or too straining may opt out. This may be less feasible for parent caregivers of children.

Caregiver burden over time

Multiple observations were available for a proportion of the total study population (n = 49; median follow-up 1.5; range 0.25–2.1 years). Over time, no significant changes were observed in terms of volume of care provided, caregiver burden, the domains of the CarerQol or in caregiver well-being. This might be explained by the chronic nature of the disease and the long disease duration at baseline. Regarding the caregiver burden, caregivers may also accept and adapt to the caregiving situation, which can be considered a coping effect. If coping plays a role, all other things being equal, caregivers of patients who became care dependent more recently might experience a stronger burden than those who have cared for a longer period. In that context, it should be noted that most caregivers had been providing care for a long time at the time of the study and coping may have affected their responses. In addition, the time span used here between the two measurements may have been too short to study changes in caregiving situations in the context of Pompe disease, as the disease is slowly progressive. Here again, the inherent problem of small sample size should also be taken into account.

Comparison to other studies

The burden of caregiving and the scores on the seven dimensions of the CarerQol for caregivers of Pompe disease patients shows similarities with burden of caregivers of adult patients with Duchenne muscular dystrophy - a genetic neuromuscular disease [138]. However, the volume of care provided of Duchenne caregivers (10.6 hours/week) was lower than for caregivers of Pompe disease patients (17.7 hours/week). The difference is partly explained by the absence of children in the Duchenne study. Adult Pompe patients received a more comparable 12.8 hours per week of informal care. The caregiver burden for patients with Pompe disease (3.2) was significantly lower than for Duchenne patients (5.4; $p < 0.001$).

Caregivers of patients with Rheumatoid Arthritis (RA) experienced a lower burden (2.5) than caregivers of patients with Pompe disease (3.2), although RA caregivers on average provided more (i.e. 27) hours of informal care per week [124]. In contrast to informal caregivers of patients with Pompe disease, the mean level of happiness derived from providing care for RA caregivers was negative (–0.1).

Caregivers in our study provided 17.7 hours of informal care weekly; this figure was 12.8 hours for caregivers of adult patients. In an earlier study, adult patients with Pompe disease reported receiving 19 hours of informal care per week [102]. These patients mostly received this amount of care from more than one caregiver. In the present study, only one caregiver per patient was included, as the objective of this study was to examine the burden of the primary caregiver. This is likely to explain the difference between the estimated number of hours of informal care provided by the caregiver and that received by the patient.

Study limitations

First, studies in orphan diseases are inherently hampered by the small numbers of patients. In addition, Pompe disease is characterized by a heterogeneous disease course, which makes comparisons between relevant subgroups important. Given the small sample size, statistical differences for subgroups were therefore difficult to establish, even at a 10% confidence level. Nonetheless, it should be noted that, while on the one hand, the absolute number of observations in this study was small, on the other hand, the relative number, i.e. the response rate, was high.

Previous studies have shown that the characteristics of informal caregivers, such as the caregivers' own health and whether the caregiver has a paid job, can influence the volume of care caregivers provide, caregiver burden and well-being of caregivers [124, 133, 135]. A second limitation was that only a limited number of characteristics of informal caregivers were available in this study.

Third, in this study, the EQ-5D was used to derive patient's health-related quality of life. However, for very young patients, the instrument might not be fully appropriate. Hence, as a sensitivity analysis, utilities for patients under the age of 6 were excluded from the analyses to identify the relationship between informal caregiving and patients' health-related quality of life. This, however, did not change the results.

Fourth, studies in informal caregivers typically face a selection bias, with an overrepresentation of less burdened caregivers, who commonly have a higher response rate. Although the response rate in this study was high, selection bias cannot be ruled out.

Fifth, generic questionnaires were used, so descriptions were not Pompe disease specific. This may have contributed to the small percentage of time spent on nursing activities - despite the fact that some Pompe patients need tracheal suctioning. In future research, disease specific descriptions might be useful.

Implications

This study showed that informal caregivers of patients with Pompe disease provide substantial amounts of informal care. Overall, the impacts in terms of caregiver burden and well-being tended to be modest. This may partly be explained by the positive aspects related to informal care, in view of the finding that, on average, well-being would decrease if all their care tasks were to be handed over to someone else; caregivers appreciate taking care of their loved ones. Still, the modest overall impact appears to mask important differences between subgroups. Caregiver burden was experienced in particular by caregivers providing informal care to more severely affected patients. In providing

support to caregivers, it is therefore this group that requires attention, to avoid these caregivers becoming overburdened and dropping out. Providing assistance to caregivers when required may help to limit the negative effects on the health and well-being of caregivers due to caregiving, and may result in a longer provision of informal care.

Future research

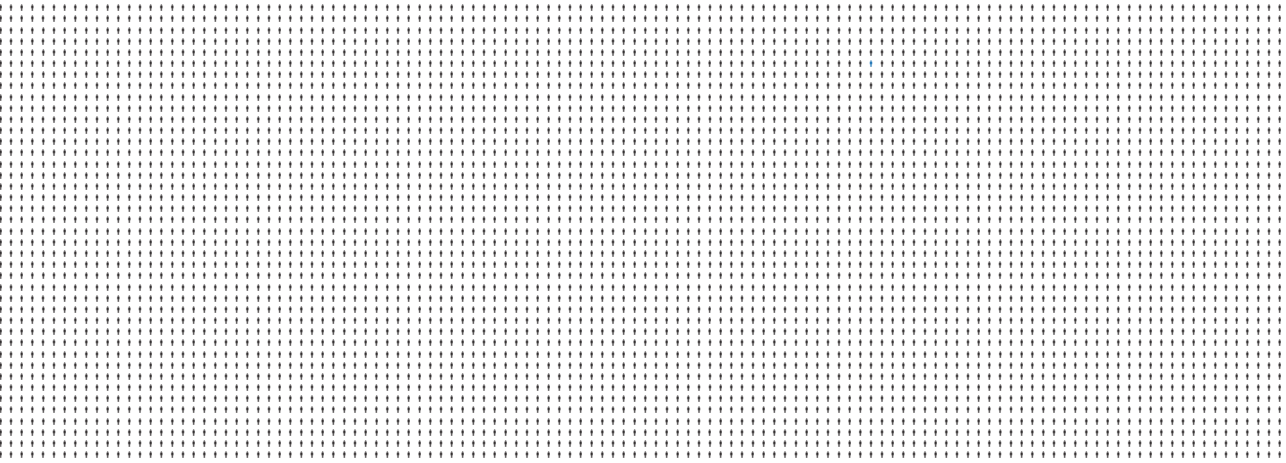
Important areas for future research can be indicated. First, more knowledge on the impact of informal care in subgroups is required. This may be best investigated in larger studies, potentially in international collaborations. Then, cultural differences in relation to informal care need to be accounted for. Longitudinal studies of informal care in this context, with a long follow-up, can shed more light on the developments in volume of care provided and burden as well as in well-being over time. Such studies may also help to disentangle the different effects on well-being (family and caregiving effect). Studying the effects of formal care (and other types of support) on informal caregivers is also important. In this respect, it will be interesting to study whether enzyme replacement therapy also has an effect on the volume of care and burden of caregiving. Comparisons between treatment groups could not be made in the current study due to data limitations (only eight patients did not receive enzyme replacement therapy at baseline; for only four of them follow-up data were available).

Conclusions

In conclusion, this study shows that providing informal care to patients with Pompe disease causes burden to the informal caregiver. Problems with daily activities due to informal care provision are present in 50% of informal caregivers and 40% of caregivers experience psychical and/or mental problems. Despite the negative aspects of informal care, it is important to stress that the majority of caregivers obtain fulfillment from providing care and that, on average, caregivers derive utility from providing informal care to patients with Pompe disease. Still, beneath this average surface, important differences exist.

Acknowledgements

The authors would like to thank Renske Hoefman for her comments on draft versions of the paper.



CHAPTER 6

A conceptual disease model for adult Pompe disease

Kanters TA, Redekop WK, Rutten-van Mölken MPMH, Kruijshaar ME, Güngör D, Van der Ploeg AT, Hakkaart L

Orphanet J Rare Dis (2015) 10:112

Abstract

Background: Studies in orphan diseases are, by nature, confronted with small patient populations, meaning that randomized controlled trials will have limited statistical power. In order to estimate the effectiveness of treatments in orphan diseases and extrapolate effects into the future, alternative models might be needed. The purpose of this study is to develop a conceptual disease model for Pompe disease in adults (an orphan disease). This conceptual model describes the associations between the most important levels of health concepts for Pompe disease in adults, from biological parameters via physiological parameters, symptoms and functional indicators to health perceptions and final health outcomes as measured in terms of health-related quality of life.

Methods: The structure of the Wilson-Cleary health outcomes model was used as a blueprint, and filled with clinically relevant aspects for Pompe disease based on literature and expert opinion. Multiple observations per patient from a Dutch cohort study in untreated patients were used to quantify the relationships between the different levels of health concepts in the model by means of regression analyses.

Results: Enzyme activity, muscle strength, respiratory function, fatigue, level of handicap, general health perceptions, mental and physical component scales and utility described the different levels of health concepts in the Wilson-Cleary model for Pompe disease. Regression analyses showed that functional status was affected by fatigue, muscle strength and respiratory function. Health perceptions were affected by handicap. In turn, self-reported quality of life was affected by health perceptions.

Conclusions: We conceptualized a disease model that incorporated the mechanisms believed to be responsible for impaired quality of life in Pompe disease. The model provides a comprehensive overview of various aspects of Pompe disease in adults, which can be useful for both clinicians and policymakers to support their multi-faceted decision making.

Background

Research in rare diseases is complicated by several methodological difficulties, which especially arise from insufficient statistical power due to low patient numbers [10]. Despite these methodological difficulties, policy makers require information on the burden of the disease and the therapeutic value of orphan therapies to support their decisions on reimbursement [139]. This information is especially important because orphan therapies are often associated with considerable costs per patient, accumulating to up to €600,000 per patient per year for some orphan drugs [18].

In the absence of long-term follow-up data on sufficiently large numbers of patients – as is the case for many orphan diseases – conceptual models can be used to describe the disease and assess treatment benefits. Such models allow the extrapolation of outcomes based on relatively short-term follow-up data of a limited number of patients, by combining available data with known disease-specific correlations.

The conceptual model developed by Wilson and Cleary (1995) provides a conceptual framework. It describes the relationship between different aspects of the disease (from biological parameters to functioning), health perceptions and overall quality of life [140]. The Wilson-Cleary model consists of five distinct levels of health concepts: 1) biological and physiological factors, focusing on the function of cells, organs, and organ systems; 2) symptom status, the patient's perception of an abnormal physical, emotional or cognitive state, including, for instance, fatigue, worry and depression; 3) functional health, the ability of the individual to perform particular defined tasks; 4) general health perceptions, a patient's subjective rating of an integrated concept of all health aspects; and 5) overall quality of life, the individual's state of overall well-being. The model combines clinical and social science models by categorizing health outcomes into underlying health concepts and by identifying causal relationships between the different concepts. As such, the model describes a causal pathway from clinical outcome parameters to quality of life. The model can be used to estimate quality of life on the basis of patients' clinical data.

Pompe disease is an inherited, metabolic orphan disease. It is caused by a deficiency of the enzyme alpha-glucosidase needed for the degradation of lysosomal glycogen, and leads to storage of glycogen in many tissues [28]. Pompe disease has a broad clinical spectrum. The severe, classic infantile form is accompanied by muscle and heart malfunctioning, leading to death within the first year of life [26, 33, 44]. The majority of Pompe patients (~80%) present at adult ages with muscle weakness. Limb girdle and respiratory muscles are predominantly affected [26, 141, 142]. Eventually, most patients

require ambulatory and respiratory support and life expectancy is decreased compared to the general population [38].

Enzyme replacement therapy (ERT) with alglucosidase alfa has proven to be effective in Pompe disease [46, 49, 77, 131]. Treatment of adult patients with Pompe disease with ERT is lifelong and associated with annual costs of up to €382,000 per patient [18]. Such high treatment costs potentially translate in a high incremental cost-effectiveness ratio.

To support reimbursement decisions, information on the burden of disease in untreated patients is needed, as well as on the effect of treatment and its cost-effectiveness. Ultimately, a model to estimate the cost-effectiveness of a treatment requires information on survival and quality of life in both treated and untreated patients as well as on the costs of treatment.

The purpose of this study is to develop a conceptual model for Pompe disease in adults and statistically test it in untreated patients. The structure of the conceptual model was established by applying the concept of the Wilson-Cleary model to Pompe disease, describing the associations between biological and physiological variables, symptoms, functional status, general health perceptions and health-related quality of life for this disease. The model can be used to predict health outcomes and can also be the starting point of a cost-effectiveness model, if information about disease progression, treatment effects and costs are added to it.

Methods

Part 1: Application of the Wilson-Cleary model to Pompe disease

Modelling guidelines prescribe extensive consultations with clinical experts in the development of a model [143]. Therefore, variables were included in the draft conceptual model for Pompe disease based on clinical relevance, as derived from clinical expert opinion and review of the literature. The model was discussed with experts from the Dutch Center of expertise for Pompe disease repeatedly until consensus was reached on the draft model. Next, the selected variables were assigned to the different levels of health concepts of the Wilson-Cleary model.

Part 2: Statistically testing of the relationships of the model

To come to a final conceptual model, the relationships between the different levels of health concepts of the draft conceptual model were quantified in the second part of the study. In line with modelling guidelines, which recommend that a conceptual model

should not be driven by data availability [143], clinical plausibility rather than statistical significance of an association determined whether variables were included in the final model.

Study sample and data collection

The study population consisted of patients with a proven diagnosis of Pompe disease by enzyme analysis and/or mutation analysis. Data were collected between January 2005 and January 2011. During this period, 103 adult Pompe patients were followed at Erasmus Medical Center in Rotterdam, the Dutch national center of expertise for Pompe disease. Clinical data were collected during regular standardized follow-up examinations at the Erasmus Medical Center. Patient reported outcome data were obtained from the ongoing International Pompe Association (IPA) survey in which all Dutch patients participate [38] and a burden of illness study in Pompe disease in adults [102]. The dataset consisted of multiple observations per patient, obtained at irregular time intervals and with a variable number of observations per patient. Only data on adult patients who were untreated at the time of observation were included in the analyses. No other inclusion criteria were applied; meaning that all adult patients diagnosed with Pompe disease were eligible for inclusion in the study, from mild to severely affected patients. Only patients for which data were available on at least two adjacent levels of health concepts were included in the regression analyses. All patients provided informed consent and the studies were approved by the Medical Ethics Committee of Erasmus MC.

Statistical analyses

We explored the strength of the relationships depicted in the conceptual model by means of random effects linear regression analyses. The regressions estimate relationships for a cross sectional unit during a particular time. Explanatory variables and dependent variables are dated at the same point in time (e.g. functioning at $t = 1$ is used to model general health perceptions at $t = 1$) [144]. The regression analyses account for interdependence of multiple observations per patient. The analyses represent cross-sectional analyses on multiple observations per patient. A separate regression analysis was run for each relationship between levels of health concepts in the conceptual model. In total eight different sets of analyses were performed, shown as models I to VIII in the results section. The different levels of health concepts of the conceptual model were first used as dependent variables in the regression analyses and subsequently as explanatory variables in the model for the next level. Levels of health concepts in the model (i.e. biological and physiological variables, symptom status, functional status, health perceptions and quality of life) could entail multiple variables. For each regression model, the combined significance of all variables was tested by means of a Wald Chi square test. The number of patients and observations per patient varied in the different

regression analyses. The significance level was set at $p = 0.05$. The percentage of variance explained by the model was assessed by the overall R2 of the regression models. Statistical analyses were performed using Stata version 13 (StataCorp, 2013).

Results

Part 1: Development of a conceptual model for Pompe disease based on the Wilson-Cleary model

Biological and physiological variables

The first level of health concepts of the Wilson-Cleary model essentially describes two aspects: biological factors and physiological factors. In the conceptual model for Pompe disease, these were disentangled to allow modeling of the relationship between the biological cause of Pompe disease and physiological variables. Reduced activity of the enzyme acid alpha alglucosidase is the biological cause of Pompe disease [28]. We therefore included enzyme activity (measured in fibroblasts as a percentage of enzyme activity of non-Pompe patients) in the model as a biological variable.

With respect to physiological aspects, experts proposed the use of skeletal muscle strength and respiratory function [26, 35, 46, 98, 145]. Skeletal muscle strength was assessed by manual muscle testing using the grading scale from 0 (no visible contraction) to 5 (normal strength) of the Medical Research Council (MRC). For selected muscle groups, the MRC scores were summed, and subsequently the MRC sum score was expressed as a percentage of the maximum possible score (as described in [47]). Respiratory function was measured using forced vital capacity (FVC) in sitting position. Results were expressed as a percentage of the predicted normal value derived from published data [114].

Symptom status

The second level of health concepts in the Wilson-Cleary model covers symptoms. Adult Pompe patients have been shown to experience fatigue [146, 147]. Shortness of breath is another symptom frequently experienced by Pompe patients [148]. Therefore, fatigue and shortness of breath were proposed to reflect symptom status in the draft conceptual model. Fatigue was assessed using the Fatigue Severity Scale (FSS), which examines the self-reported effects of fatigue on daily functioning [149]. The scale ranges from 1 (no fatigue) to 7 (extremely fatigued), with a score of 4 or higher indicating that a patient is fatigued. Shortness of breath was not assessed in this patient population. Since no data were available on shortness of breath, a direct relationship between physiological variables (MRC sum score and FVC) and functional status was included in the model explaining functional status, in addition to FSS.

Functional status

The third level of health concepts in the Wilson-Cleary model is functional status. The self-reported nine item Rotterdam Handicap Scale (RHS) was considered to be a suitable measure of functional status. The RHS measures participation in daily life of patients and comprises 9 items that can be scored from 1 (unable to fulfill the task or activity) to 4 (complete fulfillment of the task or activity) [150]. The RHS score ranges from 9 to 36, with lower levels of handicap being associated with higher RHS scores. Hagemans et al. (2007) applied the RHS in Pompe disease and showed that daily life was substantially affected by the disease, especially with respect to job/study performance and ability to fulfill domestic tasks [39].

General health perceptions

The fourth level of health concepts of the Wilson-Cleary model includes general health perceptions, characterized by Wilson-Cleary as 1) an integration of the health concepts discussed above plus others (such as mental health) and 2) being a subjective rating. Two patients can objectively have the same health state but may have a very different perception of their health, potentially because of differences in factors like coping or self-efficacy. Health perceptions can be measured using the EQ-5D Visual Analogue Scale (EQ-5D VAS) [151]. Patients indicate their perceived health status on a thermometer ranging from 0 (worst perceived health status) to 100 (best perceived health status).

Quality of life

The final level of health concepts of the Wilson-Cleary model is quality of life (QoL). Previous studies have shown that QoL is lower in patients with Pompe disease compared to the general Dutch population [37, 102, 145]. QoL can be measured using the Mental Component Scale (MCS) and Physical Component Scale (PCS) of the Short-Form 36 (SF-36) [152] as well as in utilities derived from the EQ-5D. Utilities range from 0 (representing death) to 1 (representing perfect health). The SF-36 is a validated instrument to describe a patient's health status [153]. MCS and PCS can be constructed from the eight distinct domains of health derived from the SF-36. U.S. norm based scores were used to compute PCS and MCS [152]. Two studies showed that PCS was significantly lower in patients with Pompe disease compared to the general population, but found that MCS was not affected by the disease [37, 145]. The SF-36 reflects a patient's self-reported health status, whereas a utility provides a valuation of health based on the perceived importance of different domains by the general public. In our study, utilities were derived from the widely used EQ-5D [151], a validated tool to measure quality of life. The Dutch tariff was used to calculate utilities [90].

Characteristics of the individual and the environment

We hypothesized that age, gender and disease duration (time since diagnosis) could be used as individual patient characteristics potentially affecting all levels of health concepts in the conceptual Pompe disease model, except for the biological level [34, 98, 100, 101, 145, 154].

Part 2: Quantification of the relationships in the draft conceptual model

Study population

For 79 patients (77% of the total Dutch adult Pompe population) who did not receive ERT data were available on at least two adjacent levels of health concepts. Half of the population was female, average age at baseline was 49.6 years and baseline disease duration since diagnosis was 8.0 years (Table 6.1). The maximum follow-up period was 5.4 years while the median follow-up was 1.1 years. The maximum number of observations per patient was 12. The median number of observations per patient was two and ten patients had only a single observation.

Quantitative evaluation of the draft conceptual model

Table 6.2 presents the results of the multivariate regression models. Models I (MRC sum score as the dependent variable) and II (FVC) describe physiological variables, model III (FSS) represents symptom status, model IV (RHS) represents functional status, model V represents health perceptions (EQ-5D VAS), and models VI, VII and VIII (MCS, PCS and Utility respectively) describe quality of life.

Table 6.1 Patient characteristics at baseline

Number of patients	n	Mean	Min	Max
Age (years)	79	49.3	23.0	72.6
Gender (female)	79	50.6%		
Duration since diagnosis (years)	79	8.0	0.0	27.5
Enzyme activity (% of normal)	79	12.4	0.5	19.9
Muscle strength (% predicted)	64	82.1	48.3	100.0
Respiratory function (% predicted)	63	76.1	11.3	123.4
Fatigue Severity Scale	61	5.6	2	7
Rotterdam Handicap Scale	64	27.4	13.5	36.0
Visual Analogue Scale	49	65.0	30.0	95.0
Mental Component Scale	60	53.8	24.2	74.0
Physical Component Scale	60	35.4	17.6	53.3
EQ-5D Utility	50	0.736	0.201	1.000

Table 6.2 Regression coefficients based on a random effects model

Level	Physiological variables		Symptom status	Functional status	Health perceptions	Health related quality of life		
Model	**I MRC**	**II FVC**	**III FSS**	**IV RHS**	**V EQ-5D VAS**	**VI MCS**	**VII PCS**	**VIII Utility**
Constant	**83.452**	**70.526**	**8.737**	**16.989**	-9.313	**49.990**	**24.526**	**0.530**
Age	-0.069	-0.144	0.011	**-0.096**	0.126	-0.016	-0.046	0.001
Female	-0.028	**17.994**	0.307	-0.957	4.673	-1.282	-0.402	0.010
Disease duration	**-0.563**	-0.346	**-0.077**	-0.052	**0.653**	0.063	-0.086	-0.001
Enzyme activity	0.370	-0.431	0.007	-0.048	0.004	-0.359	-0.069	-0.006
Muscle strength			-0.031	**0.189**				
Respiratory function			-0.011	**0.075**				
Fatigue Severity Scale				**-0.578**				
Rotterdam Handicap Scale					**2.030**			
Visual Analogue Scale						**0.157**	**0.223**	**0.004**
patients	78	72	61	61	73	73	73	71
observations	249	257	160	158	154	152	152	161
R^2 (overall)	0.105	0.075	0.322	0.623	0.343	0.183	0.293	0.354
Wald test (p-value)	**<0.001**	**0.001**	**0.002**	**<0.001**	**<0.001**	**0.005**	**<0.001**	**<0.001**

Note: Figures in bold indicate significance at 5% level; Enzyme activity, muscle strength and respiratory function were measured as a percentage of normal values, Visual Analogue Scale, Mental Component Scale and Physical Component Scale were measured on a scale from 0-100, Fatigue Severity Scale was measured on a scale from 1-7, Rotterdam Handicap Scale was measured on a scale from 0-36, Utility was measured on a scale from 0-1

Models predicting the physiological level of health concepts (models I and II)
The MRC sum score was negatively associated with disease duration ($p < 0.001$). One additional year with the disease was associated with a 0.6 % point reduction in the MRC sum score. FVC was not associated with disease duration ($p = 0.190$). The MRC sum score and FVC were not related to age ($p = 0.411$ and $p = 0.459$, respectively). However, if disease duration was not included in the model, age was significantly related to MRC sum score (0.240 percentage points decrease per year; $p = 0.005$), but age was not significantly related to FVC ($p = 0.135$). Female patients had a higher FVC (by 18.0 percentage points) than males ($p = 0.001$) but there was no difference between males and females in MRC sum scores ($p = 0.990$). Only baseline observations were available for enzyme activity and were assumed constant for later observations. Baseline enzyme activity was not significantly related to muscle strength ($p = 0.215$) or respiratory function ($p = 0.556$).

Model predicting the symptom status level of health concepts (model III)
FSS was negatively associated with disease duration ($p < 0.001$). One additional year with the disease was associated with a 0.08 point decrease of FSS. FSS was not associated with age ($p = 0.389$), gender ($p = 0.382$), enzyme activity ($p = 0.893$), or FVC. FSS was associated with the MRC sum score only at a 10% significance level ($p = 0.070$).

No data on shortness of breath were available for this population.

Model predicting the functional status level of health concepts (model IV)
RHS was significantly affected by FSS ($p < 0.003$). Every 1 point increase in FSS was associated with a decrease of 0.5 in handicap scores. Furthermore, RHS was significantly affected by MRC sum score and FVC (both $p < 0.001$). Every 1 % point increase in MRC sum score (FVC) was associated with an improvement of 0.2 (0.1) in handicap scores. Age also had a significant association with handicap scores in that older patients had poorer scores than younger patients (0.1 points per year increase in age; $p < 0.004$). Gender, disease duration and enzyme activity were not significantly associated with RHS scores.

Model predicting the general health perceptions level of health concepts (model V)
The EQ-5D VAS was significantly associated with Rotterdam Handicap Scale ($p < 0.001$). An increase of 1 point in RHS score translated in an increase in EQ-5D VAS of 2 points. Disease duration was also positively associated to EQ-5D VAS ($p = 0.002$). Age, gender and enzyme activity were not related to EQ-5D VAS.

Models predicting the health related quality of life level of health concepts (models VI, VII and VIII)

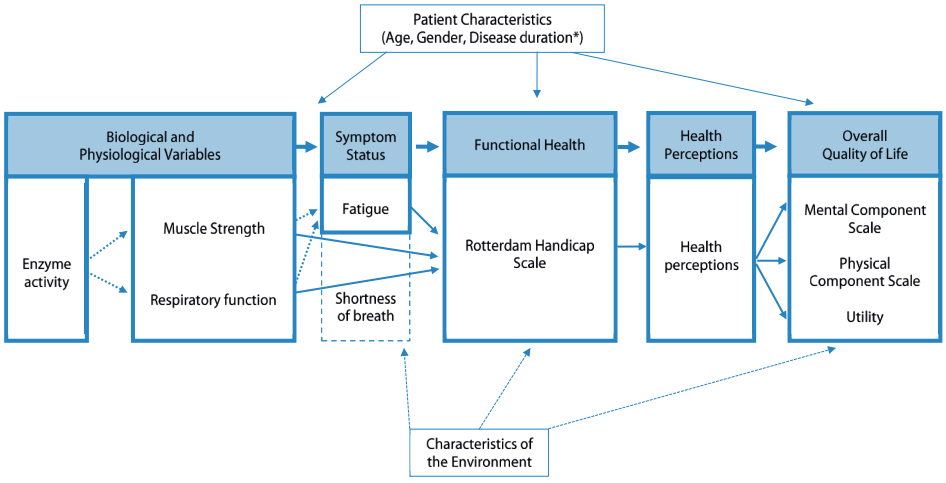
MCS was not significantly associated with age, disease duration, gender, enzyme activity. MCS was significantly associated with the EQ-5D VAS ($p < 0.001$); a 1 point increase on the EQ-5D VAS would lead to an increase in MCS of 0.2.

PCS was associated with EQ-5D VAS ($p < 0.001$); a 1 point increase in EQ-5D VAS would result in an increase of the PCS with 0.2 points. PCS was not affected by age, gender, disease duration and enzyme activity.

Utility was significantly and positively associated with EQ-5D VAS ($p < 0.001$). An increase with 1 point on EQ-5D VAS leads to an increase in utility of 0.004. Utility was not associated to age, gender, disease duration or enzyme activity.

Figure 6.1 presents the final conceptual model for Pompe disease. The conceptual model can be used to predict quality of life by inserting clinical data in the formulas found in the various models (as depicted in Supplemental Figure 6.1). In this respect, it should be noted that the estimated coefficients from the regression analyses (Table 6.2) are all surrounded with varying amounts of uncertainty, which is presented in Supplemental Figure 6.1.

Figure 6.1 Wilson-Cleary conceptual disease model applied to Pompe disease



* Disease duration since diagnosis

Discussion

It has often been stated that the common methodology for clinical and cost-effectiveness studies is unsuitable for orphan diseases, due to the limited number of patients [10, 66]. One recurring problem stemming from the low disease frequency is limited statistical power. A disease model can be used when long-term follow-up is unavailable. The concept of a disease model incorporates disease progression based on a combination of clinical plausibility and statistical analysis. Here we present a disease model for Pompe disease. Empirical data were used to test the relationships in this model. The model forms a starting point, to which information about treatment effects can be added in the future.

Purpose and validity of the model

We set out to describe the natural course of Pompe disease using an application of the Wilson-Cleary model. The appropriate structure of the model is disease dependent. For some disease progression models, classification of disease states is feasible (e.g. cancer, arthritis, multiple sclerosis, heart disease). Pompe disease is characterized by a continuous range of phenotypes, which makes identification of disease states difficult. Furthermore, accurately estimating parameter values for disease states is hampered by small sample sizes. Therefore, we applied the Wilson-Cleary conceptual model rather than a model containing health states. Content validity (i.e. the validity of the associations that were modelled) of this model is ensured by the clinical experts that were involved in the development of the model and evidence from the literature. By comparing the results of the final model to findings reported in the literature construct validity can be assessed. Such comparisons reveal that the conceptual model is largely supported by the data since many of the results correspond with findings from previous studies. Disease duration is negatively associated with MRC sum score, in line with earlier findings [34, 145, 154]. The rate of MRC sum score deterioration (0.6 % points per year) is comparable to our previous publications [47, 100]. No significant association between disease duration and FVC was found ($p = 0.190$), in contrast to findings described earlier [34, 98, 154]. However, the relatively small though nonsignificant p-value we found in our analysis may be an indication of limited statistical power, a reduced ability to detect an existing association. Female patients have higher FVC than male patients, which is similar to the findings of our earlier study [98]. Enzyme activity is not associated with the MRC sum score or FVC, which agrees with the findings of earlier studies that did not find any relationship between enzyme activity and severity in adult patients [26, 154]. Being the underlying biological explanation of the disease, enzyme activity is retained in the conceptual model, despite the absence of a statistical significant association with other variables in the conceptual model.

The genetic mutation is the underlying cause of reduced enzyme activity. However, in our population most of the patients have the same mutation. Hence, mutation is left out of the model.

FSS was not associated with MRC sum score or FVC, albeit that FSS was significantly related to MRC at the 10% level ($p = 0.070$). Our previous studies did not find a relationship between fatigue and muscle strength and pulmonary function for adult patients with Pompe disease. While more severely affected patients (i.e. those who are in a wheelchair and/or ventilator dependent) do report higher FSS scores, almost all patients report fatigue [146, 155]. For example, 71% of patients who did not use respiratory support and/or wheelchair reported a FSS score of more than 4 (reflecting fatigue), while 59% had an FSS score of more than 5 (reflecting severe fatigue). Also, even when patients are still in the pre-clinical stage of the disease they can report fatigue.

RHS is significantly affected by MRC sum score and FVC and better performance on these physiological variables are reflected by lower handicap scores. These findings resemble earlier results that showed that severely affected patients (that is, those requiring ambulatory and respiratory support) reported lower scores on RHS than other patients [39]. The significant relationships indicate that functional status is not fully explained by fatigue, but by other problems related to reduced skeletal muscle strength and pulmonary function as well. One of these problems could be shortness of breath, which was absent in the model due to lack of data.

The conceptual model we present here embodies the current state of knowledge on Pompe disease in adult patients. Data that become available in the future can be used to fine-tune the relationships in the model. Moreover, new insights in the measurement of respiratory function might lead to the replacement of FVC by maximal inspiratory pressure (MIP) or maximal expiratory pressure (MEP). Inclusion of shortness of breath in new versions of the model might be reconsidered if new insights or analyses become available in future. Similarly, a newer version of the model can include once such data are available.

Strengths and applicability of the model

The availability of a (large) cohort of Pompe patients with several outcome measures enabled statistical testing of the conceptual model. Moreover, the dataset is relatively large compared to other orphan diseases, with available data on 79 patients and multiple observations for most patients. Although the current statistical analyses were based on Dutch patients only, there are no indications that the disease processes differ between the Dutch population and patients in other countries. Therefore, the underly-

ing conceptual relationships described in the model will also be valid in other settings. The results described in this paper are also transferable for use in other countries since the measurement techniques (e.g. to describe muscle function) are widely used and not country-specific.

For many other orphan diseases, the number of patients is too small for a single institution or even a single country to assess a drug's effectiveness. Data from international disease registries can potentially be used to explore relationships between clinically relevant levels of health concepts of an orphan disease. The testing of longitudinal relationships requires systematic follow-up, which might not yet be available in orphan disease registries.

The use of random effects models appears particularly beneficial in orphan diseases since it can compensate for the low number of patients to a certain extent. For this purpose, the availability of multiple observations per patient is indispensable.

Treatment

The assessment of a treatment effect is outside the scope of the current study. The analyses were deliberately restricted to untreated patients because we aimed to develop a model that describes the conceptual intercorrelations between the various levels of health concepts for Pompe disease. However, the conceptual model could be seen as a starting point for developing a full cost-effectiveness model to evaluate the cost-effectiveness of enzyme replacement therapy, assuming that the causal pathway of the disease will not change. Enzyme replacement therapy supplements the low levels of enzyme and has been shown to influence various levels of health concepts in the model, i.e. muscle strength and respiratory function, fatigue, functional health and quality of life, presumably through the supplementation of enzyme [46, 47, 155-157]. If the model would in the future be used to estimate effects of ERT on health outcomes, this could be done in several ways. One way is to apply relative risk reductions to the outcomes as predicted by the equations in the model. These risk reductions would reflect the effect of ERT. Another approach is to re-estimate the equations with ERT as a predictor in the regression models. In both cases we would need longitudinal data on enzyme activity to estimate the impact of changes in enzyme activity on changes in health outcomes.

Limitations of the study

The number of observations and study period are relatively limited given the slow disease progression seen in Pompe disease. However, these limitations are common for studies of rare chronic diseases. This limitation could be rectified by international studies that collect relevant patient data in a standardized manner with a minimum loss to

follow-up. Another limitation of our study was lack of data on shortness of breath, which could therefore not be included in the model.

Transferability of the model

This is the first study in which the Wilson-Cleary model is applied to an orphan disease. Although our model is specifically developed to describe and quantify the relationships between specific levels of health concepts of Pompe disease in adult patients, the approach used in this study can also be applied to other Pompe patient populations, i.e. children and infantile patients, or for other orphan diseases. Obviously, it is necessary to adapt the model to ensure that it contains only relevant disease-specific information and knowledge, although parts of the model developed here for Pompe disease in adult patients may still be relevant. To model Mucopolysaccharidosis type II for instance, "physiological factors" might be expressed using joint angle range and mental retardation can be used as a measure for "functional health". As another example, Duchenne muscular dystrophy might be adequately represented using the current model if a factor for heart performance were to be included. However, in all cases, the application of the Wilson-Cleary model should be studied for each disease separately.

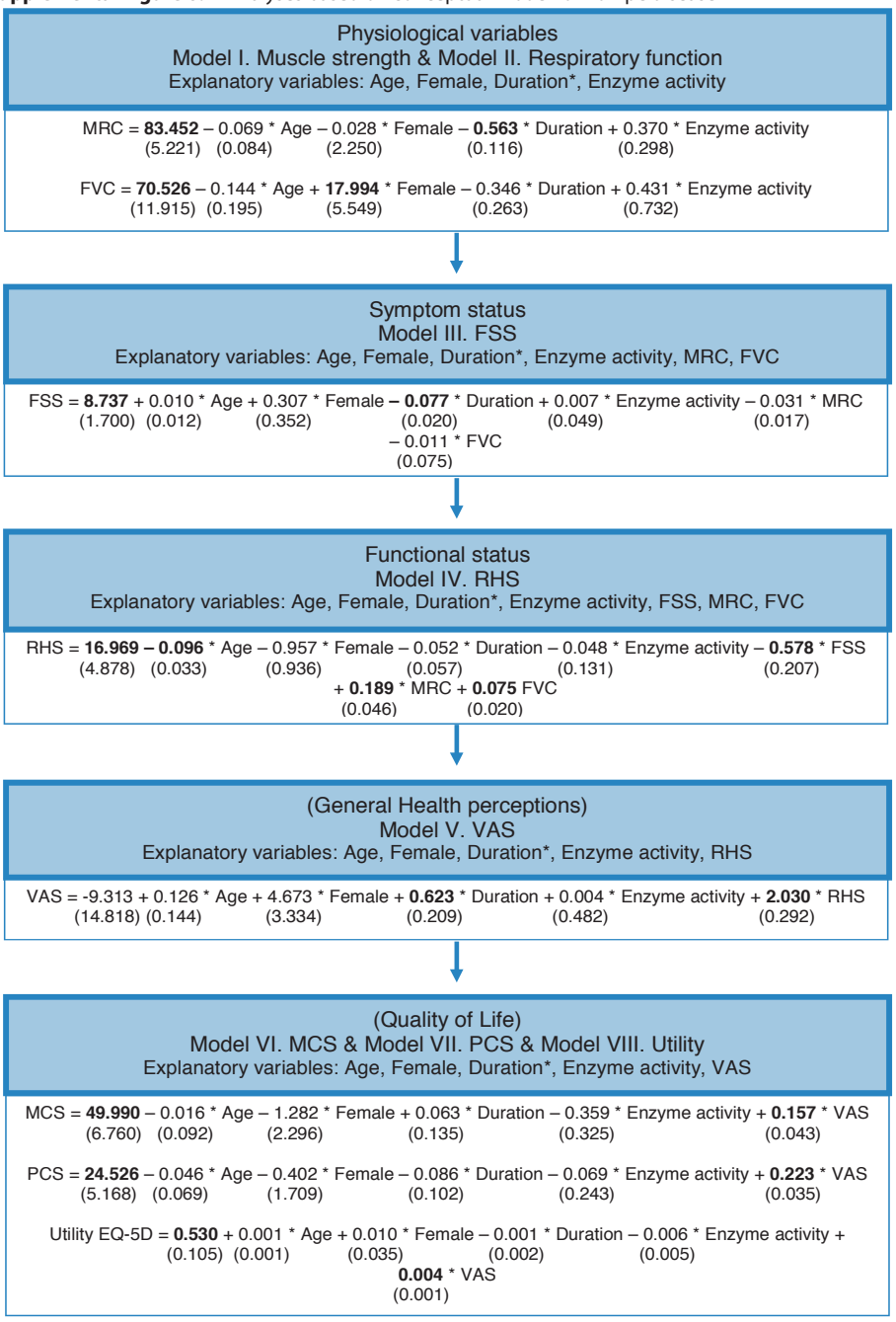
Conclusions

The Wilson-Cleary health outcomes model is a helpful tool for developing a conceptual model for Pompe disease. The conceptual model provides a comprehensive overview of all aspects of Pompe disease in adults, integrating subjective and objective health outcomes in one model. This model can be useful to clinicians and researchers who want to explore how changes in specific clinical characteristics may affect a patient's overall health outcomes. In addition, the model can be useful for policy makers who must consider various issues when making implementation and reimbursement decisions about treatments for orphan diseases. The approach used here provides a means to understand the mechanisms that drive changes in health that may occur both during natural course or if a drug is used to treat patients.

Acknowledgements

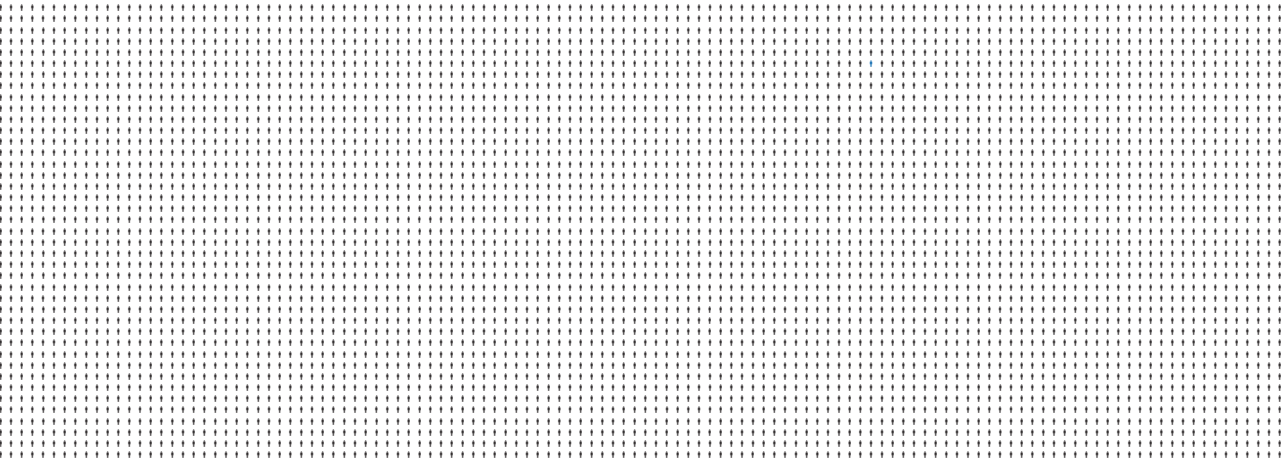
This study was financially supported by the Netherlands organization for health research and development (ZonMw; grant no. 152001005). The authors would like to thank Juna de Vries, Stephan Wens, Esther Kuperus and Chris van der Meijden for their help in the data collection.

Supplemental Figure 6.1 Analyses based on conceptual model for Pompe disease



Note: Bold figures represent significant relationships; Standard errors of coefficients are indicated in brackets below the coefficient

* Duration since diagnosis



CHAPTER 7

Cost-effectiveness of enzyme replacement therapy in adult Pompe disease

Kanters TA, Van der Ploeg AT, Kruijshaar ME, Rizopoulos D, Redekop WK, Rutten-van Mölken MPMH, Hakkaart L

Submitted

Abstract

Introduction: Pompe disease is a rare, progressive, metabolic disease, and the first treatable inheritable muscle disorder. Enzyme replacement therapy (ERT) with alglucosidase alfa is the only treatment option for patients with Pompe disease. Costs of ERT are high as for most orphan drugs. This study investigates the cost-effectiveness of ERT compared to supportive therapy in adult patients with Pompe disease.

Methods: Survival probabilities were estimated from an international observational dataset (n = 283) using a time-dependent Cox model. Quality of life was estimated on a Dutch observational dataset using a previously developed conceptual model which links clinical factors to quality of life. Costs included costs of ERT, costs of drug administration and other healthcare costs. Cost-effectiveness was estimated using a patient-level simulation model (n = 90), synthesising the information from underlying models for survival, quality of life and costs. The cost-effectiveness model estimated the (difference in) lifetime effects and costs for both treatments. Two scenarios were modelled: (1) a worse case scenario with no extrapolation of the survival gain due to ERT beyond the observed period (i.e. from 10 years onwards); and (2) a best case scenario with lifetime extrapolation of the survival gain due to ERT. Effects were expressed in (quality adjusted) life years (QALYs). Costs were discounted at 4.0% and effects at 1.5%.

Results: Substantial increases in survival were estimated – discounted incremental life years of ERT ranged from 1.9 years to 5.4 years in the scenarios without and with extrapolation of survival gains beyond the observed period. Quality of life was also significantly better for patients receiving ERT. Incremental costs were considerable and primarily consisted of the costs of ERT. Incremental costs per QALY were €3.2 million for scenario 1 and €1.8 million for scenario 2.

Conclusions: The availability of extended, prospectively collected, longitudinal observational data on the most important input parameters required to construct a cost-effectiveness model is quite exceptional for orphan diseases. The cost-effectiveness model showed substantial survival gains from ERT. Despite these substantial gains, ERT had a high cost-effectiveness ratio caused by the high drug costs.

Introduction

Pompe disease is a rare inheritable muscle disease. It is caused by a deficiency of the enzyme acid α-glucosidase [26]. The disease has a continuous clinical spectrum of phenotypes. In adult patients, it particularly affects skeletal muscle and respiratory function, and patients eventually become wheelchair bound and ventilator dependent [26, 35, 36]. Compared to the general population, adults with Pompe disease experience a reduced life expectancy and quality of life [37, 38, 102].

Enzyme replacement therapy (ERT) with alglucosidase alfa (Myozyme®, Genzyme corp.) has been developed as a treatment for Pompe disease. Before ERT became available in 2006, patients received supportive therapy (ST), consisting of respiratory support, ambulatory support, physiotherapy and/or dietary treatment. In adult patients with Pompe disease, ERT has been shown to improve muscle strength, respiratory function and quality of life [46, 48]. Furthermore, it leads to a significant improvement in survival in both infants and adults [15, 49, 77].

Like other treatments for rare diseases, ERT is expensive. Costs-effectiveness is one of the criteria on which reimbursement decisions are based. In cost-effectiveness studies, the ratio of incremental costs and incremental effects of a new treatment versus a comparator is calculated. In this study, we examined, for the Dutch situation, the cost-effectiveness of ERT compared to ST in adult patients with Pompe disease. Considering the costs associated with ERT, the treatment is not expected to have a favourable cost-effectiveness ratio. Still, it is necessary to conduct economic evaluations, as it provides policy makers with an instrument to engage in price negotiations with drug manufacturers and a comparison of the cost-effectiveness of treatments with other orphan drugs can contribute to the debate on whether or not, for orphan drugs, we may need reimbursement decisions that explicitly incorporate broader societal preferences.

Methods

The Dutch health economic guidelines were followed in this cost-effectiveness study. A patient-level simulation model was developed to assess cost-effectiveness of ERT for adult patients with Pompe disease. In such a model, outcomes are calculated for individual patients and then the average is taken over the total patient population included [158]. The model compared two treatments: supportive treatment (ST) and enzyme replacement therapy with supportive treatment (ERT). The model was composed of

three main components, i.e. survival, quality of life, and costs, which were modelled on the basis of an individual patient's characteristics for both treatments.

Survival

Survival probabilities were derived from an international dataset with observational data of patients with Pompe disease (the International Pompe Association (IPA)/Erasmus MC Pompe Survey; n = 283), which started to collect data in 2002, four years before ERT received market authorization. This database was previously used to estimate survival of adult patients with and without ERT by means of a time-dependent Cox regression model using wheelchair use, ventilator support and treatment as predictors [49]. For the cost-effectiveness model, this survival model was adapted to estimate the baseline hazard for both treatments using the same dataset. This method provides a life table for both treatments (estimated cumulative survival probabilities are provided in Supplemental Table 7.1). To make optimal use of all available data, patients contribute data to the survival estimates of both treatments; i.e. patients that received ERT also contributed data to estimate the survival in the ST group before they received ERT. For both treatments, the mean observed follow-up was approximately 3.5 years with a maximum total follow-up for ST of 8.9 years and for ERT of 8.4 years.

Because the survival after the observed period is uncertain, two scenarios were modelled. In scenario 1, a conservative approach was used, assuming no effects of ERT on survival after the observed period. Hence, from year 10 onwards, the survival probabilities estimated for ST at 9 years were kept constant and applied to both treatments in this scenario. This scenario presents a worse case scenario, as no further improvements in survival due to ERT were assumed beyond the observed survival gains, resulting in the lower boundary of survival gains due to ERT. In scenario 2, the effect of ERT on survival was extrapolated beyond the observation period, by carrying forward the estimated treatment-specific survival probabilities of year nine (see Supplemental Table 7.1) for both treatments. To adjust for an increasing risk of mortality with increasing age, the estimated probabilities were replaced by age-based mortality rates for the general Dutch population when these were larger than disease-specific mortality rates. Mortality rates for the Dutch population were derived from Statistics Netherlands [159].

Quality of life

A previously developed conceptual model for adult Pompe disease, connecting clinical parameters with quality of life [160] was used to obtain estimates for an individual patient's quality of life. The conceptual model describes the relations between enzyme activity, muscle strength, respiratory function, fatigue, level of handicap, general health perceptions, and utility. The quality of life model in the cost-effectiveness model resem-

bled the conceptual model for adult Pompe disease, except that the estimates from the conceptual model were recalculated using a model specification that included ERT as a covariate, in order to model treatment effects. The other covariates in the quality of life model were age, disease duration and enzyme activity. Using the regression estimates from the conceptual model in combination with patient characteristics (age, disease duration, enzyme activity and treatment), the patient's muscle strength and respiratory function were estimated. The estimated values for muscle strength and respiratory function were used as input values (next to the patient characteristics) in the regression model for the subsequent level in the conceptual model, i.e. fatigue. Fatigue was used, in combination with muscle strength, respiratory function and patient characteristics, to estimate the next level in the conceptual model, namely handicap level. Handicap and patient characteristics were used in turn to estimate health perceptions. The final level in the conceptual model, i.e. quality of life, was estimated on the basis of the patient's estimated health perceptions, and the patient characteristics (age, disease duration, enzyme activity and treatment). Regression estimates for the quality of life model were based on a Dutch dataset (n = 82), consisting of a sample of all Dutch patients being monitored (both treated and untreated) by the national reference center for Pompe disease (Erasmus MC, University Medical Center, Rotterdam, the Netherlands). Regression estimates are provided in Supplemental Table 7.2. The ERT covariate in the quality of life model showed a significant positive effect on utility: utilities for ERT were 0.028 points higher than for ST ($p = 0.008$, see Supplemental Table 7.2).

Quality of life was expressed in utilities, which represents the value of a patients' quality of life on a scale anchored at 1 (perfect health) and 0 (death). Utilities were derived from the EQ-5D questionnaire [106]. Dutch tariffs were used to calculate utilities [90].

Costs

Costs were calculated from the societal perspective and expressed in 2014 euros. Several costs components were included in the cost-effectiveness model.

ERT costs were based on patients' weights; dosage was 20 mg/kg body weight every two weeks. Patients' weights were estimated using a random effects model, including age and gender as explanatory variables. The estimates of bodyweight were based on a dataset from the hospital pharmacy on the Dutch patients being treated with ERT at Erasmus MC, University Medical Center, Rotterdam, the Netherlands (n = 84). Patients' weights were multiplied by the list price of medication – ERT costs per kilogram bodyweight were €5,788 per year. Because of organizational efficiency in the hospital pharmacy, spillage was very low; therefore, no costs of spillage were included.

Cost of drug administration were based on biweekly infusions. Infusions were provided outside the hospital (mostly at home) for 79% of patients. Based on bottom-up costing research, these costs of drug administration outside the hospital were estimated to be €433; compared to €507 for in-hospital drug administration. A weighted average was used to calculate costs of drug administration.

Other healthcare costs were retrieved from health economic questionnaires [102] among Dutch patients (n = 87) at Erasmus MC, University Medical Center, Rotterdam, the Netherlands. These costs related to hospitalizations, outpatient visits, GP visits, paramedical care, home care, diagnostic procedures and medical aids were included in the analyses. For valuation, reference prices were used from the Dutch costing manual [161]. Costs for informal care were added to the healthcare costs and valued using the opportunity cost method [162]. Productivity costs were retrieved from self-reported data on absence from paid work and reduced efficiency at work and were calculated using the friction cost method [88]. Both healthcare utilization costs (including informal care) and productivity costs were estimated using two GLM models (one model for ST and one model for ERT), with age, gender, disease duration as explanatory variables (regression estimates are provided in Supplemental Table 7.3).

Cost-effectiveness

Effects were expressed in life years gained and quality adjusted life years (QALYs) gained. QALYs are calculated as the number of life years gained corrected for the quality of life (i.e. utility) during these life years. Incremental cost-effectiveness ratios (ICERs) were presented as both incremental costs per life year gained and incremental costs per QALY gained. Probabilistic sensitivity analysis (PSA) was performed and the 95% confidence intervals (CI) were derived from the 2.5^{th} and 97.5^{th} percentiles of the PSA iterations.

Model settings

A double-loop model was used to represent patient heterogeneity and parameter uncertainty [163]. The double-loop model consisted of 30 simulated populations of 90 bootstrapped patients (equal to the number of patients for which data for all patient characteristics that were used as input parameters in the cost-effectiveness model were available) and 1,000 Monte Carlo simulations (see Supplemental Figure 7.1). The inner loop represented patient heterogeneity, the outer loop represented parameter uncertainty. Firstly, in the outer loop, values from the distributions of all regression coefficients in the models of survival, quality of life and cost models were drawn. These values were kept constant for a sample of 90 bootstrapped patients in the inner loop. Using the information on these 90 patients, individual estimates for survival, quality of life and costs were made, for both ST and ERT, and averaged over this population of 90

patients. This process was repeated 30 times in the inner loop. Then, this entire process was repeated 1,000 times in the outer loop.

A lifetime time horizon was used in the base case analyses. Patients in the ERT (ST) group were modelled to receive ERT (ST) until death; i.e. in the model patients did not switch treatments. Effects were discounted using a discount rate of 1.5%; costs were discounted at 4.0%, as recommended by the Dutch pharmacoeconomic guidelines [164]. Discounting is done to adjust for time preferences; the further the gains and losses occur in the future the less weight they get.

The cost-effectiveness model was programmed in Microsoft Excel 2013 (Microsoft, 2013). Survival analyses were performed using R [165]. Regression models for quality of life and costs were estimated in Stata version 14.1 (StataCorp, 2015). The analyses were performed on patient level data until the year 2011.

Sensitivity analyses

Two types of structural uncertainty were assessed by means of one-way sensitivity analyses. Firstly, a simpler regression model was used to estimate survival: survival was estimated using treatment as the only explanatory variable. Secondly, the influence of the time horizon on the ICER was assessed by using shorter time horizons for the cost-effectiveness analyses (i.e. time horizons of 5 years and 15 years).

Next to assessing the structural uncertainty of the model, the influence of specific input parameters on the outcomes was assessed in one-way sensitivity analyses. Price of medication was reduced by 20% to investigate the influence of the price of ERT on the ICER. Furthermore, analyses were run using a discount rate of 0% for both costs and effects. To test the influence of the utility gain on the ICER, utility gains were set to zero and to 0.1 in two separate sensitivity analyses. Similarly, increases in healthcare costs other than costs of ERT were set to zero to test for the influence of those costs on the ICER. Finally, a sensitivity analysis was performed in which the lifetable was used until year 8 (i.e. the point at which for at least 25% of the initial population data were still available for analysis), and this value was carried forward to later years. This sensitivity analyses was performed to assess the influence of the small sample size for the survival model in the ninth year.

Results

Patient population

Table 7.1 shows the baseline (i.e. first visit in the database) patient characteristics for the patients included in the cost-effectiveness model.

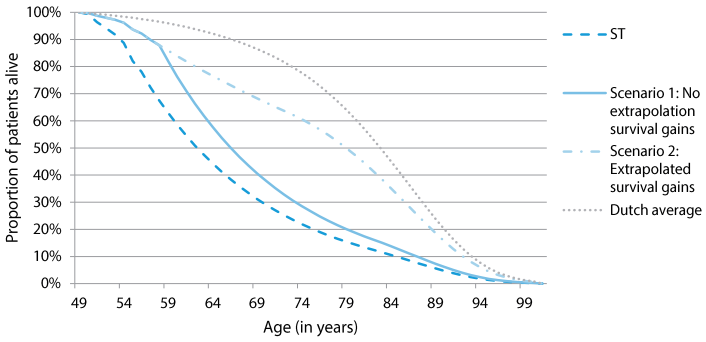
Survival

Survival probabilities for ERT were higher than for ST (Supplemental Table 7.1). The resulting survival curves for ST and ERT are given in Figure 7.1. In both scenarios, survival increased substantially due to ERT. In scenario 1, a worse case scenario with no extrapolation of survival gains after the observed period, undiscounted life expectancy was approximately 2.6 years longer for ERT patients than for ST patients (i.e. the difference between the blue and red line), using a lifetime time horizon. Table 7.2 shows that incremental life years were 1.9 years when a 1.5% discount rate on effects was applied. Survival gains were even larger in scenario 2; life expectancy increased with 8.2 years without discounting, and 5.4 years when discounting was applied.

Table 7.1 Baseline characteristics of Pompe patients included in the cost-effectiveness analyses (n = 90)

	Mean	Median	Range
Age at first visit	49.1 years	50.0 years	23.0 – 75.0 years
Disease duration (since diagnosis)	7.7 years	4.3 years	0.0 – 27.6 years
Female	48%		
Residual Enzyme activity (in fibroblasts)	12.0%	12.0%	0.5 – 19.9%
Wheelchair use	31%		
Ventilation use	27%		
Period at risk in ST survival analyses	3.5 years	3.5 years	0.0 – 8.9 years
Period at risk in ERT survival analyses	3.4 years	3.7 years	0.2 – 8.4 years

Figure 7.1 Survival curves for both treatments derived from the cost-effectiveness model and general population in the Netherlands (average patient)



Abbreviations: ST = Supportive therapy

Table 7.2 Cost, effects and cost-effectiveness of ST and ERT (lifetime time horizon)

Scenario 1: No extrapolation of survival gains				
Incremental and total effects	**ST**	**ERT**	**Difference**	**Difference 95% CI**
Utilities	0.42	0.45	0.03	[0.02-0.05]
Life expectancy	16.33	18.21	1.89	[0.67-2.62]
QALYs	10.53	12.57	2.04	[1.30-2.57]
Incremental and total costs	**ST**	**ERT**	**Difference**	**Difference 95% CI**
Total costs	€ 329,105	€ 6,795,495	€ 6,466,827	[€ 5,686,402-€ 7,340,316]
Healthcare costs	€ 325,720	€ 6,790,671	€ 6,464,951	[€ 5,683,798-€ 7,342,186]
ERT costs	€ 0	€ 6,258,915	€ 6,258,915	[€ 5,513,466-€ 7,019,921]
Costs of drug administration	€ 0	€ 157,457	€ 157,457	[€ 95,399-€ 223,444]
Other healthcare costs	€ 325,720	€ 374,299	€ 49,390	[€ -264,511-€ 301,652]
Productivity costs	€ 3,411	€ 5,662	€ 2,268	[€ -2,916-€ 13,822]
Incremental cost-effectiveness ratios				
Cost / life year gained		€ 3,417,713		[€ 2,237,739-€ 10,714,797]
Cost / QALY gained		€ 3,167,914		[€ 2,348,946-€ 5,485,622]
Scenario 2: Extrapolated survival gains				
Incremental and total effects	**ST**	**ERT**	**Difference**	**Difference 95% CI**
Utilities	0.42	0.45	0.03	[0.02-0.05]
Life expectancy	16.42	21.84	5.44	[1.24-9.21]
QALYs	10.60	14.85	4.26	[1.77-6.62]
Incremental and total costs	**ST**	**ERT**	**Difference**	**Difference 95% CI**
Total costs	€ 324,967	€ 7,879,226	€ 7,554,844	[€ 6,885,851-€ 8,210,521]
Healthcare costs	€ 321,558	€ 7,874,627	€ 7,553,917	[€ 6,844,436-€ 8,210,008]
ERT costs	€ 0	€ 7,206,219	€ 7,206,219	[€ 6,684,091-€ 7,705,496]
Costs of drug administration	€ 0	€ 179,589	€ 179,859	[€ 106,760-€ 257,239]
Other healthcare costs	€ 321,558	€ 488,819	€ 168,109	[€ -172,810-€ 508,039]
Productivity costs	€ 3,435	€ 5,590	€ 2,173	[€ -2,684-€ 12,621]
Incremental cost-effectiveness ratios				
Cost / life year gained		€ 1,389,925		[€ 838,539-€ 5,317,415]
Cost / QALY gained		€ 1,774,390		[€ 1,164,826-€ 4,159,592]

Note: Discount rate effects 1.5%; Discount rate costs 4.0%

Quality of life

The average difference in discounted utilities found in the cost-effectiveness model was 0.03 (Table 7.2). Estimated utilities for both treatments decline over time, due to worsening clinical parameters which translate into utility decreases through the conceptual quality of life model. Discounted QALYs were 2.0 (scenario 1) and 4.3 (scenario 2) higher for ERT than for ST over a lifetime period.

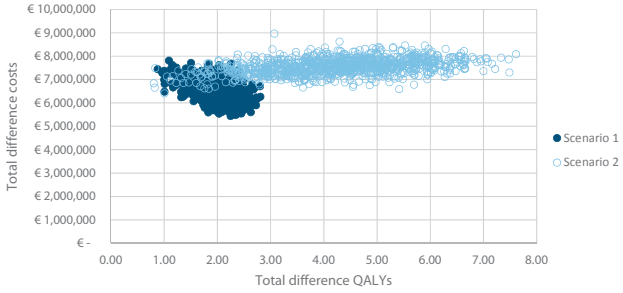
Costs and cost-effectiveness

Undiscounted annual treatment costs for an average weight patient was €450,000. Table 7.2 further shows costs for both treatments. In scenario 1, discounted lifetime incremental costs were approximately €6.5 million, consisting mainly (96.7%) of drug costs. Incremental costs for scenario 2 were €7.6 million, because patients lived longer and received ERT for a longer period of time. ERT did not reduce other healthcare costs, because ERT improves survival and during these additional years of life patients still need routine monitoring and other forms of healthcare and informal care.

For scenario 1, the ICER was estimated at €3.4 million per life year gained and €3.2 per incremental QALY. The ICERs for scenario 2 were lower; €1.4 million per life year gained and €1.8 million per incremental QALY.

A cost-effectiveness plane visualizes the variation in incremental effects and incremental costs, as it presents the results for each of the outer loop iterations. The cost-effectiveness plane in Figure 7.2 shows the outcomes of the 1,000 model iterations for both scenarios (i.e. each dot represents one outer loop, given the 30 simulated heterogeneous populations of 90 patients that were drawn in the inner loop). Uncertainty is primarily present concerning the difference in effects, especially when extrapolating survival gains in scenario 2. Uncertainty surrounding survival gains is the underlying determinant of the variation in PSA outcomes. The cost-effectiveness acceptability curve in Figure 7.3 shows the percentage of simulations with a cost-effective outcome

Figure 7.2 Cost-effectiveness plane; incremental costs and incremental effects of ERT over ST



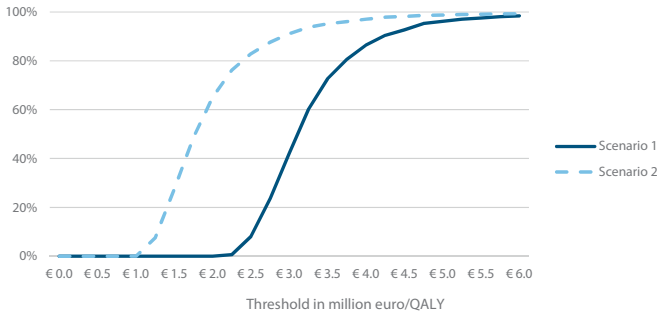
under a pre-specified cost-effectiveness threshold. Using a cost-effectiveness threshold of either €50,000 or €80,000/QALY (the upper limit in the Netherlands, depending on the severity of the disease), 0% of iterations would be considered cost-effective in either of the scenarios. When a threshold of €4.7 million per QALY is used 95% of iterations would be considered cost-effective in scenario 1, for scenario 2 this occurs at a threshold of €3.5 million per QALY.

Sensitivity analyses

Table 7.3 shows the outcomes of the various sensitivity analyses. The effect of using a simpler model specification for survival, i.e. using treatment as the only covariate, on the ICER was limited. Changing the time horizon had the largest influence on the ICER. The ICER was higher with shorter time horizons; using a 5-year horizon the ICER was €15.6 million per life year gained (€7.0 million per QALY) and using a 15-year horizon the ICER was 3.9 million per life year gained (€3.6 million per QALY). Both incremental costs and effects were lower for the shorter time horizons than in the base case. The ICER increased mainly because of the lower survival gains. In the analyses with the 15-year time horizon discounted incremental life years were estimated to be 1.2 years. Discounted incremental life years were 0.1 years in the analyses with a 5-year time horizon; this survival gain was exclusively based on observed data. This is consistent with Figure 7.1 and Supplemental Table 7.1, which showed that gains in survival increased after five years.

When an ERT-price reduction of 20% was modelled, incremental costs decreased to €5.2 million. The ICER decreased to €2.6 million per life year gained and €2.5 million per QALY gained. Without discounting, the ICER was €4.3 million per life year gained and €4.2 million per QALY. Discounting affected both costs and effects, but due to the differential discount rates it reduced the net present value of costs more than the net present value of effects. Disregarding utility gains reduced the incremental QALYs, but the impact on the ICER was limited. When the improvement in quality of life due to ERT was kept

Figure 7.3 Cost-effectiveness acceptability curve: percentage of model iterations (y-axis) below CE threshold (X-axis)



constant at 0.1 instead of 0.03 as derived from the quality of life model, incremental costs per QALY was €2.2 million. Excluding differences in other healthcare costs, or using survival data until year 8, had virtually no effect on the ICER. The sensitivity analyses for scenario 2 showed similar findings.

Table 7.3 Results one-way sensitivity analyses

Scenario 1: No extrapolation of survival gains					
	Incr. LY	**Incr. QALY**	**Incr. Costs**	**Cost/LY**	**Cost/QALY**
Base Case	2.03	2.13	€ 6,486,112	€ 3,195,040	€ 3,050,814
Structural uncertainty					
Survival: ERT as only covariate	2.15	2.08	€ 5,780,738	€ 2,692,018	€ 2,772,920
5 year time horizon	0.13	0.29	€ 2,043,440	€ 15,558,121	€ 6,958,412
15 year time horizon	1.19	1.31	€ 4,681,908	€ 3,944,770	€ 3,567,548
Input values					
Medication costs 20% reduced	2.03	2.13	€ 5,234,010	€ 2,578,258	€ 2,461,874
Discount rates 0%	2.61	2.69	€ 11,186,321	€ 4,287,545	€ 4,162,930
No utility gain	2.03	1.26	€ 6,486,112	€ 3,195,040	€ 5,138,186
Utility gain of 0.10	2.03	3.03	€ 6,486,112	€ 3,195,040	€ 2,139,947
No difference in healthcare costs except for cost of ERT	2.03	2.13	€ 6,418,842	€ 3,161,903	€ 3,019,173
Survival: last value carried forward from year 8 onwards	1.98	2.08	€ 6,387,051	€ 3,231,592	€ 3,073,535
Scenario 2: Extrapolated survival gains					
	Incr. LY	**Incr. QALY**	**Incr. Costs**	**Cost/LY**	**Cost/QALY**
Base Case	5.67	4.38	€ 7,564,035	€ 1,334,081	€ 1,726,636
Structural uncertainty					
Survival: ERT as only covariate	5.44	4.14	€ 6,749,881	€ 1,241,847	€ 1,629,079
5 year time horizon	0.13	0.29	€ 2,043,440	€ 15,558,121	€ 6,958,412
15 year time horizon	1.59	1.58	€ 4,836,654	€ 3,047,385	€ 3,053,857
Input values					
Medication costs 20% reduced	5.67	4.38	€ 6,121,967	€ 1,079,741	€ 1,397,456
Discount rates 0%	8.22	6.12	€ 14,480,052	€ 1,761,281	€ 2,367,014
No utility gain	5.67	3.34	€ 7,564,035	€ 1,334,081	€ 2,265,117
Utility gain of 0.10	5.67	5.47	€ 7,564,035	€ 1,334,081	€ 1,382,324
No difference in healthcare costs except for cost of ERT	5.67	4.38	€ 7,390,957	€ 1,303,555	€ 1,687,127
Survival: last value carried forward from year 8 onwards	5.65	4.36	€ 7,478,037	€ 1,323,777	€ 1,716,538

Note: Base case results differ somewhat from Table 7.2 as sensitivity analyses were performed using deterministic analyses

Discussion

This study assessed the cost-effectiveness of ERT versus ST in adult patients with Pompe disease from a societal perspective. Survival increased considerably because of ERT. Using a lifetime time horizon the model showed that discounted life expectancy increased by up to 5.4 years when survival was extrapolated (scenario 2). Furthermore, ERT had a positive effect on quality of life of patients. However, the cost-effectiveness ratio is primarily determined by the costs of ERT. In the best scenario, this resulted in an incremental cost per life year gained of €1.4 million and an incremental cost per QALY ratio of €1.8 million.

The results of our analyses are in line with other studies that show that orphan drugs are usually not cost-effective under common cost-effectiveness thresholds, primarily because of their high prices. In comparison, ERT in Fabry disease for instance was associated with an incremental cost of €3.3 million per QALY gained [166].

When compared to various expensive cancer therapies, the effectiveness of ERT in Pompe disease is much larger in terms of absolute life years gained. For example, nivolumab increased survival of lung cancer patients by 0.61 years when compared to docetaxel [167] and pertuzumab increased survival of breast cancer patients by 1.4 years in comparison to trastuzumab/docetaxel [168]. This study has shown an increase in life expectancy due to ERT of 5.4 years (in scenario 2). Despite these larger effects, the cost-effectiveness ratio is less favourable for ERT in Pompe disease (nivolumab: €134,000 per QALY; pertuzumab: €148,824 per QALY) [167, 168]. As such, the study particularly shows the effect of the high price of ERT on the ICER. The exact causes of the high price remain unclear, because a breakdown of this price in different components is not publicly disclosed. It could be due to several factors, such as high R&D costs, high production costs (particularly for complex manufacturing processes like the production of recombinant alglucosidase alfa), lack of competition and the high perceived value of the drug. Transparency about price setting of orphan drugs is needed to justify their high prices. Medication costs of ERT are further increased because of the relatively high dose needed to reach muscle tissue; research has shown that a dosage of at least 20 mg/kg is needed to be effective [26, 77, 169].

Strengths and limitations

Research in orphan drugs in general may be hampered by small patient numbers and lack of data and this also holds for cost-effectiveness studies [170, 171]. However, in the current study we had access to a large international longitudinal dataset with observational data to estimate survival. In addition, quality of life and costs were estimated by using an extensive dataset containing long-term follow-up on both ST and ERT. The

availability of data for both ST and ERT was essential to perform an adequate cost-effectiveness study. When survival is affected, using an international dataset might be the only option to gather enough data to estimate cost-effectiveness. The availability of the relatively large amount of data for the various components in a cost-effectiveness study, i.e. survival, quality of life and costs, is exceptional, given the rarity of the disease.

Pharmacoeconomic guidelines prescribe the use of a time horizon that captures all benefits and costs of a treatment. In this respect, a lifetime horizon was most appropriate for modelling the cost-effectiveness in adult Pompe disease. If the time horizon is longer than the follow-up of the data (as was the case in this study), observed (survival) data need to be extrapolated. Because extrapolation (particularly of effects) is associated with uncertainty, especially when the time horizon is lifetime, we present two different scenarios. In scenario 1, in which we only include the survival gains in the observed period, we assume no gains in survival beyond the observed period, as a worse case scenario. In scenario 2, we extrapolated survival gains beyond the observed period. ICER estimates ranged from €3.2 million (scenario 1) to €1.8 million per QALY (scenario 2). Although this is a broad range in absolute terms, it also showed that the ICER is high even when the largest expected survival gain is modelled.

The number of patients in the dataset used to model survival was not sufficient to incorporate other explanatory variables in the Cox proportional hazard model than wheelchair use and ventilator support. Therefore, the effect of age on disease-specific survival could not be modelled. Hence, the effect of age on survival was limited to modelling of background mortality. A final limitation with regard to modelling survival was that beyond the observed period, the last-observed value from the life tables was carried forward. Actual survival was observed for a period up to nine years; estimated 9-year survival probabilities were extrapolated beyond this period. Sensitivity analyses showed that results were not affected when the values of year 8 were carried forward instead of the values for year 9. Ideally, a parametric survival function would have been fitted to the observed data, but this was not possible with the available dataset in which the same patients were on ST for a certain period after which they could switch to ERT. Information on long-term effects of ERT in Pompe disease with respect to survival is needed to assess the plausibility of the two scenarios.

The data used in this study were derived from observational studies. Observational studies can suffer from various types of biases, such as performance bias, selection bias and loss to follow-up [172, 173]. Performance bias occurs when patients and clinicians are not blinded, and can lead to an overestimation of treatment effects [173]. Selection bias can lead to differences in patient characteristics between groups, which can obscure the

determination of treatment effects; i.e. when patients have different prognosis at start of treatment it cannot be established whether effects are caused by the treatment or by the initial differences in prognosis of patients [172]. In our study, the impact of selection bias on the estimated survival was reduced because in the time-dependent Cox proportional hazard model, the patients that received ERT also contributed survival data to the ST group. Furthermore, by including age, gender and disease duration in the quality of life and costs regression models, and by using wheelchair and ventilator use in the survival model, we tried to correct for differences in patient characteristics as far as the data allowed. Loss to follow-up was limited for the Dutch patients in the study, because in the Netherlands all patients with Pompe disease are referred to the single expert centre at the Erasmus MC. Erasmus MC uses an extensive standardized follow-up protocol for all patients, which are either treated at the Erasmus MC, or elsewhere under supervision of Erasmus MC. Furthermore, loss to follow-up is reduced as patients are obligated to complete specific measurements and questionnaires. Hence, this study did capture the vast majority of the total Dutch population (>80%) of adult patients with Pompe disease.

Policy implications

Evidence-based policy making and health technology assessment (HTA) may assist policy makers to effectively prioritise health interventions and make consistent decisions. This study showed that despite significant survival gains, the treatment for this very rare disease will never be titled cost-effective at the current price-level of the drug. Considerable price reductions will be needed to improve the cost-effectiveness ratio of this effective therapy. To address this challenge, collaboration between national healthcare authorities may support to increase negotiation power and reduce drug prices. Currently, the governments of the Netherlands, Belgium, Luxembourg and Austria collaborate in this respect, but this coalition preferably needs to be extended to other countries to further increase negotiation power. What could also contribute to reducing the ICER is to better target the therapy to those who benefit most. Start and stopping rules for ERT in Pompe disease have always been applied in the Netherlands and entail that treatment should only be initiated in symptomatic patients and treatment should be discontinued if patients do not show response to treatment. As more evidence becomes available, these start and stopping rules can be improved over time. European recommendations on these start and stopping rules will shortly be published by the European Pompe Consortium [50].

Whether the cost-effectiveness criterion should play a role in the reimbursement of orphan drugs has been debated, both in scientific literature [66, 83, 174] as well as in a broader societal setting [65]. Cost-effectiveness is used to maximize health under a given budget constraint. The cost-effectiveness threshold quantifies the societal willing-

ness to pay for one unit of health gain. In the Netherlands, cost-effectiveness thresholds are used to guide discussions on cost-effectiveness, but these thresholds are not a conclusive reimbursement criterion. The Dutch threshold is dependent on the severity of a disease: for diseases with a severity between 0.1 and 0.4 the threshold is €20,000/QALY; for diseases with a severity between 0.41 and 0.7 the threshold is €50,000/QALY; and for diseases with a severity between 0.71 and 1 the threshold is €80,000/QALY [54]. Theoretically, the cost-effectiveness threshold should reflect the opportunity costs of healthcare spending. When the ICER of an intervention is smaller than the threshold, the health gains of a new intervention exceed the health effects of the interventions that are displaced elsewhere in the healthcare system to compensate for the additional costs of the new technology. Empirical data on the value of displacement costs in the Netherlands are not yet available. The use of a higher cost-effectiveness threshold for orphan drugs has been suggested [175]. The basic questions are whether a societal preference for rarity and inherited diseases exists and how much society wants to avoid denying access to treatment for patients with these diseases. Several positive reimbursement decisions for orphan drugs in various countries imply that policy makers believe this preference to exist. Other criteria also seem to play a role in reimbursement decisions. A systematic literature review found nine other criteria that were used in decision making on orphan drugs: uniqueness of the indication, prevalence of the disease, disease severity, advancement of technology, complexity of manufacturing, unmet medical need, scientific evidence on effectiveness, drug safety, and budget impact [176]. In addition to these criteria, other studies identified the availability of alternative treatments, social impact of the disease and treatment, whether follow-up research will be performed, and whether the drug is disease modifying or not as criteria that can be important in reimbursement decisions on orphan drugs [177, 178]. From the perspective of the physicians and the patients, the fact that Pompe disease is still the first and only proven treatable inheritable skeletal muscle disorder may also play a role. The knowledge obtained may be used for the better understanding of similar diseases and in the development of next generation and other innovative therapies.

Conclusions

This model-based cost-effectiveness study has shown the significant benefits of ERT in adult Pompe disease in terms of survival and QALYs over a life-time horizon. The study in this rare orphan disease could be performed due to the start of prospective collection of data four years before ERT was registered. It has also shown that the high price of ERT for this ultra-rare disease results in a cost-effectiveness ratio of ERT that by far does not meet the conventional threshold values.

Supplemental Table 7.1 Survival: Cox regresssion estimates

Time dependent Cox regression estimates ERT=0					
		No ventilation		Ventilation	
	Year	Cumulative survival	Standard error	Cumulative survival	Standard error
No ambulation	0	1.000	0.000	1.000	0.000
	1	0.997	0.002	0.994	0.005
	2	0.985	0.006	0.965	0.015
	3	0.975	0.009	0.944	0.022
	4	0.965	0.012	0.921	0.029
	5	0.951	0.017	0.891	0.040
	6	0.919	0.027	0.825	0.063
	7	0.900	0.034	0.785	0.076
	8	0.871	0.045	0.728	0.094
	9	0.845	0.058	0.679	0.117
Ambulation	0	1.000	0.000	1.000	0.000
	1	0.992	0.006	0.982	0.013
	2	0.955	0.019	0.901	0.031
	3	0.928	0.027	0.843	0.039
	4	0.900	0.035	0.785	0.048
	5	0.862	0.046	0.712	0.061
	6	0.781	0.071	0.567	0.084
	7	0.733	0.086	0.490	0.095
	8	0.666	0.106	0.393	0.105
	9	0.609	0.127	0.321	0.122
Time dependent Cox regression estimates ERT=1					
		No ventilation		Ventilation	
	Year	Cumulative survival	Standard error	Cumulative survival	Standard error
No ambulation	0	1.000	0.000	1.000	0.000
	1	0.999	0.001	0.998	0.002
	2	0.995	0.003	0.989	0.007
	3	0.992	0.004	0.982	0.010
	4	0.989	0.006	0.974	0.013
	5	0.984	0.008	0.964	0.018
	6	0.973	0.011	0.940	0.026
	7	0.967	0.014	0.925	0.031
	8	0.956	0.017	0.903	0.039
	9	0.947	0.022	0.883	0.049
Ambulation	0	1.000	0.000	1.000	0.000
	1	0.998	0.002	0.994	0.005
	2	0.985	0.008	0.967	0.015
	3	0.976	0.012	0.947	0.023
	4	0.967	0.016	0.925	0.029
	5	0.953	0.021	0.897	0.036
	6	0.923	0.031	0.833	0.047
	7	0.905	0.004	0.795	0.052
	8	0.877	0.045	0.740	0.059
	9	0.852	0.056	0.693	0.075

Supplemental Table 7.2 Quality of life: regresssion estimates conceptual disease model

Coefficients quality of life model						
	FVC	**MRC**	**FSS**	**RHS**	**VAS**	**Utility**
Constant	60.359*	63.185*	6.459*	24.887*	6.903	0.580*
Age	-0.089	0.130	0.020	-0.126*	0.084	0.000
Female	13.688*	-0.033	0.384	-1.551*	3.413	-0.011
Disease duration	-0.184	-0.257*	-0.067*	-0.035	0.512*	-0.006*
Enzyme activity	0.952	0.924*	0.061	-0.064	-0.073	-0.001
FVC			-0.008	0.079*		
MRC			-0.024*	0.120*		
FSS				-0.721*		
RHS					1.662*	
VAS						0.003*
ERT	0.118	1.370*	-0.045	-0.265	6.227*	0.028*
Standard errors quality of life model						
	FVC	**MRC**	**FSS**	**RHS**	**VAS**	**Utility**
Constant	10.421	5.052	1.128	2.917	10.294	0.097
Age	0.175	0.085	0.011	0.027	0.107	0.001
Female	5.256	2.437	0.302	0.735	2.589	0.036
Disease duration	0.202	0.102	0.017	0.043	0.152	0.002
Enzyme activity	0.672	0.318	0.043	0.105	0.375	0.005
FVC			0.006	0.014		
MRC			0.011	0.029		
FSS				0.135		
RHS					0.199	
VAS						0.000
ERT	0.559	0.341	0.100	0.253	1.169	0.011

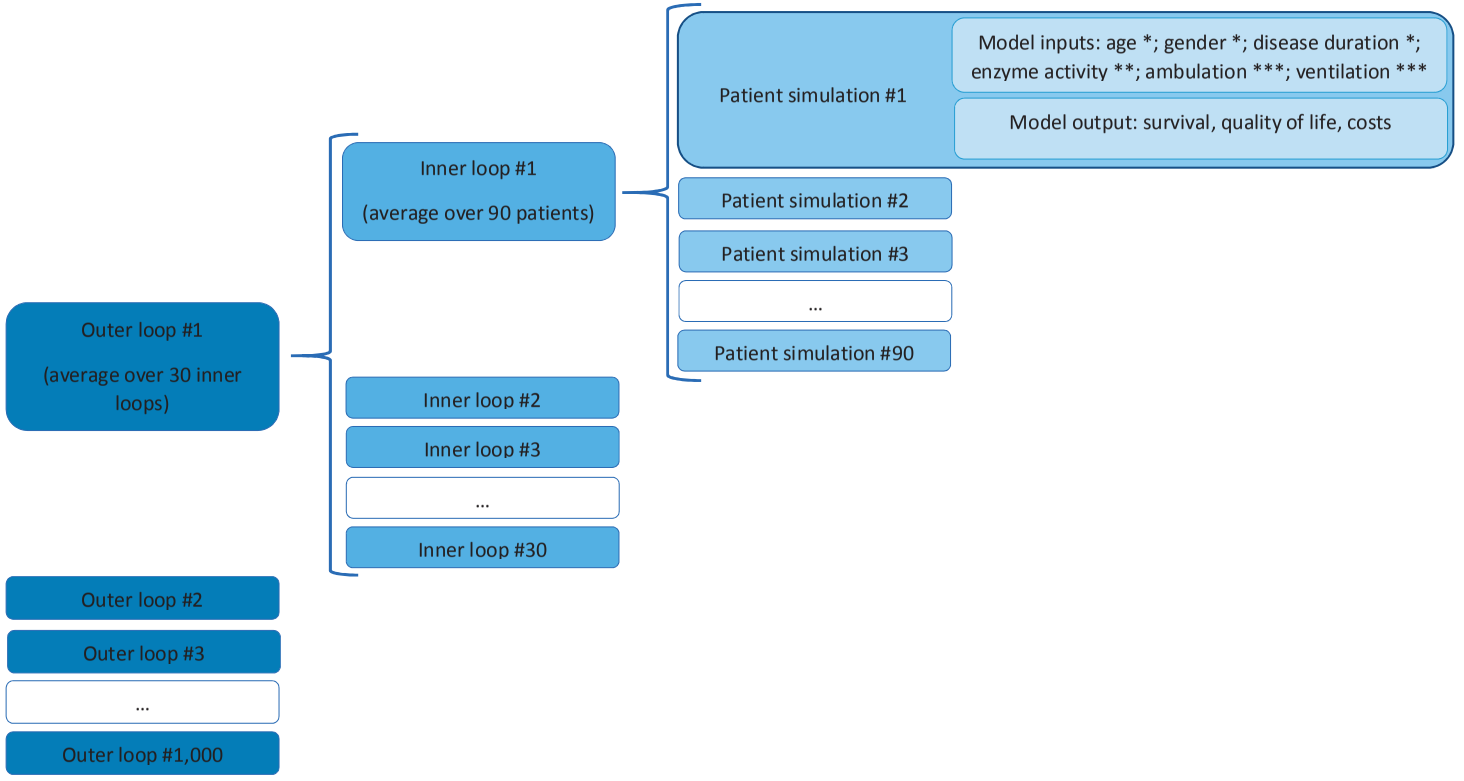
Abbreviations: FVC = Forced Vital Capacity; MRC = Medical Research Council; FSS = Fatigue Severity Scale; RHS = Rotterdam Handicap Scale; VAS = Visual Analogue Scale; ERT = Enzyme Replacement Therapy
* Indicates significance at 0.05 level

Supplemental Table 7.3 Costs: regression estimates healthcare costs and productivity costs and input cost parameters

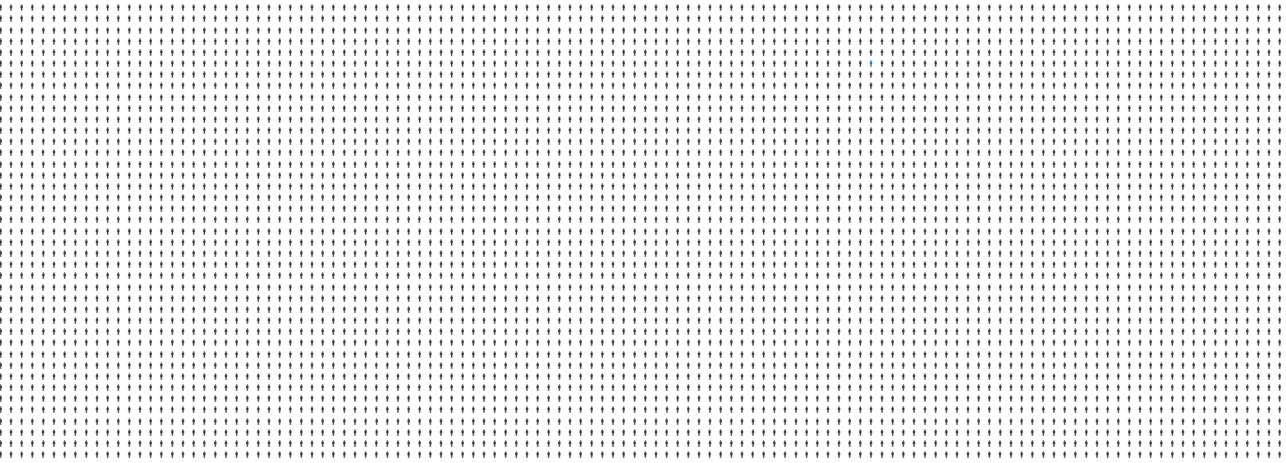
Regression estimates healthcare costs and productivity costs model ST				
	Coefficients (log transformed)		Standard errors	
	Healthcare costs	Productivity costs	Healthcare costs	Productivity costs
Constant	7.958*	9.245	0.586	1.514
Age	0.031*	-0.046	0.011	0.027
Disease duration	0.021	-0.102*	0.016	0.035
Female	-0.525	-0.734*	0.275	0.572
Regression estimates healthcare costs and productivity costs model ERT				
	Coefficients (log transformed)		Standard errors	
	Healthcare costs	Productivity costs	Healthcare costs	Productivity costs
Constant	9.272*	10.921*	0.536	2.048
Age	0.002	-0.094*	0.009	0.037
Disease duration	0.045*	-0.050	0.011	0.026
Female	-0.457*	-0.213	0.222	0.683
Treatment costs: regression estimates patient's weight				
	Coefficients	Standard errors		
Constant	58.148*	2.592		
Age	0.493*	0.031		
Female	-13.360*	2.803		
Treatment cost: input parameters				
	Values	Remarks		
ERT treatment costs / kilogram	€ 5,788	Dosage 20mg/kg; one infusion per two weeks		
Costs of administration				
Costs of administration (per year)	€ 11,660	One infusion per two weeks		
Home costs	€ 433	Source: bottom-up costing study (2014 prices)		
Hospital costs	€ 507	Source: bottom-up costing study (2014 prices)		
Proportion treated in hospital	21%			

* Indicates significance at 0.05 level

Supplemental Figure 7.1 Double loop model structure



* Used as input variable for costs and quality of life models; ** Used as input variable for quality of life model; *** Used as input variable for survival model



CHAPTER 8

Cost-effectiveness of enzyme replacement therapy with alglucosidase alfa in classic-infantile patients with Pompe disease

Kanters TA, Hoogenboom-Plug I, Rutten-van Mölken MPMH, Redekop WK, Van der Ploeg AT, Hakkaart L

Orphanet J Rare Dis (2014) 9:75

Abstract

Background: Infantile Pompe disease is a rare metabolic disease. Patients generally do not survive the first year of life. Enzyme replacement therapy (ERT) has proven to have substantial effects on survival in infantile Pompe disease. However, the costs of therapy are very high. In this paper, we assess the cost-effectiveness of enzyme replacement therapy in infantile Pompe disease.

Methods: A patient simulation model was used to compare costs and effects of ERT with costs of effects of supportive therapy (ST). The model was filled with data on survival, quality of life and costs. For both arms of the model, data on survival were obtained from international literature. In addition, survival as observed among 20 classic-infantile Dutch patients, who all received ERT, was used. Quality of life was measured using the EQ-5D and assumed to be the same in both treatment groups. Costs included the costs of ERT (which depend on a child's weight), infusions, costs of other healthcare utilization, and informal care. A lifetime time horizon was used, with 6-month time cycles.

Results: Life expectancy was significantly longer in the ERT group than in the ST group. On average, ST receiving patients were modelled not to survive the first half year of life; whereas the life expectancy in the ERT patients was modelled to be almost 14 years. Lifetime incremental QALYs were 6.8. Incremental costs were estimated to be €7.0 million, which primarily consisted of treatment costs (95%). The incremental costs per QALY were estimated to be €1.0 million (range sensitivity analyses: €0.3 million - €1.3 million). The incremental cost per life year gained was estimated to be €0.5 million.

Conclusions: The incremental costs per QALY ratio is far above the conventional threshold values. Results from univariate and probabilistic sensitivity analyses showed the robustness of the results.

Introduction

Since the introduction of orphan drug regulations, the number of orphan drugs (i.e. drugs for rare diseases) has grown vastly. This confronts policy makers with a trade-off between access and affordability. On the one hand, the overall proportion of orphan drugs in healthcare expenditures is substantial and continues to grow [21]. On the other hand, healthcare authorities would like to provide rapid access to promising new treatments, even when the evidence base might not be mature yet. To deal with this trade-off, policy makers can turn to 'coverage with evidence development schemes', which enable patients to obtain access to the treatment while effectiveness is simultaneously studied in a real-world setting [175, 179]. When a cost-effectiveness analysis is performed at the same time, policy makers also gain insight in the economic consequences of the new treatment. In 2006, such a scheme was installed in the Netherlands for high-priced in-hospital orphan drugs. During a coverage with evidence development period of four years, effectiveness and cost-effectiveness were studied for orphan drugs listed on a specific policy rule [139].

One of the drugs reimbursed through this policy rule is a drug to treat Pompe disease. Pompe disease is a rare metabolic disease and presents as a broad clinical spectrum, with the rapidly progressive classic-infantile form at the most severe end and late-onset or adult-onset Pompe disease at the least severe end [26, 131]. In all cases, the disease is caused by a deficiency of the enzyme acid α-glucosidase. The incidence of classic-infantile Pompe disease is 1 in 138,000 births [30]. In classic-infantile Pompe disease, symptoms present in the first months of life and involve respiratory and feeding problems, airway infections, and generalized muscle weakness. Patients also show progressive thickening of the heart (hypertrophic cardiomyopathy) which eventually leads to heart failure. These children generally die before the first year of age from cardiorespiratory failure and the median age of death has been estimated to be 6 to 9 months [32, 33].

Enzyme replacement therapy (ERT) with alglucosidase alfa (Myozyme®, Genzyme corp.) was developed as a treatment for Pompe disease. ERT has proven to have a substantial effect on survival in classic-infantile Pompe patients, reducing the 3-year mortality risk by 95% compared to an untreated historical control group [15, 45]. Cardiac, respiratory and motor functions of patients have been shown to improve by therapy.

Orphan drugs are often very expensive and this is also true for ERT to treat Pompe disease [18]. As of 2006, ERT for Pompe disease is reimbursed in the Netherlands under a coverage with evidence development scheme, during which the cost-effectiveness of the treatment needs to be assessed, even though this was expected to be unfavorable

upfront. This study reports on the cost-effectiveness of ERT in classic-infantile Pompe disease.

Methods

Patients and treatments

All Dutch patients with classic-infantile Pompe disease were enrolled in an observational study. Diagnosis of Pompe disease was confirmed by enzyme assay in leukocytes or fibroblasts and/or mutation analysis. All patients were treated by Erasmus MC Center for Lysosomal and Metabolic Diseases, Rotterdam, the Netherlands. The Institutional Review Board approved the studies. Written informed consent was provided by parents.

Currently ERT is the only available registered treatment for Pompe disease. In this study, the comparative treatment therefore consisted of usual supportive therapy (ST), including for example (nightly) ventilation, surgical correction of scoliosis, or nutritional support.

The registered dose of ERT is 20 mg/kg/2 weeks. Patients in the Netherlands received doses ranging from 20 mg/kg/2 weeks to 40 mg/kg/week. Since 2008 the majority of patients use the higher dose. The majority of the Dutch data were collected in patients using this dose. In the base case analyses of the model we therefore used the maximum dose of 40 mg/kg/week.

Study design and model structure

A patient simulation model was used to compare costs and effects of ERT with costs and effects of ST for patients with classic-infantile Pompe disease. The model was filled with data on survival, utilities and costs. For both treatment arms, the model generated costs, survival, quality of life and quality adjusted life years (QALYs). In addition, the model generated an estimate of the cost-effectiveness of treatment, expressed as cost per QALY.

Effects

Survival

Survival for the ST cohort was retrieved from two international studies on the natural course of infantile Pompe disease (n = 172; maximum 24 months follow-up [33] and 119 cases from literature [32]). Survival for the ERT cohort was obtained from three sources to increase sample size, i.e. a trial extension study (n = 18; maximum 36 months follow-up) [45], an international open-label study (n = 21; median follow-up 28 months) [180]

and data from Dutch infantile patients under treatment at Erasmus MC (n = 20; median follow-up 32 months). For all cohorts, patient-level data were available to include in the survival analysis. Table 8.1 provides characteristics of the patients in the three cohorts; the proportion of patients that died and used ventilation differed between cohorts, as did the dosage regimens. To extrapolate survival beyond the observed period, parametric survival models were fitted. Several distributions were investigated (exponential, Weibull, lognormal, and loglogistic). The choice of distribution was based on visual inspection and fit of the model to the data according to Akaike Information Criterion (AIC) and Bayesian Information Criterion BIC) [181]. When predicted survival was higher than in the general population, we have applied the mortality rates of the Dutch population [159].

Quality of life

Quality of life was assessed in Dutch patients using the Euroqol-5D (EQ-5D), completed by parents of patients every six months. The EQ-5D is a validated instrument for measuring and valuing generic health related quality of life [151]. The instrument describes 245 health states, and each health state is associated with a utility using a scoring formula. Utility scores typically range from zero (death) to 1 (perfect health). Utility scores were estimated using the Dutch tariff [90]. Only observations for patients above the age of two years were included (n = 6; median follow-up 24 months). The average utility was 0.62, ranging from 0.24 to 0.82. For five patients, multiple observations were available; their average utility was used in the analyses.

Table 8.1 Patient characteristics for patients in survival analyses

	Kishnani (2009)	Nicolino (2009)	Erasmus MC
n	18	21	20
Deaths	5 (28%)	6 (29%)	4 (20%)
Age at end study in months [range]	34.5 [19.7-44.0]	41.0 [7.7-80.3]	60.9 [3.2-178.8]
Patients using ventilation	9 (50%)	7 (33%)	5 (25%) **
Dosage (every other week)			
15 mg/kg	0	0	2[†,‡]
20 mg/kg	9	21 *	8 ***
40 mg/kg	9	0	10 [‡]

* Eight patients switched to 40 mg/kg after 26 weeks due to clinical deterioration; ** Two patients died; [†] Both patients switched to 30 mg/kg and later to 40 mg/kg; [‡] Every week; *** Five patients switched to 40 mg/kg

Costs

Costs were calculated from a societal perspective. This implies that all costs are included, no matter to whom they accrue. Total costs for patients treated with ERT consisted of four components: the cost of the drug alglucosidase alfa, infusion-related costs, costs related to other healthcare use and informal care costs. Patients receiving ST did not incur costs of the drug and infusion-related costs. Costs were expressed in 2009 euro values.

Treatment costs

Costs of the drug alglucosidase alfa are dependent on patient's weight. In the Netherlands, costs per vial (50 mg) are €556.50. In the Netherlands the doses applied in infants with classic-infantile Pompe disease range from 20 mg/kg/2 weeks to 40 mg/kg/week bodyweight (since 2008 the majority of patients use the higher dose). For the model we used the maximum dose of 40 mg/kg/week so drug costs per kilo bodyweight were €445.20. With weekly infusions (52 infusions per year), yearly medication costs per kilo are €445.20*52 = €23,150.40. Data from the Dutch cohort were collected between May 2007 and October 2012. Patients' weights were estimated on the basis of available data on Dutch patients (n = 17; median follow-up 35 months), and increased with the patient's age to a maximum of 75 kilograms.

Infusion-related costs were based on detailed time studies using the methodology described in the Dutch costing manual [84]. The total costs for infusion consisted of cost associated to physician and nursing time during infusion, overhead, capital, materials, informal care and travel time. A distinction was made with respect to treatment location of patients; patients receive infusions at home or in hospital. The estimated mean cost per infusion at home was €426 compared to €520 per infusion at the hospital. A total percentage of 68% of the Dutch patients were treated in the home situation. Based on weekly infusions (52 infusions per year), the annual infusion costs were estimated to be €23,710.

Other costs

Data of other healthcare utilization were collected by means of a health economic questionnaire, completed by the parents of the Dutch patients (n = 12; median follow-up 11 months). Bottom-up methodology was used to calculate the total direct medical costs; that is, the total number of physician and other caregiver contacts multiplied by unit costs of the corresponding healthcare services. Reference unit prices of healthcare services from the Dutch costing manual [84] were applied. Costs of informal care were valued using the shadow price method, also following the costing manual. The estimation of healthcare costs was described in more detail for adult non-treated patients [102]; for infantile patients the same methodology was used. Table 8.2 provides the unit costs used. Due to their age, infantile patients did not incur indirect costs from productivity losses.

Table 8.2 Cost components and associated unit costs (2009 prices)

Cost component	Cost per unit **	Source
Hospital day		
Regular ward	€ 394 *	[84]
Intensive care	€ 1,847	[84]
Ambulatory care		
Hospital day visits	€ 69 *	[84]
General practitioner visit	€ 22	[84]
Physiotherapy	€ 25	[84]
Other paramedical	€ 14 - € 91	[84]
Home care per hour	€ 29 - € 65	[84]
Medication		[86]
Other medical costs		
Tests & procedures	€ 54 - € 181	[84]
Respiratory support per day	€ 5	[87]
Medical devices	€ 18 - € 1,500	Market prices
Informal care costs per hour	€ 9	[84]

* Weighted average of academic and general hospital costs; ** Costs per unit are based on average unit costs for medical procedures, consultations and admissions [84]

Other healthcare utilization costs were estimated using a generalized estimated equation (GEE) model, a logarithmic link function and a gamma distribution (n = 12). Age was the only predictor variable used in this model.

Model assumptions

No data were available on health related quality of life (utility) for patients receiving ST. Utilities were therefore assumed to be equal in the two treatment arms. Hence, differences in QALYs only resulted from differences in life expectancy between the two treatment arms. Healthcare utilization costs were only available for patients receiving ERT. We assumed that patients receiving ST incurred the same costs as ERT-treated patients with the exception of treatment costs. Differences in costs therefore only resulted from treatment costs and differences in life expectancy between the two treatment arms.

Analyses

Cost-effectiveness was expressed in incremental cost per QALY gained and incremental cost per life year gained. Costs were discounted at a rate of 4% and effects were discounted at a rate of 1.5% in accordance with Dutch guidelines for pharmacoeconomic research [164]. A lifetime time horizon was used and a cycle length of ½ year was used.

Univariate sensitivity analyses were performed to examine the impact of the assumptions of the model on the results. We varied the following input variables: ERT dosage (the registered dose of 20 mg/kg/2 weeks as opposed to the mostly used dose in the Netherlands of 40 mg/kg/week in the base case analysis); costs of treatment (€11,575.20 per kilo per infusion as opposed to €23,150.40 per kilo per infusion); time horizon (5 years as opposed to lifetime in the base case); quality of life (0.49 and 0.74 in both cohorts and 0.31 in the ST cohort combined with 0.62 in the ERT cohort – implying a treatment effect on quality of life – as opposed to 0.62 in both cohorts); survival in the ERT cohort (varying the distributions used in the parametric survival analyses); and costs incurred by the ST cohort (double costs and no costs for the ST-cohort instead of assuming that 'other healthcare costs' were the same as the costs seen in ERT-treated patients).

Next to the univariate sensitivity analyses, probabilistic sensitivity analyses were performed to examine the impact of the uncertainty around the values of the input variables on the estimated effectiveness and cost-effectiveness of ERT. For this purpose, 1,000 populations were randomly drawn from relevant distributions in a Monte Carlo simulation procedure. The results from the probabilistic sensitivity analyses were presented in a cost-effectiveness plane (CE-plane). The CE-plane shows total incremental costs and total incremental effects of ERT against ST.

Results

Patient characteristics

Estimates for healthcare utilization costs were based on data of 12 Dutch classic-infantile patients; 8 male patients and 4 female patients. At first measurement, average age of these patients was 3.5 years. Data on quality of life were available for six patients; four male patients, average age 6.1 years (range 2.2 – 11.1) at baseline.

Effects

Figure 8.1 provides observed and modeled survival in both cohorts. On average, ST-treated patients did not survive the first half year of life (mean life expectancy 0.40 years), depicted by the steep decline of the solid black curve in Figure 8.1. Life expectancy was considerably longer in the ERT cohort. The exponential survival function best fitted the data for ERT-treated patients and is depicted in Figure 8.1 by the dashed line. The modeled survival followed the observed survival very closely in the first four years. From the age of 5 years, no deaths were observed in the ERT-group (solid grey curve) and the observed ERT-curve becomes flat accordingly. For this period, observed survival is heavily influenced by a small number of patients with a long follow-up. The observed

and modeled survival curves for the ERT-group diverge from this point on. Table 8.3 shows the results for the total and incremental effects. The life expectancy in the ERT cohort was estimated to be 13.8 years (mean QALYs: 7.00). Lifetime incremental QALYs were estimated to be 6.75 (7.00 vs. 0.24). Effects were discounted at a rate of 1.5% per year in both cohorts. For the ERT cohort the influence of discounting is larger, as effects occur over a longer time span, than for the ST cohort.

Costs

Table 8.3 also shows the total and incremental costs for classic-infantile patients. The majority of the incremental costs consisted of drug costs (95% of incremental costs). In addition, infusion costs were estimated to be €212,793 (3.0%). ERT-treated patients incurred higher costs than ST-treated patients not simply because of the ERT treatment they received but also because they lived much longer. Incremental costs were estimated to be €7.0 million.

Figure 8.1 Observed and modeled survival curves

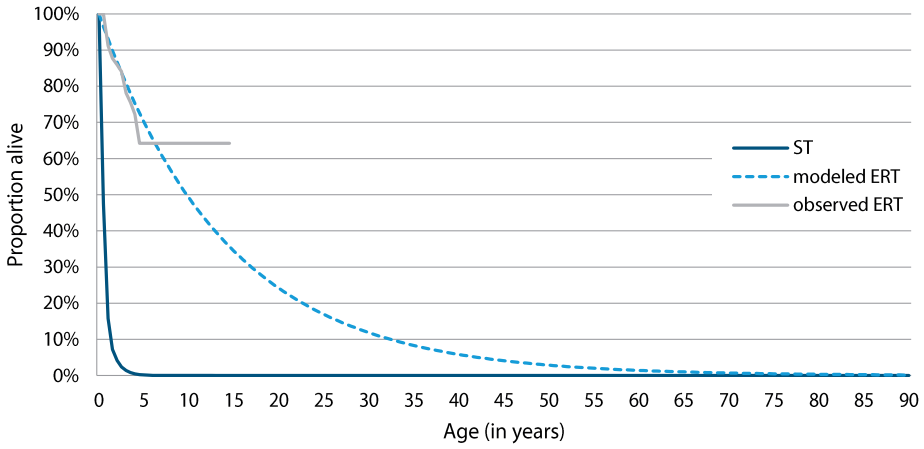


Table 8.3 Total and incremental costs and effects

	ST	ERT	Difference	[95% Confidence Interval]
Life expectancy (years)	0.40	13.79	13.39	[1.55 – 25.23]
QALYs	0.24	7.00	6.75	[2.32 – 11.19]
Total costs	€ 32,871	€ 7,032,899	€ 7,000,028	[€ 1,869,635 – € 12,130,422]
- ERT costs	€ -	€ 6,630,525	€ 6,630,525	[€ 1,615,059 – € 11,645,991]
- Infusion costs	€ -	€ 212,793	€ 212,793	[€ 121,477 – € 304,108]
- Other costs	€ 32,871	€ 189,582	€ 156,711	[€ 131,728 – € 181,694]

Abbreviations: ST = supportive therapy; ERT = enzyme replacement therapy; QALY = quality adjusted life year

Cost-effectiveness

Table 8.4 shows the incremental cost-effectiveness ratio for the treatment of classic-infantile Pompe patients with ERT. The incremental costs per QALY were estimated to be €1.0 million. The incremental cost per life year gained was estimated to be €0.5 million.

Sensitivity analyses

Table 8.4 also provides the results from the sensitivity analyses. The first sensitivity analysis examined the effect of dosage on the ICER. Total costs for ERT-treated patients were considerably lower in the 20 mg/kg/2 weeks analysis than in the base case analysis, because less medication was administered. Incremental costs were estimated to be €1.9 million. The ICERs at the lower, biweekly dose were about 3.6 times lower than the ICER in the base case analysis.

In a sensitivity analysis, the influence of treatment costs on the ICER was examined by halving these costs. The ICER dropped substantially (47%), indicating the prominent role of treatment costs in the analyses.

When a shorter time horizon of 5 years was used, the ICER was lower relative to the analyses with a lifetime horizon. During this period, patients' body weights' were relatively low, which considerably decreased treatment costs leading to more favorable ICERs. Incremental costs in this analysis were estimated to be €1.2 million and the incremental effects to be 2.20 QALYs.

Since information on utility (quality of life) was limited, we varied the utility value used in the base case analysis by 20% to determine how much it affected the results (range: 0.49 to 0.74). A change in quality of life can only affect QALY gain and thereby the ICER;

Table 8.4 Incremental cost-effectiveness ratios (dosage 40 mg/kg/week unless otherwise specified)

	Costs/QALY gained	Costs/life year gained
Base case analysis dosage 40 mg/kg/week	€ 1,043,868	€ 525,873
Registered dosage regimen (20 mg/kg/2 weeks)	€ 286,114	€ 144,137
Lower treatment costs (costs divided by 2)	€ 549,280	€ 276,713
Shorter time horizon (5 years)	€ 571,701	€ 92,634
Lower utility (0.49) in both cohorts	€ 1,304,835	€ 525,873
Higher utility (0.74) in both cohorts	€ 869,890	€ 525,873
Lower utility in ST-treated patients	€ 1,021,610	€ 525,873
Lognormal survival distribution	€ 1,050,595	€ 452,669
No costs incurred by ST-treated patients	€ 1,049,203	€ 528,560
Double cost incurred by ST-treated patients	€ 1,031,836	€ 520,387

it has no impact on the incremental costs. A lower value for quality of life reduced QALY gains and led to an increase in the ICER. When a higher utility value was used, the QALY gain increased and the ICER decreased. The use of a lower utility in the ST-treated patients only (implying a treatment effect on utility) did not change the ICER substantially.

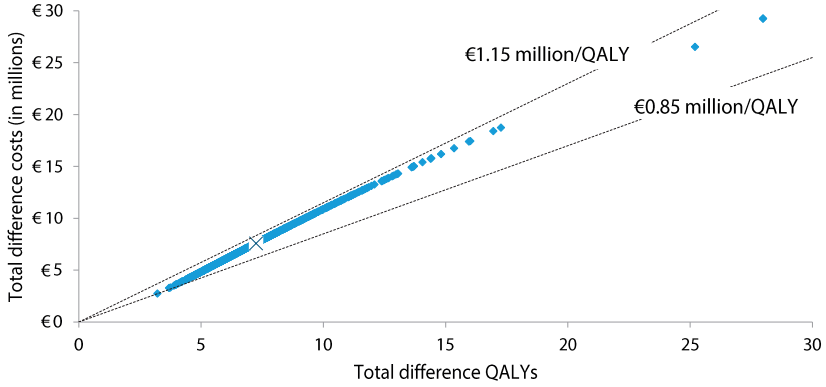
Survival in the ERT-treated patients was based on an exponential survival distribution, because that fitted the data best. Use of the lognormal distribution, which had the second lowest BIC, increased life expectancy from 13.8 to 21.9 years, primarily because the predicted survival later in life was higher. Incremental QALYs increased to 9.3 in this analysis. This longer life expectancy increased the incremental costs to €9.7 million. However, this did not affect the ICER, which remained €1.04 million/QALY. Two other distributions were also tested (Weibull, log-logistic), but they did not have any substantial effect on the ICER (Weibull: life expectancy 14.9 years; ICER €1.05 million/QALY; log-logistic distribution: life expectancy 20.6 years; ICER €1.03 million/QALY).

Since no data were available regarding costs of ST treatment we assumed in the base case analysis that these costs were the same as the costs seen in the ERT-treated group (excluding ERT-related costs). We tested the importance of this assumption by doubling the costs for the ST cohort and by setting the total costs in the ST cohort to zero. However, since the costs for the ST cohort in the base case analysis were limited because of the short life expectancy in this group, changes in the costs for the ST cohort had no appreciable influence on the ICER.

Probabilistic sensitivity analyses

Figure 8.2 provides the results from the probabilistic sensitivity analyses in a cost-effectiveness plane (CE-plane). All outcomes of the probabilistic sensitivity analyses are in the northeast quadrant of the CE-plane, i.e. all draws resulted in better health outcomes and higher costs. Furthermore, the CE-plane shows a strong positive association between incremental costs and effects. The CE-plane further shows that the dispersion of incremental costs and effects from the average incremental costs and effects (depicted by the X in the CE-plane) is quite large. However, the variation of the ICERs is very limited; all estimates are within a range of €0.85 million/QALY and €1.15 million/QALY.

Figure 8.2 Cost-effectiveness plane: incremental costs and incremental effects of enzyme replacement therapy relative to supportive therapy



Discussion

This is one of the first studies to assess the cost-effectiveness of an orphan drug, evaluating the cost-effectiveness of enzyme replacement therapy with alglucosidase alfa (Myozyme®) in classic-infantile Pompe disease. The incremental cost-effectiveness was calculated on the basis of available data, a pharmacoeconomic model and assumptions on disease course. The cost per QALY was estimated to be €1.0 million; cost per life year gained was €0.5 million.

The results from the univariate sensitivity analyses and probabilistic sensitivity analyses showed the robustness of the model. Uncertainty with regard to the ICER is limited; in all cases the ICER is beyond any conventionally used cost-effectiveness threshold. While the absolute gains in life years, incremental QALYs, and incremental costs differ between various sensitivity analyses, ICERs are not affected.

For instance, using log-normal and log-logistic distributions to estimate survival had a large impact on the life expectancy. This was primarily caused by a higher survival later in life. However, despite the large gains in survival, the ICER was relatively unaffected, due to the significant costs of therapy. This shows the paradoxical situation of performing an economic evaluation with a therapy of such high annual costs; better effectiveness did not lead to a better cost-effectiveness ratio.

This study was performed using currently available information, but the available evidence on (infantile) Pompe disease is increasing as the follow-up period increases. For instance, some patients have already survived to the age of 15 and hope to reach

adulthood. Increases in the number of patients and follow-up time will lead to more stable estimates of survival.

Limitations of the study

There are a number of limitations of the study that need to be stressed. Most limitations are due to the relatively scarce availability of data, both with respect to number of patients (due to orphan disease status) and time period involved.

Firstly, survival estimates from various sources were combined to increase sample size. Hence, the implicit assumption was that survival probabilities for patients were comparable, although the doses used in these groups of patients varied. The number of patients was too small to perform subgroup analysis by dosage. Furthermore, survival was modeled using an exponential survival distribution, which assumes a constant hazard over time. The choice of the distribution was made on the basis of visual inspection and best fit of the data [181]. Although a constant hazard might not be a realistic assumption, the sensitivity analyses showed that the choice of the distribution did not have a large influence on the ICER.

Secondly, the pharmacoeconomic model was based on observations of a limited period. We assumed that these results could be extrapolated into the future. Accordingly, we assumed that patients did not change therapy over the course of time. In addition, costs and effectiveness of the treatment were assumed not to change.

A third point of attention concerns the valuation of health related quality of life, which was assessed using a proxy version of the EQ-5D. The use of a proxy to make statements on a subjective measure as quality of life can be difficult. However, for young children alternatives are limited [182]. In addition, we only used the utility observations of children older than two years of age to estimate the utility of the entire group, because of reasons of applicability of the EQ-5D items. The assumption of equal utilities in both treatment arms was made due to these data constraints, and represented a conservative scenario. Sensitivity analyses showed that the utility level in the ST-cohort did not influence the results.

Finally, in the current model we used a base case in which patients received 40 mg/kg/week, since this is the dosage regimen used by the majority of Dutch patients. We also used information on patients receiving other dosages (particularly 20 mg/kg/2 weeks) to build the model. For these patients, treatment costs are lower and effects are likely to be lower. In the sensitivity analyses, the effect of dosage on costs was examined, keeping effectiveness constant. A lower dosage and fewer infusions reduced the ICER

substantially. However, it is likely that a lower dosage also leads to a reduction in effects. In that case, the ICER would increase.

Future research

The current study assesses the cost-effectiveness of ERT in Pompe disease only in the severe infantile form of the disease; results may differ for other populations.

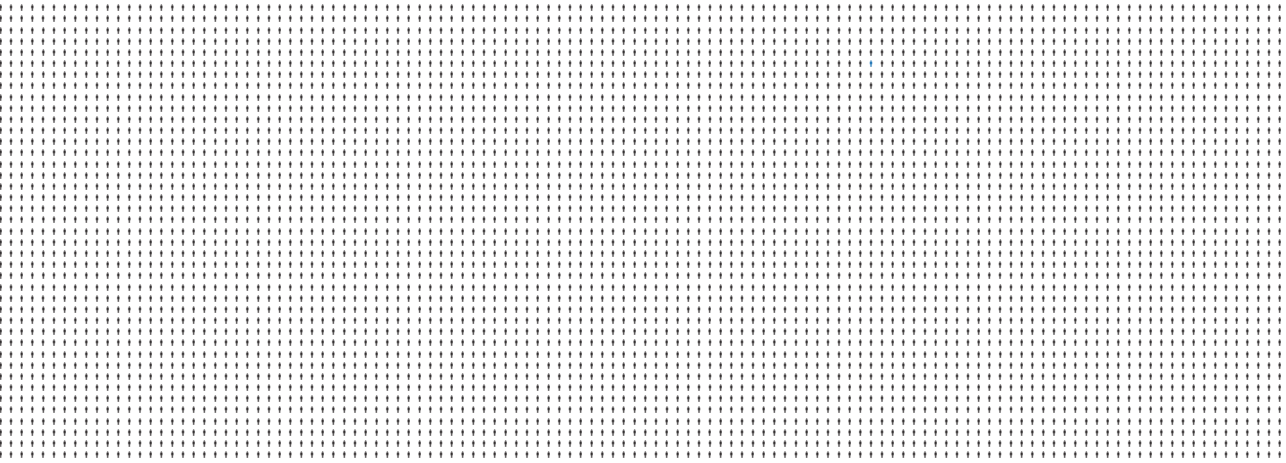
A lively debate has taken place in the literature as to whether or not orphan drugs should be excluded from any cost-effectiveness assessment [83, 174]. The most prominent question is whether society is willing to pay a premium because of the rarity of a disease. A recent study showed that this might not be the case, at least in Norway [183]. In contrast, the Dutch Health Care Insurance Board seems to place extra value on rarity, judging by the advice to the Minister of Health to reimburse Myozyme® in infantile Pompe disease in 2012. This decision is probably also driven by the relatively small budget impact. Other factors thus play a role in reimbursement decisions. This hints at the potential role for multi-criteria decision analyses in reimbursement decisions of orphan drugs, although deriving weights for the different criteria might be a major challenge.

Conclusions

In this study, the cost-effectiveness of enzyme replacement therapy with Myozyme® in classic-infantile Pompe disease was assessed. Incremental costs per QALY were estimated to be €1.0 million.

Acknowledgements

The authors would like to thank the participants of the 5th Low Lands Health Economics Study Group for the fruitful discussion on a draft version of the paper. Furthermore, the authors would like to thank Carin van Gelder and Jan-Dietert Brugma for providing data used in this paper.



CHAPTER 9

Access to orphan drugs in western Europe: can more systematic policymaking really help to avoid different decisions about the same drug?

Kanters TA, Hakkaart L, Rutten-van Mölken MPMH, Redekop WK

Expert Rev Pharmacoecon Outcomes Res (2015) 15(4):557-559

When the Scottish government recently launched a £21 million fund to provide patients with rare diseases access to treatment, Alex Neill, the Scottish Health Secretary, stated that '*it was only right that Scottish patients with rare conditions had access to innovative medicines which were clinically justified, and that they were not disadvantaged due to the very high cost of these treatments*'. This statement raises questions about the criteria that play a role in reimbursement decisions on orphan drugs. This editorial examines the criteria that were used in the decisions about the reimbursement of an orphan drug for Pompe disease and explores methods to improve the transparency and consistency of reimbursement decisions for orphan drugs in general.

Orphan drugs/enzyme replacement therapies

Orphan drugs are drugs for rare diseases, and the number of orphan drugs available on the market is increasing [1]. The reimbursement of these drugs is often a dilemma for decision-makers because the treatment costs per patient are generally much higher than for non-orphan drugs. Examples of orphan drugs are enzyme replacement therapies (ERTs), which are therapies for metabolic diseases. Examples of ERTs are laronidase for mucopolysaccharidosis I, idursulfase for mucopolysaccharidosis II, and agalsidase alfa and beta for Fabry disease. These therapies are associated with high costs, with annual costs ranging from €200,000 to 600,000 per patient [18].

The case of Pompe disease & ERT in the Netherlands

Alglucosidase alfa is an ERT for the treatment of Pompe disease, a rare metabolic disease (1 per 40,000) with two distinct forms (classic-infantile and late-onset). Without treatment, patients with the infantile form will not survive their first year of life. Adult patients can survive until their 60s or 70s, but their average life expectancy is still much shorter than in the general population [38]. Patients with Pompe disease have a health-related quality of life (hrQoL) of 0.72 (based on the Euroqol 5D), which is lower than the Dutch average of 0.87 [102]. In the past, only the symptoms of the disease (particularly muscle weakness and reduced respiratory function) could be treated. However, about 10 years ago, the introduction of alglucosidase alfa gave patients and their families hope that their disease could finally be treated effectively. The Dutch government added alglucosidase alfa to a newly made positive list of orphan drugs which were temporarily reimbursed (i.e., for 4 years), conditional on collecting additional evidence of the real-world effectiveness and cost–effectiveness in the Netherlands. After 4 years, the reimbursement dossier informing the re-assessment was submitted to the Health Care

Insurance Board (College voor Zorgverzekeringen [CVZ]), which advised the Ministry of Health. At the time of re-assessment, there was evidence that ERT dramatically improved life expectancy of infantile patients [45] and improved muscle strength and respiratory function in adult patients [46]. There were also indications that ERT may improve survival in adult patients, but little was known about its effect on hrQoL [49]. Ultimately, CVZ found that there was sufficient evidence that ERT increased survival in infants but limited evidence regarding its effectiveness in adults. Partly due to the substantial costs of ERT, the incremental cost–effectiveness ratios (ICERs) of ERT versus no ERT (i.e., symptom management) were high (infants: €900,000 per QALY gained; adults: €15 million per QALY gained). When the reimbursement dossier was submitted, there were 113 patients with Pompe disease in the Netherlands, 92 of whom received ERT (2009 data) and the annual budget impact of treating all eligible patients was €41 million.

In the summer of 2012, the preliminary recommendation by CVZ on the reimbursement of ERT leaked to the press, who gave much attention to CVZ's recommendation to reimburse ERT only for the infantile form of Pompe disease. However, following a storm of criticism, the Health Minister began price negotiations with the manufacturer. This resulted in what was called a 'substantial' price reduction of the drug, but the actual size of the discount was kept confidential. In October 2013, the minister announced that ERT was to be reimbursed for all patients, both infants and adults.

The status of ERT for Pompe disease in other countries

In Scotland, a reimbursement dossier was submitted to the Scottish Medicines Consortium (SMC) and was evaluated in 2007 [184]. The SMC concluded that ERT increases survival for infants, but concluded that its effectiveness among adults was not yet established. The cost-effectiveness ratios were £244,000–318,000 per quality adjusted life year (QALY) gained for infantile patients and £819,000 per QALY gained for adults. The SMC concluded that the economic case supporting reimbursement was not sufficiently demonstrated. The annual budget impact of treating all patients was estimated to be £2.8 million. The SMC did not recommend reimbursement for either patient group.

In Wales, ERT is reimbursed for infants but not for adults due to limited evidence on clinical effectiveness [185]. Treatment is reimbursed for juvenile patients with the late-onset form.

In England, various ERTs, including ERT for Pompe disease, have been funded through a specific policy agreement since 2008 [186]. Patients are treated according to a clinical

protocol with clear start and stop criteria, and only receive treatment in designated treatment centers.

In France, the Transparency Committee concluded in 2006 that ERT had a substantial benefit in the treatment of the infantile form of the disease, leading to a positive reimbursement decision [187]. For late-onset patients, the committee concluded that the benefit was insufficient in the absence of a formal demonstration of efficacy. The committee re-assessed the therapy in 2010 on the basis of new evidence, concluding that there was a minor benefit from ERT. Consequently, the committee recommended an annual assessment of the effects of ERT in late-onset patients. A re-assessment in 2012 yielded the same recommendations. The committee wants to be informed about the reason of discontinuation when a patient's treatment is stopped.

In Italy, ERT was placed on the national formulary in 2006 for infantile and late-onset patients with Pompe disease [188].

ERT is reimbursed in Belgium for both infantile and late-onset patients [189].

Multi-criteria decision analysis

The example of ERT in Pompe disease illustrates the great variability in reimbursement decisions of orphan drugs between European countries. This is not an isolated case; similar differences between countries have been observed for other orphan drugs [190]. One could argue that all countries with a centralized reimbursement system make decisions in two steps: first by gathering the necessary information (the assessment phase) and then making a decision (the appraisal phase). The observed differences in reimbursement decisions might result from differences between countries in both phases.

In the assessment phase, the evidence on efficacy is unlikely to differ between countries. For Pompe disease, the various countries, indeed, based their conclusions on the same efficacy studies (e.g., AGLU 1602 for infantile patients [15]; AGLU 2804 for late-onset patients [191]). However, data on incidence and prevalence of the disease, severity distribution, treatment patterns, drug prices, absolute and relative treatment costs, budget impact and/or cost–effectiveness may vary considerably. Country-specific cost–effectiveness studies are, therefore, required to reflect these differences.

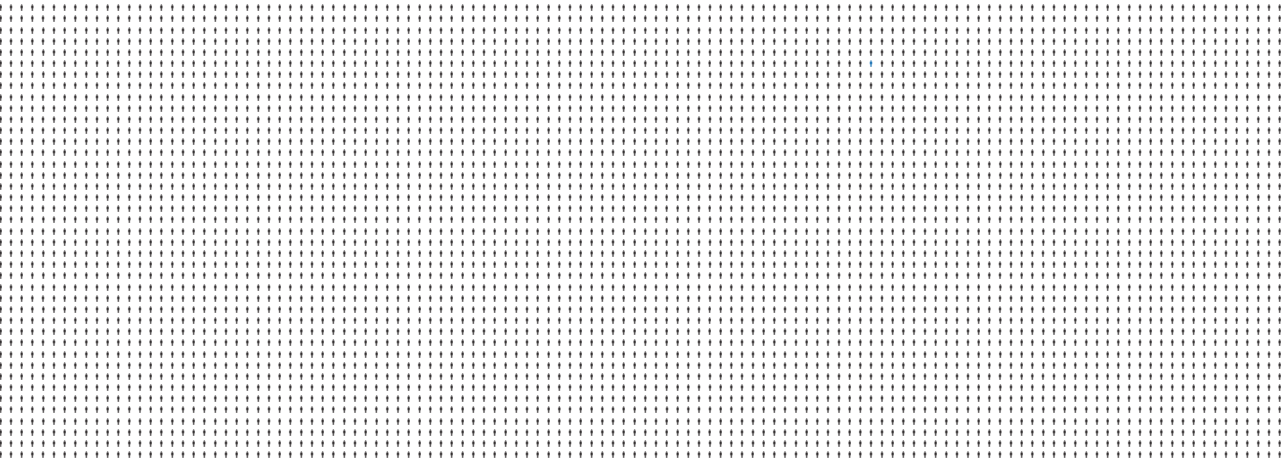
In the appraisal phase, the available evidence is weighted and additional criteria and societal preferences come into play. The criteria used in the reimbursement decisions

and their corresponding weights differ internationally, contributing to differences in judgments between countries. In the case of Pompe disease, equity considerations such as the right of equal access to innovative drugs for patients with rare diseases may play a role. Perhaps, decision-makers are willing to accept higher cost–effectiveness ratios to compensate for the fact that the society has neglected rare diseases and failed to develop treatments for them. The life-threatening nature of infantile Pompe disease, which leads to babies dying during their first year of life, is a crucial factor in decision-making. There is, indeed, evidence from stated preference studies that concepts such as 'fair innings' [192] and 'the rule of rescue' [193] are considered relatively important when people are asked to choose between different treatments [194].

Currently, we do not know how much the differences in reimbursement decisions between countries result from differences in the assessment and appraisal phase. This is because transparency in decision-making is lacking; we neither know which criteria are used in reimbursement decisions nor know how these are weighted and traded off against each other. If transparency is truly desired, an alternative framework for decision-making is needed. Multi-criteria decision analysis (MCDA) provides an explicit and systematic way of using various criteria to inform decision-making [195]. MCDA may support the justification and communication of reimbursement decisions to the public, as these reimbursement decisions result from a transparent and reproducible process. However, the pathway to MCDA requires a sufficient understanding of the criteria and their relative weights. Furthermore, we have to realize that the proper use of MCDA will not necessarily lead to identical reimbursement decisions across countries. For one thing, different criteria might be used in different countries. But even if the same criteria were to be used, differences might still persist, because criteria weights may be country-dependent, partly reflecting differences in how strongly policymakers and the general public feel about the equity considerations mentioned above. As the one-incremental cost-effectiveness ratio-fits-all paradigm slowly fades and a new MCDA one slowly emerges, more research is needed for a better understanding of its consequences in various fields, including reimbursement decisions about orphan drugs.

Acknowledgements

This study was financially supported by the Netherlands Organization for Health Research and Development (ZonMw; grant no. 152002045).



CHAPTER 10

Evaluation of orphan drugs in the Netherlands: can HTA offer guidance to healthcare policy?

Kanters TA, Hollak CEM, Van der Ploeg AT,
Rutten-van Mölken MPMH, Hakkaart L

Submitted

Abstract

Objectives: Specific legislation increased the number of available orphan drugs in Europe substantially. Although market authorisation is provided at EU level, national governments decide whether patients can get access to these drugs. In this study, we assess the applicability of guidelines for conducting pharmacoeconomic research to orphan drugs. In addition, the use of additional criteria for reimbursement decisions was investigated.

Methods: Semi-structured interviews were conducted with stakeholders directly involved in the decision making process on reimbursement of orphan drugs in the Netherlands. In addition, publicly available reimbursement dossiers on three orphan drugs were studied. Furthermore, two dossiers (which have not yet been evaluated by the National Health Care Institute and were not yet publicly accessible) were available to the researchers for this study.

Results: Twelve persons (clinical experts, health economists, policy makers) were interviewed. Respondents indicated that, in principle, the level of evidence with respect to effectiveness, i.e. the hierarchy of evidence based on type of study, does not necessarily have to be lower for orphan drugs than for other drugs. Furthermore, they acknowledged that pharmacoeconomic and budget impact guidelines were valid for orphan drugs. For the appraisal process, next to regular reimbursement criteria (necessity, effectiveness, cost-effectiveness and feasibility) additional criteria were either retrieved from the dossiers or suggested by the respondents on top of the criteria used for non- orphan drugs, i.e. budget impact, rarity, age of population, identifiability of patients and availability of alternative treatments. Evidence from reimbursement dossiers resembled the findings from the interviews.

Conclusions: In the opinion of stakeholders, pharmacoeconomic guidelines can be applied in the assessment of orphan drugs. Reimbursement dossiers on orphan drugs resembled these findings. In comparison to non-orphan drugs, additional criteria for appraisal were used.

Introduction

In Europe, a disease is labelled as an orphan disease when it affects less than 5 per 10,000 people [2]. It has been estimated that there are approximately 7,000 orphan diseases, affecting 30-40 million people in the European Union [1]. Historically, the pharmaceutical industry was not very keen on making investments in the rare disease field. This changed when specific legislation for rare diseases came into place. As of 2000, European orphan drug legislation followed legislation elsewhere around the world [196]. Since then, the number of approved orphan drugs has grown substantially. Since 2000, 96 orphan drugs have received marketing authorization in the EU [197]. Many more orphan drugs are under development.

Although the budget impact of a particular orphan drugs might be small, these drugs account for an increasing share of total pharmaceutical spending, with estimates ranging from 2.5% to 4.2% in 2012 in different countries [25, 198]. This is due to the increasing number of orphan drugs on the market in combination with the drugs' high prices. In addition, the number of patients being treated with orphan drugs is increasing. The present situation therefore poses policy makers for a difficult task. To reach a reimbursement decision they have to weigh the increasing expenditures on orphan drugs against the added value of orphan drugs in comparison to other treatments. Health technology assessment (HTA) uses a multidisciplinary, systematic analysis of available evidence [199] and is increasingly being used as a means of guiding policy makers through this decision making process. This process usually consists of two steps: 1) a technical assessment of available evidence presented in a reimbursement dossier; and 2) a societal appraisal of the outcomes.

In 2012, the first assessments of orphan drugs in the Netherlands – for agalsidase alfa and agalsidase beta (EMA marketing authorization in 2001; results were combined in one dossier) for treatment of Fabry disease and for alglucosidase alfa (EMA marketing authorization in 2006) for the treatment of Pompe disease – were performed by the National Health Care Institute (ZIN, formerly CVZ). The assessment consisted of two steps: a technical assessment of a reimbursement dossier by the Committee of Pharmaceutical Aid (CFH) and a societal judgment by the Appraisal Committee (ACP) [200]. ZIN's reimbursement advice is formally based on four criteria: necessity, effectiveness, cost-effectiveness and feasibility [58]. Necessity has at least two dimensions. One is the question whether the burden of disease (for instance measured in disability adjusted life years; DALYs) and medical need are large enough to reimburse treatment [58, 201]. The other is the more fundamental question whether the type of intervention justifies coverage by healthcare insurance (e.g. whether individual patients are able to afford the

drugs themselves, and whether expenses are recurrent or occur only once). For orphan drugs, both questions are answered affirmative. The second reimbursement criterion is effectiveness; only treatments proven effective should be included in the basic benefit package. The third criterion is cost-effectiveness. In assessing the cost-effectiveness of a new treatment, the incremental costs and effects of that treatment are compared to current standard of care. No formal cost per quality adjusted life year (QALY) threshold is applied in the Netherlands (an implicit maximum threshold of €80,000/QALY is used, but deviations from this threshold are possible). Feasibility entails the financial feasibility (budget impact on a macro level), administrative burden for healthcare professionals and possible substitution effects to other healthcare providers. In addition to the four formal criteria, other criteria may be considered as well. The preliminary ZIN assessments of treatments for Fabry disease and Pompe disease, which leaked to the press before the appraisal had taken place, tended to advise against reimbursement of the treatments, except for application of one of the drugs in a subpopulation (i.e. alglucosidase alfa for infants with Pompe disease). These preliminary advices were largely based on the high incremental cost-effectiveness ratios, resulting in a heated societal debate [65]. Eventually, the final advice to the Minister of Health was adapted. In 2013, the Minister of Health communicated that (after undisclosed price negotiations with the pharmaceutical companies) the three drugs will be reimbursed up to and including 2016 [63]. Since then, no further advice to the Minister of Health on any of the other orphan drugs on the policy rule were prepared. The Pompe and Fabry discussions have prompted ZIN to reconsider their policy of appraisal, resulting in a policy document on cost-effectiveness as a reimbursement criterion [54] and a policy document on orphan drugs [202].

Against this background, the aim of this study was to investigate whether the appropriate methods of effectiveness research, the Dutch guidelines for pharmacoeconomic research and guidelines for budget impact analyses are considered equally applicable to orphan drugs as to other drugs. We specifically evaluated the perceived usefulness of the four years of additional evidence development in outcomes research. Furthermore, we aimed to identify the criteria that played a key role in appraising orphan drugs. These two phases of HTA, assessment and appraisal, will be used consistently throughout the paper.

Methods

Interviews

Semi-structured interviews were conducted with stakeholders involved in the reimbursement process on orphan drugs. A sample of Dutch researchers in the orphan drug

field (clinical researchers and health economic researchers) and policy makers from ZIN (assessors of reimbursement dossiers and policy makers) were interviewed. Table 10.1 provides the background of the respondents and how they were involved in the field of orphan drugs. Twelve persons were interviewed: two clinical experts in the field of orphan diseases (Pompe disease, Mucopolysaccharidoses, Fabry disease, Gaucher disease), three health economists that have been co-writers of reimbursement dossiers for orphan drugs, two members of the CFH, one member of the ACP, and four policy makers from ZIN.

Face to face interviews were conducted between March 2014 and May 2014. The interview (Appendix 10.1) consisted of 15 questions that were divided in the two domains, assessment and appraisal, reflecting the aims of the study.

Assessment

To study the experiences during the assessment phase, we included questions on the applicability of existing guidelines on pharmacoeconomic research to orphan drug research and the added value and shortcomings of outcomes research and disease registries (questions 1-5, 7, 12-14). In answering the questions in the methodological domain, the relevant Dutch pharmacoeconomic guidelines [164] were presented to the respondents. Furthermore, the evidence-based guideline development (EBRO) classification of evidence was presented to the respondents [203]. This guideline provides a theoretical classification of clinical evidence, with a systematic review of RCTs being the highest level of evidence and expert opinion being the lowest level of evidence. A single RCT, a non-randomized comparative study, and a non-comparative study (in

Table 10.1 Background respondents

Respondent ID	Background	Specific involvement in orphan drugs
R1	Health economist	Performed cost-effectiveness analyses for an orphan drug
R2	Health economist	Performed cost-effectiveness analyses for orphan drugs
R3	Health economist	HTA association the Netherlands
R4	Clinician	Treating physician; submitted an orphan drug dossier
R5	Clinician	Treating physician; submitted multiple orphan drug dossiers
R6	CFH Member	Evaluated orphan drug dossiers
R7	CFH Member	Evaluated orphan drug dossiers
R8	Policy maker	Evaluated orphan drug dossiers
R9	Policy maker	Appraised orphan drug dossiers
R10	Policy maker	Developed specific policy on orphan drugs
R11	Policy maker	Evaluated orphan drug dossiers
R12	Policy maker	Developed specific policy on orphan drugs

that order) represent intermediate levels of evidence. Finally, respondents were asked to answer three yes/no statements, on the use of outcomes research, the value of cost-effectiveness and assessment of orphan drugs relative to assessment of non-orphan drugs.

Appraisal
To evaluate the experiences during the appraisal phase, questions on the criteria used in reimbursement decisions on orphan drugs and differences compared to non-orphan drugs (questions 6, 8-11, 15) were included.

The interviews were audiotaped with permission of the interviewee. The audiotapes and extensive notes (of both interviewers when applicable) were used to conduct the analysis. Appropriate citations are shown in italics, with the interviewee identification number (provided in Table 10.1) in square brackets.

Desk research of dossiers

Next to the interviews, we examined reimbursement dossiers for orphan drugs in the Netherlands.

Assessment
Firstly, we evaluated whether and to what extent the Dutch guidelines for pharmaco-economic research [164] and the ISPOR guidelines for budget impact analyses [68] were applied in the reimbursement dossiers. These guidelines were not specifically developed for orphan drugs.

Appraisal
Furthermore, we evaluated whether and how the four criteria (necessity, effectiveness, cost-effectiveness and feasibility) were used to appraise these orphan drugs in the appraisal reports and which additional criteria were used in decision making on orphan drugs.

Reimbursement dossiers and appraisal reports were publicly available for three orphan drugs [51, 204]. In addition, two reimbursement dossiers were available to the researchers that have been submitted to ZIN, but were not yet evaluated nor publicly available. Table 10.2 shows for which orphan drug a reimbursement dossier or appraisal report was available. All dossiers were on drugs for diseases with a prevalence of less than 1:50,000, and therefore classified as ultra-orphan drugs [205]. Statements from reimbursement dossiers are shown in italics, with the dossier identifying number (Table 10.2) indicated in square brackets.

Table 10.2 Reimbursement dossiers and appraisal reports

Dossier ID	Orphan Medicinal Product	Disease	Reimbursement dossier	Appraisal report
D1	Myozyme	Pompe disease	Yes	Yes
D2*	Fabrazyme	Fabry disease	Yes	Yes
D3*	Replagal	Fabry disease	Yes	Yes
D4	Elaprase	MPS II	Yes**	No
D5	Naglazyme	MPS VI	Yes**	No

* Combined submission; ** Not yet evaluated by ZIN

Results

Assessment

Assessment of effectiveness

Respondents [R1, R2, R3, R6, R7] indicated that, the level of evidence with respect to effectiveness of orphan, i.e. the hierarchy of evidence based on type of study according to the EBRO classification [203], drugs should not necessarily be lower than for other drugs. However, practical reasons hinder the highest level of evidence to be obtained. Respondents [R2, R4, R5, R7, R8] stated that a systematic review of multiple randomized clinical trials (RCTs), seen as the best level of evidence, is not feasible for orphan drugs because the small numbers of patients involved do not allow multiple RCTs. One respondent [R2] stated that an additional problem would be to obtain funding for a second RCT, because of the absence of treatment alternatives. The second highest level of evidence according to the EBRO classification, a single RCT, is attainable for orphan drugs according to the respondents [R1-R3, R5-R7]. However, most RCTs require adjusted study protocols due to the limited size of the patient population. Respondents [R4, R7] stated that RCTs for orphan drugs would often have to rely on surrogate endpoints, because in these neglected diseases little is known about final outcomes. Such surrogate endpoints are not yet validated and vary per disease, implying that additional studies on the association between intermediate and final outcomes are required. Given the small number of patients international trials might be necessary [R4, R6, R8, R9]. One respondent [R1] suggested that a so called N=1 trials, i.e. a multiple cross-over trial in a single patient, could be used as an alternative to RCTs.

During the temporary period of reimbursement of orphan drugs, outcomes research was performed, which was reported in the reimbursement dossiers. Over the past years, all respondents have obtained extensive experience with outcomes research, either from a performing or evaluating point of view. Overall, respondents [R1-R5, R8, R9, R11]

agreed with the statement: "*Outcomes research is a good way to substantiate evaluation of orphan drugs*", although they indicated that improvements in outcomes research design are needed. Both CFH members [R6, R7] did not agree with this statement. Opinions about the usefulness of outcomes research varied between respondents. Some respondents [R2-R5, R8-R10] labelled the outcomes research useful and stated that it provided many insights; an important strength is that characteristics of the target population, dose and duration of orphan drug usage, effectiveness and safety in daily practice are documented. Other respondents [R1, R6, R7, R9] were less positive, particularly because of the inability to fully adjust for differences in patient characteristics between intervention and comparator group: "*I have serious doubts about the added value of outcomes research*" [R7]. Various respondents [R1, R5-R7, R9] identified a number of weaknesses of outcomes research. The major weaknesses were selection bias, confounding and the absence of a clear aim of the outcomes research that was agreed by ZIN. Furthermore, respondents [R1, R5] stated that the study period of four years is too short and should be varied depending on the disease under investigation. Moreover, one respondent [R4] stated that the disease populations in the Netherlands are too small, necessitating international collaborative studies.

A sufficiently long follow-up of patients is of utmost importance, especially in orphan diseases for which knowledge about the disease is often limited. The most appropriate format of such follow-up is yet unclear. One frequently applied way of monitoring effectiveness of therapy is through (pharmacy driven) patient registries, which are sometimes mandated by the EMA as a post-marketing requirement. Respondents were not unanimous regarding the added value of patient registries. Some respondents [R1, R2, R5, R6, R12] stated that registries are useful for generating hypotheses and observation of daily practice, especially on long-term effectiveness and safety. However, some respondents [R1, R2, R7] argued that causal relationships cannot be established with the use of this type of registries. Respondents stated that the following improvements were required to make registries more useful: registries should include all patients with a particular orphan disease, regardless of their treatment [R4]; data should be collected internationally using standardized outcome measures [R2, R3, R8, R12]; inclusion in a registry should be a condition for reimbursement [R4, R9]; the influence (on data collection, analyses and reporting) of the industry should be decreased [R2, R4, R5, R8]; time and costs for doctors should be acknowledged [R5] and all relevant data should be collected (e.g. data on productivity losses are necessary for adopting the societal perspective in economic evaluations) [R4]. Natural course data are often lacking at the time the drug receives market authorization. Therefore, data collection should preferably be started before a drug comes to the market. This facilitates that treatment data can be compared with natural course data when a drug comes available.

Assessment of cost-effectiveness

Table 10.3 describes the application of pharmacoeconomic guidelines to orphan drugs as perceived by respondents and observed in dossiers. All respondents acknowledged that, in theory, the Dutch pharmacoeconomic guidelines are all valid to orphan drugs. In practice, respondents [R1, R5, R7] indicated particular difficulties with collecting data on the appropriate comparator treatment, because alternative treatments generally do not exist for (ultra-) orphan diseases. Timely start of data collection (prior to the availability of the orphan drug and before any selection bias can take place) was claimed to be essential. The relevance of guideline 5 on identifying and measuring costs was questioned in one of the interviews: "*Some costs are irrelevant in comparison to the high drug prices*" [R11]. One respondent claimed that quality of life has not been studied sufficiently in rare diseases with slowly progressive disease courses [R4].

Table 10.3 also shows that the evidence from the reimbursement dossiers confirmed the claims made by respondents concerning the applicability of the pharmacoeconomic guidelines. In all cases, application of the guidelines was feasible. However, a healthcare perspective was adopted in the base case analyses and productivity costs were included in scenario analyses, while the guidelines prescribe that the societal perspective (including productivity costs) should be adopted [D2, D3]. In some instances the dossiers' authors argued that some guidelines were not relevant. The dossier on treatment for Fabry disease reported that a detailed breakdown of healthcare costs was not considered relevant as these costs were only limited compared to cost of treatment [D2, D3]. Finally, probabilistic sensitivity analyses were not reported in the dossiers for MPS II and MPS VI [D4, D5].

Assessment of budget impact

None of the respondents identified obstacles to carry out a budget impact analysis for orphan drugs. In contrast, some respondents [R4, R5, R7, R9, R11] held the opinion that it might be easier than for other drugs, because of concentration of patients and knowledge in a single or a few number of clinical expert centres.

The ISPOR guidelines for budget impact analyses (described elsewhere [68]) were found to be applicable as well, except for the presence of sensitivity analyses. However, the absence of sensitivity analyses was not due to technical obstacles, but because sensitivity analyses were not required by ZIN in the reimbursement dossier.

Table 10.3 Application of pharmacoeconomic guidelines for orphan drugs: perception interviewees and assessment reimbursement dossiers

Pharmacoeconomic guidelines	Potential problems identified by interviewees	CFH dossiers (technical assessment)
1. Perspective		
1.1 Societal perspective – incorporate all costs and effects	No deviations from guidelines necessary	Primary analyses from healthcare perspective (but not due to technical difficulties) [D2, D3]
2. Comparator		
2.1 Comparison with standard treatment or usual treatment	Data collection can be difficult [R1, R7]; Essential to start early on with data collection in comparator group (before therapy becomes available) /natural course [R5]	No deviations from guidelines observed
2.2 Same comparator as claim therapeutic added value	No deviations from guidelines necessary	No deviations from guidelines observed
3. Type of analyses		
3.1 CUA when quality of life is an important effect	No deviations from guidelines necessary	No deviations from guidelines observed
3.2 CEA when no effect on quality of life	No deviations from guidelines necessary	Not applicable
3.3 CMA when no therapeutic added value	No deviations from guidelines necessary	Not applicable
4. Time horizon		
4.1 Appropriate time horizon	No deviations from guidelines necessary	No deviations from guidelines observed
5. Costs - identification, - measurement, and – valuation		
5.1 Use of Dutch costing manual	Some cost parameters are deemed less important because of high treatment costs [R11]	No deviations from guidelines observed
5.1a Direct and indirect costs within and outside healthcare sector	Productivity costs can be included, but usefulness needs to be assessed prior to study start [R2]	Primary analyses from healthcare perspective (but not due to technical difficulties) [D2, D3]; Paediatric patients; productivity costs not applicable [D4, D5]
5.1b Friction cost method to calculate productivity losses	No deviations from guidelines necessary	Not applicable; primary analyses from healthcare perspective [D2, D3]; Paediatric patients; productivity costs not applicable [D4, D5]

Table 10.3 Application of pharmacoeconomic guidelines for orphan drugs: perception interviewees and assessment reimbursement dossiers (continued)

Pharmacoeconomic guidelines	Potential problems identified by interviewees	CFH dossiers (technical assessment)
5.1c Reporting with and without productivity losses	No deviations from guidelines necessary	Reported only with productivity losses (but not due to technical difficulties) [D1]; Primary analyses from healthcare perspective (but not due to technical difficulties) [D2, D3]; Paediatric patients; productivity costs not applicable [D4, D5]
6. Valuing quality of life and QALYs		
6.1 Effects measured in QALYs when CUA is applied	Quality of life measurement is difficult in rare diseases with progressive disease courses [R4]	No deviations from guidelines observed
6.1a Valuation and survival reported separately	No deviations from guidelines necessary	Not reported separately (but not due to technical difficulties) [D2, D3]
7. Modelling		
7.1 Transparent model as simple as possible	No deviations from guidelines necessary	No deviations from guidelines observed
7.2 Preferably based on peer-reviewed publications	Little is known about the disease [R4]	Not applicable
8. Incremental analyses		
8.1 Reporting of incremental costs and effects	No deviations from guidelines necessary	No deviations from guidelines observed
9. Discounting future effects and costs		
9.1 Primary analyses: costs 4%, effects 1,5%	No deviations from guidelines necessary	No deviations from guidelines observed
10. Uncertainty analyses		
10.1 Quantifying the effects of assumptions on results	No deviations from guidelines necessary	No deviations from guidelines observed
10.2 PSA in modelling studies	No deviations from guidelines necessary	PSA were not reported [D4, D5]
10.3 Explanation of parameters and ranges	No deviations from guidelines necessary	No deviations from guidelines observed
11. Expert panel		
11.1 Consultation with clinical experts if data are absent	No deviations from guidelines necessary	No deviations from guidelines observed

* Respondent ID and Dossier ID are provided in brackets

Appraisal

Generic appraisal criteria

Eight respondents [R1, R2, R4, R6-R10] agreed with the statement: "*Orphan drugs should be appraised in the same way (i.e. using the same criteria)* as other *drugs*"; in theory the same criteria should apply. Two respondents [R3, R5] did not agree; they did not think it would be feasible to apply the same criteria.

Table 10.4 shows the criteria that were used in the appraisal of orphan drugs. According to the respondents, all four criteria (necessity, effectiveness, cost-effectiveness, and feasibility) used to evaluate new technologies in the Netherlands are also applicable to orphan drugs. "*All criteria are important, but the weighting differs from other drugs*" [R8]. Respondents stated that every orphan drug is likely to pass the necessity criterion because these drugs are used to treat severe diseases. "*Effectiveness and cost-effectiveness will be the bottlenecks*" [R1]. One respondent [R5] stated that cost-effectiveness research for orphan drugs is not needed.

Table 10.4 Criteria reimbursement decisions on orphan drugs

Criterion	Remarks by interviewees	Remarks in ACP dossiers (societal appraisal)
Necessity	Ethical factors are captured by necessity [R8, R12] Every drug will pass this criterion [R1]	High disease burden [D1-D3] Treatment costs are too high to be borne by an individual patient [D1-D3]
Effectiveness	Effectiveness and cost-effectiveness will be the bottlenecks [R1] Effectiveness is the most important criterion [R5]	Study design limits firm statements on effectiveness [D2, D3] Unanswered questions on (long-term) effects, diagnostics [D2, D3] Unanswered questions on identifying good responders [D1]
Cost-effectiveness	Effectiveness and cost-effectiveness will be the bottlenecks [R1]	Disease burden, rarity and health risks increase acceptable threshold [D1-D3] Uncertainty, high dosage for some patients and budget impact decrease acceptable threshold [D1] Low budget impact, identifiability and appropriate use increase threshold [D2, D3]
Feasibility	Budget impact is captured by feasibility [R12]	Budget impact is captured by feasibility [D1-D3] Ethical factors are captured by feasibility [D1]
Additional criteria	Budget impact [R2-R5, R7, R9, R12] Rarity [R2-R5, R7, R8, R12] Age [R3-R5, R7, R12] Identifiability of patients [R7, R12] Availability of alternative treatments [R3, R6, R7]	Rarity [D1-D3] Identifiability of patients [D2, D3] Health risks [D1]

The four criteria normally used for reimbursement decisions in the Netherlands for drugs (necessity, effectiveness, cost-effectiveness and feasibility) were sequentially described in the appraisal reports [D1-D3]. The evidence from the appraisal reports showed that all three appraised orphan drugs passed the necessity criterion, whereas effectiveness and cost-effectiveness were not judged as sufficient. The appraisal reports showed that budget impact was included as part of the feasibility criterion.

Additional appraisal criteria used for orphan drugs
The last row of Table 10.4 shows criteria additional to the formal criteria that were suggested to be used in reimbursement decisions on orphan drugs during the interviews and were found in reimbursement dossiers for orphan drugs. According to the respondents budget impact [R2, R3, R6], rarity [R2-R5, R7, R8, R12], age of the target population [R1, R4-R8, R12], identifiable patients versus statistical patients [R7, R12], and availability of alternative treatment options [R3, R7] play a more important role in the appraisal for orphan drugs than non-orphan drugs. Additional appraisal criteria identified in the reimbursement dossiers were disease burden [D2, D3], rarity [D1-D3], identifiability of patients [D2, D3], and health risks [D1].

Budget impact was thought to play a role in the appraisal phase; i.e. drugs with a smaller budget impact were assumed to have an increased chance of reimbursement. However, not all respondents [R1, R6, R7, R9] were convinced that budget impact should play a role in reimbursement decisions. In addition, two respondents [R4, R5] stated that the growing budget impact is not sustainable in the long- run, due to the increasing number of orphan drug, and the associated increasing pressure on the total healthcare budget. Some respondents [R1, R7, R8] mentioned that the budget impact of all available orphan drugs is already substantial.

Some respondents [R2-R5, R7, R8, R12] stated that rarity, i.e. the number of patients, plays a role in the evaluation of orphan drugs, particularly in combination with budget impact (i.e. budget impact of an orphan drug is small as a consequence of the limited number of patients). Three respondents [R4, R6, R9] stated that this was not appropriate. Rarity was also mentioned in the reimbursement dossiers as a factor that influences reimbursement decisions: "*The government must ensure that patients do not suffer from the fact that they have a disease, condition or handicap that occurs sporadically*" [D1].

Age of the patient population was thought to play a role in reimbursement decisions; i.e. younger patients are prioritized over older patients. Many respondents [R1, R3-R5] believed that this was appropriate. However, this is not specific to orphan drugs.

Identifiability, i.e. the preference for recognizable patients rather than unidentified (statistical) patients, also plays a role in reimbursement decisions [R7, R12]. Policy makers might decide differently in the presence of patients during public appraisal committee meetings or when patients appear in the media. "*Emotions play a bigger role when patients can be identified*" [R7]. One respondent [R12] argued that this is not wrong, as the decision concerns these particular patients. Identifiability of patients was also mentioned in the dossiers [D2, D3] as a factor affecting reimbursement decisions.

Availability of alternative treatment was considered to be important in reimbursement decisions as well [R6, R7]. Drugs for diseases for which no treatment alternatives are available are more likely to be reimbursed. Respondents believed that this was appropriate.

Health risks was another factor identified in a reimbursement dossier that can affect reimbursement decisions; when neglecting a disease can constitute a danger to patients or the environment it could be useful to remove financial obstacles [D1], although this might not be restricted to orphan drugs.

One respondent [R4] claimed that impact beyond health outcomes should be the most important factor in decisions. Another respondent [R5] argued that stimulation of science and knowledge development should be acknowledged in the appraisal process. It is not clear if these aspects are currently taken into account in reimbursement decisions.

According to the respondents [R1, R3-R9, R12], patients, physicians and the general public should be involved in the appraisal of orphan drugs. In addition, one respondent [R1] indicated that the societal view should be represented in the appraisal process because public resources are used to fund treatment. Various respondents [R4, R7, R8, R12] argued that these stakeholders should have a prominent role at the beginning of the trajectory, particularly to discuss appropriate endpoints of the outcomes research and evaluation process. "*Patients and industry should be involved early on in the process, to determine appropriate endpoints. However, the assessment should be done by an independent organization*" [R8].

Future directions

Many respondents [R4, R6, R8, R9] indicated that international collaboration is crucial for data collection to increase sample size. Many RCT's for orphan drugs already take place in an international, multi-centre setting. One respondent [R8] indicated that collaboration between HTA agencies, possibly supported and facilitated by European network

of Health Technology Assessment (EUnetHTA), might alleviate problems concerning transferability, facilitating international pharmacoeconomic studies to be set up.

Another recurring point made by the respondents [R4, R5, R8, R12] was the need for a timely debate between decision makers and researchers, patient organizations and clinicians. These discussions should take place before market introduction of a drug. During these discussions, appropriate outcome measures for (long term) effectiveness should be decided on and effectiveness thresholds should be defined. Furthermore, respondents claimed that clear start and stopping rules should be established, to avoid that treatment is continued in patients with insufficient treatment responses. These can have a major effect on (cost-) effectiveness of the therapy. Finally, appropriate disease-specific time horizons for outcomes research should be agreed upon instead of a uniform 4-year period.

Definition of orphan diseases

Respondents from various backgrounds [R3, R6-R8, R11] stated that the current prevalence-threshold that is used to define orphan diseases (i.e. 5 per 10.000) is too high. "Using *the current definition it is still possible to find a study population in the Netherlands consisting of thousands of patients*" [R11]. Furthermore, orphan drug legislation is sometimes misused by pharmaceutical companies by subdividing a more prevalent disease into smaller subgroups to obtain orphan status (known as 'salami slicing' or 'disease stratification' [206]). Existing policies to stimulate research and development in orphan drugs should not apply for such artificial sub indications, but should only be applied to treatments for 'genuine' orphan diseases, i.e. those diseases with a low disease prevalence.

Discussion

This study described the applicability of Dutch HTA guidelines and reimbursement criteria for orphan drugs in the Netherlands. According to interviewees and as observed from the Dutch reimbursement dossiers available for orphan drugs, requirements with respect to level of evidence on effectiveness, pharmacoeconomic studies and budget impact analyses were similar to non-orphan drugs. However, in practice orphan drugs face particular problems which policy makers do take into account.

Prices for orphan drugs can be very high; estimated annual treatment cost ranged of orphan drugs on the specific Dutch policy rule on orphan drugs were up to €600,000 per patient [207]. Prices are high because they are based on perceived value and not on

actual cost of R&D, manufacturing and distribution cost plus a reasonable profit margin. In many countries, the unfavourable cost-effectiveness ratio is improved by undisclosed negotiations about reduction in drug price. That the price remains secret creates a problem for future HTA studies that use the orphan drug as comparator. Moreover, the negotiation power of a single country may not be large enough to achieve substantial price reductions. If countries join forces in case a price is considered unreasonably high, greater reduction may be achieved.

Recently, ZIN published a policy document on the appraisal of orphan drugs, which showed many similarities to our findings [202]. ZIN concluded that, in principle, there are no reasons why the appraisal of orphan drugs should be different from non-orphan drugs. Furthermore, they describe that other factors can make an unfavourable cost-effectiveness ratio acceptable. ZIN provides the following examples of such criteria: whether alternative treatments exist; the magnitude of improvements in quality of life; and future foreseen improvements in the cost-effectiveness. Similar to the Dutch situation, Canadian policy makers claimed that there was no separate decision making process required for orphan drugs in place in Canada [208]. In contrast, drugs for very rare diseases are assessed distinctly in England and Wales [177]. In England, the vulnerability of the small patient populations in combination with limited alternative treatments, the nature and extent of the evidence, and the challenge to derive a reasonable return on investment for manufacturers are included in the decision making process for drugs for very rare diseases [209]. In Wales, other criteria are taken into account when cost-effectiveness for orphan drugs is unfavourable, namely disease severity, unmet need, whether a treatment is a disease modifier, whether the treatment can serve as a bridging therapy for a definitive therapy under development, the innovative nature of treatment, and added value to patient and family not yet reflected in QALY [210]. With respect to appraisal, Belgian policy makers also stated that other factors, including innovative nature of the drug, economic importance and ethical arguments, do play a role in reimbursement decisions for orphan drugs, than for other drugs [211].

Respondents identified several problems of outcomes research. The role of outcomes research in reimbursement decisions needs to be better specified, especially in relation to available evidence from RCTs. The availability of RCTs appeared not sufficient for positive reimbursement decisions; but whether this is due to the perception that effectiveness of treatments were too limited or due to other aspects (such as treatment costs or use of surrogate markers) is not always clear.

One respondent stated that N=1 trials could be an alternative to traditional RCTs. In such a trial design, treatment effects are measured in individual patients, in a cross-over

design [212]. Each patient receives both treatments sequentially for a given period and effectiveness is measured by the difference in outcomes between the two periods. As such, patients serve as their own controls. The concept of N=1 trials is interesting for orphan drugs, as large numbers of patients are not a prerequisite to study treatment effects. However, N=1 trials do require that the disease is relatively stable, and that the effect of treatment is washed out shortly after discontinuation of treatment, in order for patients to return to a disease state that is comparable to a disease state prior to the intervention [213]. This limits the number of orphan drugs in which N=1 trials can provide an alternative to traditional RCTs.

Respondents also acknowledged the importance of discussing the design of outcomes research with reimbursement authorities, to manage expectations on the deliverables. In this respect, endpoints should also be discussed, as some endpoints might not be feasible for all patients; e.g. walking test cannot be performed by patients in a wheelchair.

Our study has a number of limitations. Various stakeholders from different fields of expertise were interviewed during the course of this study. However, representatives from some stakeholder groups, most notably representatives of patients and of the Ministry of Health, could not be included in the study, despite multiple invitations.

Only a limited number of reimbursement dossiers and appraisal reports were available at the time of this study, due to delayed assessment by ZIN. The dossiers that were available were on ultra-orphan drugs. Therefore, the generalizability of the findings from the dossiers and reports to other orphan drugs is unclear.

Decision making might be different for orphan drugs and other drugs, despite the fact that the same requirements apply in theory. Evidence from the literature shows that, in Belgium, the percentage of orphan drugs that are reimbursed is higher than for other drugs, even with limited quality of evidence [214]. This suggests that other factors do play a role in reimbursement decisions. A combination of various factors (the absence of an alternative treatment, the severity of the disease and the relatively small budget impact for an individual orphan drug) might provide reasons for high reimbursement probabilities for orphan drugs. This hints at a potential role for multi-criteria decision analyses (MCDA). MCDA aims to improve transparency, consistency, accountability, credibility, and acceptability of decision making by assessing treatment alternatives on the basis of explicit aims, for which measurable criteria are established and weighted [215]. In essence, MCDA calculates a weighted composite score for each alternative. MCDA allows for transparent and systematic trade-offs to be made between multiple, and sometimes conflicting criteria. Because the criteria weights can be elicited from

different perspectives, i.e. from different groups of stakeholders, it makes differences in opinion among stakeholders about the relative importance of criteria more explicit [216]. For example, an MCDA among treating physicians is likely to demonstrate the importance of finally having a treatment for patients for whom formerly no treatment existed. An MCDA among payers and policy makers is likely to demonstrate the importance of the cost criterion. However, MCDA does not solve these differences in opinion among the different stakeholders. It just makes them more transparent. In the end, even when applying MCDA, there will be debate about which criteria should be included in such an analysis and which opinions should count most. One of the most heavily debated issues is whether or not to include costs as a criterion in MCDA. A recent review found that 10 out of 23 MCDAs included cost as a criterion [217]. By including costs as a criterion, respondents explicitly trade-off costs against the other criteria in the analysis, which is equivalent to estimating willingness to pay values for benefits [218]. Those who oppose including costs as a criterion argue that this does not adequately capture the opportunity costs of alternative uses of healthcare resources [219]. They argue that MCDA creates a new composite score of benefit and that the main question to be answered is what the opportunity costs are of one unit of additional benefit on that composite score – in other words, how much additional money can be spent at maximum for one unit of this composite score. It is widely recognized that MCDA does not provide a solution to the challenge of estimating opportunity costs [218].

Acknowledgements

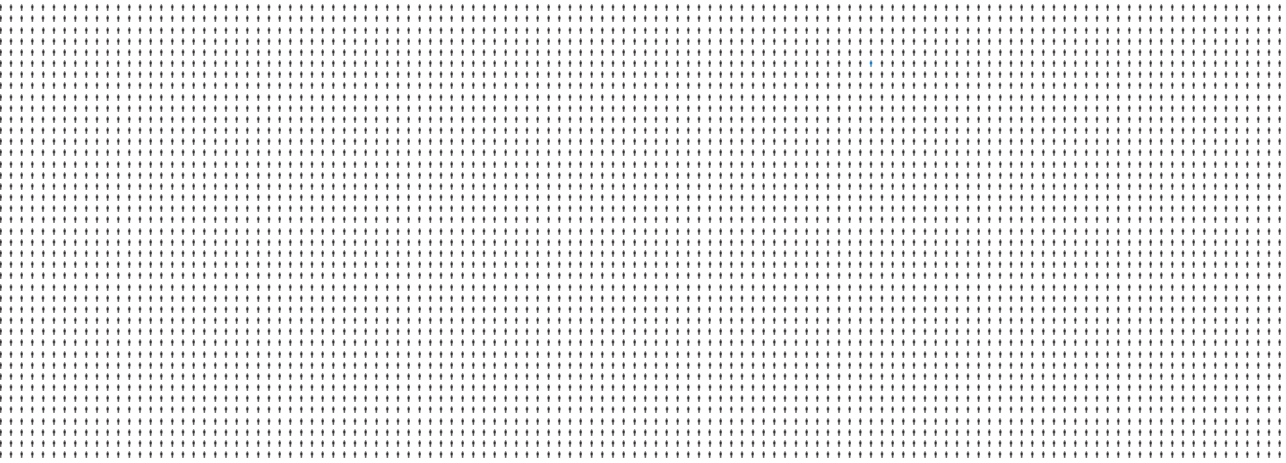
The authors would like to thank all the interviewees for their participation in our study. This study was financially supported by the Netherlands Organization for Health Research and Development (ZonMw; grant no. 152002045).

Appendix 10.1

Interview questions

1. What level of evidence for effectiveness (EBRO classification) can be demanded for orphan drugs? *The EBRO classification was presented to the respondent during the interview.*
2. To what extent can the current pharmacoeconomic guidelines be applied to orphan drugs? What aspects need to be changed? *The pharmacoeconomic guidelines were presented to the respondent during the interview.*
3. What are the obstacles to perform a budget impact analysis?
4. What are the differences compared to non-orphan diseases regarding clinical and pharmacoeconomic research for non-orphan diseases?
5. How useful is the current design of outcomes research for rare diseases? What are the strengths and weaknesses of the current design?
6. To what extent are reimbursement decisions for orphan drugs based on the four reimbursement criteria as described in the Dutch health insurance law, namely: necessity, effectiveness, cost-effectiveness and feasibility?
7. To what extent can evidence based medicine be applied to orphan drugs?
8. What are the differences with respect to reimbursement decisions for non-orphan diseases? What other aspects play a role in evaluating orphan drugs, apart from necessity, effectiveness, cost-effectiveness and feasibility?
9. Does the absolute number of patients play a role in evaluation of orphan drugs? If yes, is that just? If no, should it play a role?
10. Does the age of patients play a role in evaluation of orphan drugs? If yes, is that just? If no, should it play a role?
11. Does the total budget impact play a role in evaluation of orphan drugs? If yes, is that just? If no, should it play a role?
12. What should be the role for HTA-research in the evaluation of orphan drugs?
13. What is the contribution of HTA-research in the debate on orphan drugs? Should this knowledge be applied in the reimbursement decisions?
14. What role do disease registries play in orphan drugs? Is this an optimal role?
15. What stakeholders should have a role in the evaluation of orphan drugs? What role should they have?

A. Orphan drugs should be assessed in the same way as other drugs.
B. Cost-effectiveness research is redundant for orphan drugs.
C. Outcomes research is a good way to substantiate evaluation of orphan drugs.



CHAPTER 11 Discussion

Rationale

The increasing availability of orphan drugs has enabled thousands of patients with rare diseases for which treatments did not exist in the past to receive treatment. Worldwide, these treatments have improved the lives of many patients and their families [220]. Orphan drugs can increase patients' life expectancy, improve quality of life and enable participation in society. Furthermore, orphan drugs can reduce hospitalizations and associated costs [221]. Unfortunately, orphan drugs are often very expensive. Annual treatment costs can easily exceed €100,000 per patient [18]. Combined with the various incentives in the current orphan drug legislation (described in the introduction), this has resulted in the fact that from a financial perspective, profitability of orphan drugs is higher than for non-orphan drugs [222]. As a result, the budget impact of orphan drugs has been increasing. However, healthcare resources are scarce and budgets are constrained. Thus making choices on what to reimburse and what not is unavoidable. When reimbursing a new drug, fewer resources are available for other drugs or services, unless health insurance premiums or taxes are increased to fund the rising healthcare expenditures. To maximize health gains given a particular budget constraint, the new drug should at least generate as much health as the drugs and services that are displaced. The forgone benefits of these alternative uses of resources are called opportunity costs of the new drug [52]. In health technology assessment (HTA) studies and in particular in cost-effectiveness studies, the health gains are compared to the additional costs of the intervention, and expressed as a cost per quality adjusted life year (QALY) ratio. Under a given budget constraint, health is maximized if the cost per QALY ratio is below a specific threshold value, which represents the opportunity costs per QALY.

This thesis aimed to conduct HTA studies of ERT in Pompe disease and contribute to decision making with respect to reimbursement of orphan drugs. This purpose was addressed in three parts: 1) assessing the burden of disease from different perspectives; 2) conducting cost-effectiveness analyses of ERT in Pompe disease; and 3) evaluating the use of HTA in decision making on orphan drugs. Pompe disease was considered to be a suitable case study to demonstrate the issues associated with HTA in orphan drugs for several reasons, including that it is the first treatment for a rare inheritable muscle disorder, there has been a long tradition of international collaboration among experts in this disease and the availability of a patient registry that was initiated years before ERT was approved by the European Medicines Agency.

Main findings

Objective 1: Assessing the burden of disease from different perspectives

Chapter 2 described the burden of disease from a financial perspective, assessing the budget impact of orphan drugs in the Netherlands. It described that the number of orphan drugs available in the Netherlands increased from 11 to 43 over the period 2006-2012. The number of patients using these drugs increased from 2,189 in 2006 to 9,762 in 2012, with the majority of these patients being treated in an outpatient setting. As a result, the impact on the Dutch healthcare budget has also increased considerably, from €61 million in 2006 to €260 million in 2012. The proportion of total pharmaceutical expenditures spent on orphan drugs increased from 1.1% in 2006 to 4.2% in 2012.

Chapter 3 addressed the burden of Pompe disease from a patient's perspective and a societal perspective by investigating the impact of the disease on patient's quality of life, and societal costs (including healthcare use, productivity loss, and informal care) related to the natural course of the disease without treatment. Patients untreated with ERT had an average utility of 0.72, constituting a 17% decrease compared to the general Dutch population. The impact of the disease on the patient's life was further illustrated by the finding that the majority of patients had stopped working or had reduced their working hours. Patients received 8 hours of home care and 19 hours of informal care per week. Average societal costs were €22,475 per patient per year and were primarily related to home care and nursing home admissions. Annual costs could be as high as €169,539 per patient. Both quality of life and costs were related to the severity of the disease.

Chapter 4 described the ability of two generic questionnaires (EQ-5D and SF-6D) to measure the health-related quality of life for patients with Pompe disease. Utility values derived from both instruments were similar. However, both instruments had some limitations. The EQ-5D showed a better discrimination between utilities of patients with and without wheelchair use and ventilator use than the SF-6D, whereas the SF-6D seemed to be more responsive to changes in respiratory function and muscle strength over time.

The fifth chapter addressed the burden of Pompe disease from the perspective of the informal caregiver. The study showed that the disease not only affected the patient himself, but also the environment of the patient. On average, caregivers (e.g. parents, spouses, other family members, and friends of the patient) provided 17.7 hours of informal care per week. Caregivers reported to experience both mental and physical health problems due to caregiving. Caregivers also indicated that they derived happiness from providing informal care to their loved ones.

In chapter 6, a conceptual disease model was presented that aimed to link clinical outcomes to quality of life in Pompe disease. This model included enzyme activity levels, muscle strength, respiratory function, fatigue, level of handicap, general health perceptions and health related quality of life. The conceptual model is used as an important building block in the cost-effectiveness study of ERT compared to standard of care for adult patients with Pompe disease.

Objective 2: Cost-effectiveness analyses of ERT in Pompe disease

In chapter 7, the first chapter of the second part of this thesis, the cost-effectiveness of ERT in adult Pompe disease was addressed. Using two scenarios (a worse case scenario in which we include the survival gains in the observed period, but assume no gains in survival beyond the observed period, and a best case scenario with extrapolation of survival gains), the cost-effectiveness model showed a substantial effect of ERT on life expectancy, especially when survival gains were extrapolated to a lifetime horizon. Quality of life also increased due to therapy. Associated lifetime incremental costs were between €6.5 million and €7.6 million per patient. Incremental costs per life year gained were €3.4 million and incremental costs per quality adjusted life year (QALY) were €3.2 million without extrapolation of survival gains, or €1.4 million per life year gained and €1.8 million per QALY when survival gains were extrapolated.

The next chapter described the cost-effectiveness of ERT compared to standard of care in classic-infantile patients. The cost-effectiveness model showed enormous effects on survival (13.4 life years gained). At the same time, costs of ERT treatment were substantial (€7.0 million, using a lifetime time horizon). The incremental cost-effectiveness ratios (ICERs) were €0.5 million per incremental life year and €1.0 million per QALY gained.

Objective 3: Evaluating the use of HTA in decision making on orphan drugs

The third part of this thesis discusses the use of HTA in decision making on orphan drugs. It starts with chapter 9 revealing the international differences that exist in reimbursement decisions on ERT in Pompe disease. Most countries (Belgium, England, France and Italy) reimbursed ERT for all patients, while ERT was only reimbursed for classic-infantile and juvenile patients in Wales. In Scotland ERT was not reimbursed. More transparency on decision making is needed to determine whether international differences in reimbursement decisions resulted from differences in the technical assessment of available evidence or the societal appraisal of the evidence, or both. This chapter also provided a link to chapter 10, which assessed how reimbursement decisions are made for orphan drugs. This chapter did not focus on Pompe disease, but deals with orphan drugs in general.

Chapter 10 showed that, in principle, assessment of orphan drugs is not different from assessment of non-orphan drugs; Dutch pharmacoeconomic guidelines for non-orphan drugs were judged by the interviewees to be applicable for orphan drugs. Furthermore, the same criteria (i.e. necessity, effectiveness, cost-effectiveness and feasibility) are applied in reimbursement decisions for orphan drugs, although budget impact, age, rarity, whether alternative treatments are available, and identifiability of patients were suggested by respondents as additional criteria in reimbursement decisions on orphan drugs.

The main conclusions of the chapters of this thesis are summarized in Table 11.1. In the remainder of this chapter, the implications of the various studies for policy making are discussed. Furthermore, this chapter describes methodological challenges in research on orphan drugs, contemplates on the issues related to policy making on orphan drugs and discusses options for future research.

Orphan drug policy in the Netherlands: the example of Pompe disease

Preliminary advice on reimbursement of ERT for Pompe disease

ERT for the treatment of Pompe disease was the first newly registered orphan drug that was listed on the policy rule for orphan drugs. This policy rule was installed in 2006. Orphan drugs listed on this policy rule were reimbursed under a coverage with evidence development (CED) scheme, for a period of four years. During these four years,

Table 11.1 Main conclusions from chapters 2 to 10

Chapter 2	Budget impact of orphan drugs has increased considerably
Chapter 3	Pompe disease is associated with a significant burden of illness in terms of quality of life and societal costs
Chapter 4	EQ-5D and SF-6D are equally appropriate to assessing quality of life of patients with Pompe disease
Chapter 5	Caregiving for Pompe disease patients is burdensome, but also provides happiness to caregivers
Chapter 6	Clinical factors can be linked, through symptom status, functional status and health perceptions, to quality of life for patients with Pompe disease
Chapter 7	ERT in adult Pompe disease leads to substantial survival gains but also to high costs, resulting in a high ICER
Chapter 8	ERT in classic-infantile Pompe patients leads to major survival gains and high costs, resulting in a high ICER
Chapter 9	Reimbursement status of ERT for Pompe disease varies between European countries
Chapter 10	HTA guidelines apply to orphan drugs as they do to non-orphan drugs, but additional criteria are used in reimbursement decisions

additional research had to be performed on the effectiveness, cost-effectiveness and budget impact of the drug. The evidence that was gathered during the CED period was submitted to the Dutch National Health Care Institute (ZIN; formerly Health Care Insurance Board, CVZ) in 2011, and included preliminary results of the information presented in this thesis.

The quantification of burden of illness (chapter 2) was used to determine the severity of the disease and, as such, to assess (part of) the necessity criterion. Furthermore, results on quality of life and societal costs for patients not receiving ERT were included in the reimbursement dossier.

For classic-infantile patients the reimbursement dossier included approximately the same cost-effectiveness ratio as reported in chapter 8 of this thesis. Chapter 7 presents a more recent and accurate estimate of the cost-effectiveness of ERT in adult patients as included in the reimbursement dossier.

The information in the reimbursement dossier was used by ZIN to draft a preliminary advice to the Minister of Health in 2012 [62]. The advice stated that reimbursement of ERT for classic-infantile patients had to be continued, but reimbursement of ERT for other patients should be discontinued.

Different perspectives on the preliminary advice

The preliminary advice was leaked to the press and a heated societal debate followed that clearly illustrated the different viewpoints from which the different stakeholders looked at the same evidence that was available at the time. Especially the results of the pivotal clinical trial in adult Pompe disease were interpreted very differently by various stakeholders, which is understandable considering the different reference points that the stakeholders may use. The pivotal trial reported a significant increase of 28 meters on the six minute walk test and a significant 3.4 percentage point increase in forced vital capacity compared to placebo [46]. Such improvements can be considered considerable when the reference point is a continuous deterioration of ambulatory and respiratory function if left untreated, whereas the same improvements can be considered less important when the reference point is another highly effective treatment. The preliminary advice stated that the effectiveness of ERT in adult patients was limited [62]. ZIN also stated in the preliminary report that the therapy was not considered cost-effective. ZIN invited various stakeholders to respond to the draft advice. The written replies illustrated the stakeholders' different perspectives, which are summarized below.

Perspective of the patient

Patients and patient organizations responded that these conclusions did not correspond to their own experiences. They claimed that the effectiveness of ERT was not in question. Individual patients and their families appeared on television and were interviewed by newspapers to express the positive effects of treatment. Patient organizations were also convinced that the advice would endanger the development of drugs for other orphan diseases (which were spurred by the development of ERT in Pompe disease).

Perspective of the physician

Physicians from Erasmus MC stressed that Pompe disease is a continuous spectrum ranging from the classic-infantile form to presentations in childhood and late adulthood. All patients share the same but different degree of inheritable enzyme deficiency. Studies in infants had provided the proof of concept. Also, based on prospectively gathered data, physicians claimed that discontinuation of reimbursement would seriously threaten patients' health, particularly as no alternative treatments existed. Physicians stressed that important effects of treatment had been shown but that the follow-up period of the studies was too short to judge the full effect of long-term ERT. They also felt that it was unethical and socially irresponsible to withdraw a treatment with proven effectiveness from patients that previously received it. Physicians also expressed their concerns about the broader negative effects of the advice on innovation for other orphan drugs and advancement of knowledge brought by this therapy.

Perspective of the pharmaceutical company

Genzyme, the pharmaceutical company that marketed alglucosidase alfa, also felt that the effectiveness of ERT was attenuated by ZIN. Genzyme further claimed that it was irresponsible to withhold an available treatment from patients on the basis of financial reasons only and stated that the legal grounds for the advice were lacking. The branche organization of pharmaceutical companies in the Netherlands also stressed that temporarily reimbursing the drug gives hope to and raises the expectations of patients. This organization also claimed a controversy in on the one hand raising incentives to develop orphan drugs by orphan drug regulation, and on the other hand not reimbursing developed orphan drugs.

Perspective of the general public

The Dutch media provided a platform for the public debate. On the one hand, some opponents of the advice from the general public claimed that reimbursement should be continued, because patients had not chosen to suffer from this rare disease and should therefore not be neglected because of the low prevalence of this disease. They further argued that a well-developed country such as the Netherlands should never put

patients' health at risk for financial reasons. On the other hand, proponents of the advice to discontinue reimbursement argued that the advice was justified in order to keep the healthcare system financially sustainable. They claimed that limits had to be set on what we should be willing to pay for some healthcare services, because these resources are no longer available to fund other services that may generate greater health benefits.

Perspective of policy makers
Many political parties and Members of Parliament did not support the advice of ZIN for the same reasons that were raised by other stakeholders. They probably also considered the electoral consequences. ZIN did not publicly respond to the discussion. The Minister of Health awaited the final report to be presented before commenting on the issue.

In the heat of this debate, the HTA researchers did their best to remain objective and concentrate on the available evidence at hand.

Final reimbursement decision on ERT for Pompe disease

The preliminary advice was discussed during the meeting of the Appraisal Committee (ACP) in September 2012. During the meeting, the various perspectives were expressed by various stakeholders in addition to their written responses. All these perspectives were discussed by the members of the ACP. Following the meeting, ZIN published its final advice to the Minister, which read that reimbursement of ERT for all patients with Pompe disease should be continued [51]. In 2012, the Minister engaged in price negotiations with Genzyme. In 2013, the Minister consequently announced to continue reimbursement of ERT for all eligible patients in the Netherlands [63]. The outcomes of the price negotiations were confidential, but according to the Minister, the price of the drug was reduced substantially by the pharmaceutical company. The reduced price results in a lower cost-effectiveness ratio, albeit that the price is unlikely to be reduced to the extent that ERT would meet conventional cost-effectiveness thresholds. A condition for the positive reimbursement decision was the further development and implementation of even more stringent start and stopping rules to ensure appropriate use of the drug [63, 223]. Start and stopping rules were already used by Erasmus MC. These entailed that treatment is only initiated in symptomatic patients. Many clinical and functional tests are collected from patients and a multidisciplinary team with an independent chair decides when to initiate treatment and evaluates the effect of treatment for each individual patient. Treatment is discontinued if there is no treatment effect. Start and stopping rules were continuously improved and are currently being redefined on a European level by the European Pompe Consortium, with clinical experts of the Erasmus Medical Center being in the lead [50]. These treatment guidelines will be published shortly.

Reimbursement of ERT for Pompe disease is agreed upon up to and including 2016, which is also the year when the market exclusivity on alglucosidase alfa expires. It is yet unclear what will happen with respect to reimbursement of ERT after 2016. If ZIN decides to reassess the data on effectiveness and cost-effectiveness of ERT in Pompe disease it is important to acknowledge the additional evidence that has become available since the submission of the dossier in 2011, described in this thesis and in other publications [47, 49, 100, 224]. The expiration of market exclusivity in 2016 should be taken into account if new price negotiations are initiated.

Current policy on orphan drugs in the Netherlands

The debate on reimbursement of orphan drugs fell silent with the Minister's decision on the reimbursement of ERT in Pompe disease. ZIN postponed decisions on other orphan drugs temporarily reimbursed under the policy rule on orphan drugs under a coverage with evidence development scheme, even for those orphan drugs for which reimbursement dossiers were already submitted. The debate on Pompe made ZIN and the Ministry of Health realize that several actions were needed to prevent the same debate to arise when a decision on another orphan drug had to be made. Most importantly, a specific policy on reimbursement of orphan drugs had to be developed. To do so, ZIN consulted various actors in the orphan drug field, much like the study described in chapter 10. In 2015, ZIN published in a policy document on reimbursement of orphan drugs [202]. The policy document included the findings reported in chapter 2, on the increasing budget impact of orphan drugs in the Netherlands, and chapter 9, on international differences in reimbursement decisions for the same orphan drug. With regard to reimbursement of orphan drugs, the report resembled much of the outcomes reported in chapter 10, albeit that our results were not available at the time of the analyses by ZIN. ZIN concluded that orphan drugs should, in principle, not be assessed differently than non-orphan drugs, because both types of drugs are paid for by public resources. Furthermore, the same reimbursement criteria apply to orphan drugs, although ZIN provided some examples of factors that could compensate for unfavourable ICERS of orphan drugs, namely whether alternative treatments exist, the magnitude of the improvements in quality of life and foreseen improvements in cost-effectiveness.

Most recently, in March 2016, the ACP discussed reimbursement of eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria; another orphan drug listed on the policy rule for orphan drugs. This was the first time the Appraisal Committee (ACP) discussed an orphan drug since the debate on Pompe disease in 2012. The cost-effectiveness ratio was high (€400,000/QALY) and the quality of the underlying pharma-

coeconomic model was questioned by the Scientific Advisory Council (WAR). Based on this information, the ACP decided to issue a negative advice on reimbursement of this orphan drug [225]. It is yet undecided if other orphan drugs that were listed on the initial policy rule for orphan drugs will also be reassessed. If so, ZIN should acknowledge that reimbursement dossiers that were submitted several years ago might have become outdated and a lot of new evidence might have become available since the submission of the dossier. An ethical argument that cannot be ignored in the appraisal of these orphan drugs is the fact that patients have already received treatment with the orphan drug for several years. Although patients could have been aware that reimbursement was temporary, this temporary period was extended without properly being communicated to patients. As such, these patients can now interpret their treatments as an acquired right. Physicians and patients could argue that the treatment has become 'standard of care according to the current state of the medical science and practice', a criterion that is otherwise used to reimburse innovative treatments for which no explicit reimbursement decision needs to be taken.

Although the initial negative reimbursement advice in 2012 on ERT in Pompe caused a storm of critique, it did initiate a societal discussion on incorporating cost-effectiveness in reimbursement decisions and financial sustainability of the healthcare system. In the aftermath of the discussion, ZIN published a policy document on incorporating cost-effectiveness as a reimbursement criterion [54]. This report described that cost-effectiveness should be used as one of the arguments in reimbursement decisions, but not as the only criterion. In their opinion the cost-effectiveness criterion should not be used too rigidly. The weight of cost-effectiveness relative to other reimbursement criteria was not described. Further research has to show whether these criteria can be included in a systematic way in reimbursement decisions. Next to publishing this policy document on orphan drugs, ZIN is also increasingly advising the Ministry of Health to engage in price negotiations with pharmaceutical companies to improve the cost-effectiveness ratios of novel therapies.

Future regulations for orphan drugs

Different adjustments of regulations have been proposed to stimulate the availability of orphan drugs while at the same time reducing their budget impact. These will be discussed below.

Market exclusivity and generic competition

One of the reasons that orphan drug prices are so high is because market exclusivity granted through orphan drug legislation prevents price competition. But also after market exclusivity has ended, competitors hardly enter the market. Generic versions of biologic drugs, i.e. biosimilars, could put pressure on orphan drug prices. A recent study showed that for 15 out of all 74 orphan drugs with EMA marketing authorization, a generic version was available [226]. For ten of these generic versions and unlicensed versions of orphan drugs prices were available, which showed that these generic versions were priced at 12.3% of the price of the branded orphan drug (range 0.001% to 74%). However, the development of generic or biosimilar products has not taken off on a wide scale. Incentives to enter the market are apparently too limited once another company has entered the market, due to small populations and high development costs [227]. Further research is needed to assess which other factors play a role with respect to entry of biosimilars. To ensure that biosimilars will be developed, additional incentives should therefore be put into place, like the incentives that were provided by orphan drug legislation. However, even if biosimilars will be developed, the question remains at what price they will be marketed. Development of biosimilar products is relatively expensive compared to generic products for small chemical entities, as biosimilar products are more difficult to produce [228], thereby increasing development costs. Moreover, regulation prescribes that biosimilars should be tested for safety and effectiveness [229, 230], contributing to R&D costs of biosimilars. In this respect, biosimilars differ from generic versions of small chemical entities, as for these drugs, companies only have to show that the chemical substance is identical to the branded drug. A practical problem for testing biosimilars is the limited number of patients with a particular orphan disease, as patients might not be willing to participate in a study in which they might receive the biosimilar instead of the reference product with proven effectiveness. Because of these reasons, cost reductions from biosimilars are difficult to predict and could be limited. Biosimilars for non-orphan drugs are expected to be priced at a 20-30% discount [231]. These price reductions would not suffice in making orphan drugs cost-effective under conventional thresholds.

Transparent price setting

The policy document on orphan drugs by ZIN acknowledges that the rising budget impact of orphan drugs puts pressure on the sustainability of the system [202]. Authorities in other countries have expressed similar concerns [232, 233]. As healthcare budgets are constrained, pricing of individual orphan drugs is not sustainable [234]. Chapters 7 and 8 of this thesis illustrated that the high prices of ERT were the main driver of the unfavourable cost-effectiveness ratios for Pompe disease; Dutch ICER estimates for ERT in other metabolic orphan diseases were similarly unfavourable [166, 235].

The Dutch Ministry of Health has engaged in price negotiations with pharmaceutical companies in order to reduce costs-effectiveness ratios and budgetary impact of treatments. As these agreements are (usually) confidential, the Ministry of Health can only make vague statements like 'substantial price reductions have been agreed upon'. Although 'substantial' is a subjective term, it is unlikely that orphan drug prices are reduced to such an extent that these drugs will meet conventional cost-effectiveness thresholds. In this respect, collaboration between national healthcare authorities of different countries can increase negotiation power. The key issue in effective price negotiations is getting insight in the actual costs of an individual drug, which is justified by the fact that society is collectively paying for these drugs from public resources. Price setting for orphan drugs does not seem to deviate from that of non-orphan drugs and depends on various factors, like the need to recoup R&D costs, perceived value of the new product, competiveness of the market and the properties of the disease and patient population [236]. It is debated whether costs of developing, producing and marketing are higher for orphan drugs than for non-orphan drugs [222, 237, 238]. Costs might also be affected by the production process itself; i.e. whether the production of the treatment is rather simple or more complicated, as is the production of a recombinant DNA product for the treatment of Pompe disease. However, providing insight in actual costs of a drug would unravel what is spent on production costs, marketing costs and R&D costs of orphan drugs and what profit margins are used. This information would also reveal what proportion of R&D costs have been borne by the pharmaceutical company, as for many orphan drugs early stages of research have been performed by academia, and sponsored by governments or patient organizations. Basic research on ERT in Pompe disease for example has been performed by Erasmus MC, research on ivacaftor (for the treatment of a form of cystic fibrosis and priced at approximately $300,000 per year) was funded by National Institutes of Health (NIH) and the cystic fybrosis patient organization [234], and alglucerase (for the treatment of Gaucher disease, also priced at $300,000 per year) was developed and tested by NIH [239]. Next to R&D costs made for a specific drug, R&D costs for drugs that have not made it to the market are taken into account in drug prices. In addition, pharmaceutical companies are commercial organizations and should be allowed to make a profit. However, the market for pharmaceuticals is not like any other market, as it also comprehends an ethical component. Marketing slogans of the industry recognize that they are involved in a special market. Out of consistency, the ethical component of the market should also be acknowledged in lower profit margins and lower prices for orphan drugs [234, 240].

Previous studies have shown that having an orphan drug designation in itself increases prices; drugs for rare diseases with an orphan designation have higher prices than drugs for rare diseases without an orphan designation [241]. Price increases have also been

observed for several drugs that had an initial indication in a common disease and subsequently got an orphan designation [230, 237, 242, 243]. An example is ibuprofen: oral ibuprofen to relief pain costs £0.08 per gram, while intravenous ibuprofen costs £6,575 per gram to treat the orphan disease patent ductus arteriosus [242]. Transparency on drug prices could prevent these seemingly unjustified price increases.

Another effect of orphan drug regulation is indication widening; some products are initially marketed in orphan drug indications, and later get registered for common diseases (e.g. bosentan was initially granted market approval for treatment of the orphan indication pulmonary arterial hypertension, but might also be used for treating heart failure) [230]. These products would wrongfully benefit from orphan drug legislation. Similarly, 30% of orphan drugs has been registered for multiple (orphan) indications [6]. When combined, the prevalence can exceed the threshold for rarity. Imatinib (trade name: Glivec®) for example had orphan designations for six orphan diseases. Chapter 2 showed that in the Netherlands alone, almost 1,500 patients were treated with this drug. Orphan drug legislation might still be necessary to provide incentives to study treatment effects in different indications. However, costs for pharmaceutical companies will be lower as companies would be able to enjoy some sort of economies of scale and costs related to R&D and phase I and II studies may be lower for existing drugs in new indications [227]; costs associated with widening of indications might primarily be limited to costs of phase III clinical trials and marketing [226, 230]. However, research has shown that having multiple orphan indications does not affect orphan drug prices [237]. In fact, the opposite is true, prices are higher for orphan drugs with multiple orphan indications than for orphan drugs with a single orphan indication [244]. As the argument that drug prices are high because costs of R&D need to be retrieved on small numbers of patients might not be applicable in these specific cases, this would increase negotiation power of the Minister of Health.

Also from a research perspective, disclosure of drug prices is necessary, because when the price of the drug remains unknown, future cost-effectiveness studies on new drugs for the same and other indications will not be possible.

Revisions of orphan drug legislation

As self-regulation by the pharmaceutical industry might be limited, next to price setting of orphan drugs, orphan drug legislation could be revised. One solution might already be available in current European orphan drug legislation, as it includes a clause stating that market exclusivity for orphan drugs can be reduced from the usual ten years to six years when the drug is 'sufficiently profitable' at the end of the fifth year [2]. To date, this has never happened, despite the fact that several orphan drugs have

reached blockbuster status – 43 drugs with at least one orphan designation had sales of more than $1 billion in 2008, of which 18 drugs were solely indicated for an orphan indication [237]. The fact that, so far, the option to reduce market exclusivity has never been used might be because orphan drug legislation does not include a definition of 'sufficiently profitable'. This is crucial to enable that this clause can actually be used in practice. An alternative solution could involve altering patent protection of orphan drugs. For instance, (hospital) pharmacies might be encouraged to compound orphan drugs themselves after a pre-specified period of time rather than purchasing them from pharmaceutical companies. This could reduce drug costs substantially [245], but also involves safety issues. However, this strategy might not be feasible for those orphan drugs with complicated production processes, like ERT for Pompe disease.

Alternative business models

As another option, alternative business models could lead to lower prices of (orphan) drugs. A system of patent buyouts has been proposed, in which the manufacturer receives a pre-specified reward for developing a drug and subsequently set drug prices equal to actual production and distribution costs [246]. Recently, the Dutch Minister of Health granted a subsidy to a Dutch initiative, which aims to develop and produce drugs at lower costs. The initiative was set up by a physician and former chair of Erasmus MC, a former employee of a pharmaceutical company and two entrepreneurs. It is supported by the Dutch university medical centers. In this plan, various stakeholders will be brought together to develop new medicines for lower profit margins and under full transparency about expenses and revenues. A description of a clear defined plan on how costs will be reduced with this initiative is being looked forward to.

Alternative prevalence thresholds for rarity

In chapter 10, various stakeholders indicated that the threshold for defining an orphan disease (European definition: less than 5 patient per 10,000 people) is not low enough. This could lead to an inadequate classification of diseases as orphan diseases, and consequently inappropriate use of the incentives for orphan drugs. In this respect, research has shown that pharmaceutical companies have concentrated on orphan diseases with a relatively high prevalence and on a few profitable disease areas [237, 247]. By using a higher threshold the incentives for orphan drugs will be restricted to genuine orphan diseases.

An unwanted effect of specifying a particular prevalence threshold is that pharmaceutical companies stratify larger indications into smaller indications to qualify as a rare disease and to benefit from orphan drug legislation, so called salami slicing [230]. Using a lower threshold to define rarity might limit salami slicing, but a more definitive solu-

tion would be a thorough assessment of the validity of the orphan designation during the registration process, to ensure that only genuine orphan drugs can benefit from the incentives provided by orphan drug regulation.

Methodological challenges and considerations

Several methodological challenges for performing clinical and pharmacoeconomic studies in orphan diseases have been identified [10, 12, 16, 66, 171], which will be discussed in this section.

Small sample sizes

By definition, research in orphan disease is confronted with small patient populations. Dedicated clinical experts and patient organizations are crucial in motivating patients to enrol in these studies [12]. International data collection has been used to alleviate problems related to small sample sizes [207]. However, adequate data management is essential in international data collection, to ensure the quality and comparability of the data. Another challenge that is related to small sample sizes is that knowledge on many orphan diseases is limited [10, 248]. This can also complicate cost-effectiveness studies; it can be more difficult to develop a plausible cost-effectiveness model if the clinical pathway is unknown, or information on specific input parameters (such as quality of life) might be missing [170].

Lack of (data on) comparator

For many orphan diseases there is no treatment available currently. However, most patients will always get some sort of supportive care, which is the appropriate comparator in cost-effectiveness studies. Lack of data on this comparator (e.g. natural course) is an important challenge. Pharmaceutical companies do not have an incentive to monitor the natural course of a disease unless they have a product available or in the pipeline that alters the disease course. Physicians should therefore be made aware of the importance to collect data on the natural course of a disease, even before a new product becomes available. Starting disease registries at the moment that orphan designation is granted might alleviate this problem [249]. Nevertheless, there may be other issues that can hinder data collection, like the sometimes greater heterogeneity of patients in orphan compared to non-orphan diseases, the sometimes rapidly progressive disease course and the fact that orphan diseases often affect children [10, 16, 250]. While these issues are not exclusive to orphan diseases, the combination of factors complicates doing research in orphan diseases.

Study design issues

Randomized controlled trials (RCTs) for orphan drugs are not per definition impossible; e.g. the efficacy of ERT in Pompe disease was also assessed in an RCT [46]. However, as Pompe disease is a chronic disease, long-term data were needed to include all treatment effects in the cost-effectiveness model. The data from the RCT of ERT in Pompe disease were limited to a period of 78 weeks. As a result, the cost-effectiveness studies in this thesis had to be based on observational data to include long-term data. Observational studies do not have the high internal validity of RCTs [251]. First of all, selection bias is a major issue for observational studies [172]. Because patients are not randomly assigned to treatment, treatment groups can have different characteristics. In particular, physicians prescribe treatment for individual patients on the basis of the patient's prognosis. This selection bias is a major issue for observational studies and can lead to confounding of the results – differences in outcomes between groups are then not necessarily caused by treatment, but might be due to the effect of other, unobserved, factors [172, 252, 253]. For medications that are true innovations (first-in-class drugs), this is a particularly prominent problem [254]. Those patients that do not receive the drug, despite its effectiveness, might have much less severe disease manifestation. This was also the case for the observational studies in Pompe disease, as ERT was initiated in patients with the most severe disease, and patients that were not severely affected did not receive ERT. It should be noted however, that the patients with the most severe disease have a higher chance of dying, while those doing relatively well and do not receive ERT have a higher chance to survive. This would have had a negative impact on the estimated survival gains. In general, when a first-in-class drug (like ERT for Pompe disease) becomes available, patients are rapidly switched to this treatment and continuation of data collection on the comparator treatment is difficult [254]. This issue is particularly prominent for orphan drugs, as often no alternative treatments exists other than supportive care. It is therefore essential to collect data prior to the moment that the drug is available for patients, in order to get data on the natural course of the disease. Greater loss to follow-up due to rapid disease progression is another problem that can occur in (long-term) observational studies in orphan diseases [255]. Finally, like in all unblinded studies, performance bias can occur when participants and clinicians are not blinded [173].

Various actions were taken to minimize biases for the studies in Pompe disease. As the same patients contributed data to both the ERT group and the group that did not receive ERT, selection bias in the survival model was reduced. Selection bias was further reduced by including various covariates (age, disease duration, gender, wheelchair use and ventilator use) in the regression models for survival, quality of life and costs. Loss to follow-up for the Dutch patients was reduced by centralization of patients in one expert center. As a result, patients could be closely followed using a standardized protocol.

All patients were regularly seen in Erasmus MC, as patients either received bi-weekly treatment at Erasmus MC or were treated elsewhere under supervision of Erasmus MC. Furthermore, patients were obliged to participate in the follow-up studies. Finally, the early initiation of prospective data collection through a standardized protocol, prior to the availability of ERT, reduced the problem of limited data on the comparator, which is often present for first-in-class drugs.

It should be noted that a drawback of RCTs could be their strict in- and exclusion criteria, which can prevent the more severely affected patients from entering the study. The observational dataset on Pompe disease at Erasmus MC included the entire spectrum of severity in Pompe disease and data of both treated and untreated patients.

For the studies on Pompe disease (chapters 3 to 8 in this thesis) a dataset was available that can be considered large for a rare disease. The dataset included clinical and economic data on both untreated patients and patients that received ERT. Patients showed to be very committed to contributing data, as they completed various questionnaires repeatedly, over periods of many years. Centralization of all Dutch patients in one center of expertise was pivotal to increase the number of patients included in the dataset and to ensure standardized follow-up. International collaboration between patient organizations and physicians enabled the use of the international IPA dataset to assess survival in adult Pompe disease. Without these datasets these studies could not have been performed. The availability of such an extensive dataset is unique for studies in orphan drugs. Timely collaboration between patients, clinicians and health economists is critical to ensure that all necessary data are collected. In this case, collaboration was initiated prior to data collection. In later stages clinicians and health economists worked together regarding the interpretation and publication of the outcomes. In this respect, the studies on Pompe disease can serve as an example for other studies in orphan drugs with regard to data collection and close collaboration between clinicians and health economists.

Lack of disease-specific outcome measures

The studies in this thesis used the EQ-5D to assess the quality of life of patients with Pompe disease, as recommended by the Dutch health economic guidelines [164]. Chapter 4 showed some limitations of applying the EQ-5D (and SF-6D) in Pompe disease with regard to responsiveness to changes in clinical measures. This could be due to a lack of sensitivity of the instrument to detect these specific clinical aspects. An alternative to using the EQ-5D to assess quality of life would be to use a disease-specific quality of life questionnaire. However, a quality of life instrument that covers all relevant aspects of quality of life is not available for Pompe disease. Alternatively, a domain could be added

to the EQ-5D (so-called bolt-on EQ-5D). A recent pilot study showed that adding a question on respiratory functioning to the EQ-5D has a significant effect on the valuation of health states [256]. Compared to the utility values derived from the original EQ-5D without a respiratory domain, utility values were higher when patients scored well on the respiratory domain, and utilities were lower when patients indicated problems on the respiratory domain. By adding a respiratory domain to the EQ-5D, respiratory problems in Pompe disease could be incorporated in quality of life values. However, the use of bolt-on versions of the EQ-5D is still under development and needs to be studied further, as it may jeopardize the comparability of EQ-5D across treatments for different diseases.

Updated cost-effectiveness analyses of ERT for adult Pompe patients

Progressing insights led to several methodological adjustments to improve the validity of the earlier cost-effectiveness model. As a result, our results concerning the ICER estimates differ from the estimates that were included in the reimbursement dossier to ZIN in 2011, in which the ICER was estimated to be €15.3 million. Our current estimates are lower for several reasons. Firstly, the present model uses a time-dependent Cox regression model to estimate survival, which is more appropriate than the person-time approach used in the previous model. For the person-time approach in the previous cost-effectiveness model, patients were divided into four age classes (i.e. 0-19 years; 20-39 years; 40-59 years and 60 and above), for which mortality rates were calculated. The number of age classes was limited to four because of the small number of patients in the dataset. However, additional analyses using the previous model (unpublished) showed that the outcomes of the cost-effectiveness model were very sensitive to the classification of the age classes; when seven classes were used instead (i.e. 0-19 years; 20-29 years; 30-39 years; 40-49 years; 50-59 years; 60-69 years and 70 and older), the ICER was reduced to €9.6 million per QALY. The person-time approach was therefore considered too simple and a time-dependent Cox regression was used in the updated model. The time-dependent Cox model accounts for so-called immortal time bias [257], in this case the bias that occurs because death on ST cannot occur in patients who start ERT, because patients can only start ERT when they survive ST up to the point that ERT is started. A time-fixed Cox regression model would not have accounted for immortal time bias; the treatment variable would have to be constant and would incorrectly include the ST period as part of ERT period. This would have led to an overestimation of the treatment effect. Alternatively, if the ST period for ERT patients would have been neglected, this would lead to an underestimation of the survival for ST [257, 258]. This is solved by using the time-dependent Cox regression. In addition, the time-dependent Cox regression included the covariates 'wheelchair use' and 'use of ventilation' (which have previously shown to influence survival in adult Pompe disease [49]), whereas the

person-time method did not include explanatory variables other than treatment and age classes. By including these covariates, survival could be estimated more accurately, especially as individual patients were simulated in the cost-effectiveness model. However, the impact of including these additional covariates on the ICER was limited, as was shown in the sensitivity analyses.

Furthermore, a lifetime time horizon was used in the current analyses, while in the previous model the time horizon was set at 15 years. A lifetime horizon is recommended by the Dutch guidelines on pharmacoeconomic research. Using a shorter time horizon increases the ICER, because survival gains increase relatively faster over time than total costs. This was also shown in the sensitivity analyses, in which shorter time horizons lead to higher ICER estimates.

Finally, a more elaborate regression model was used to model quality of life. The cost-effectiveness model in the reimbursement dossier was partly based on an earlier version of the conceptual disease model described in chapter 6. Since the submission of the dossier, the conceptual model was further developed to include all five levels of health concepts presented in the Wilson-Cleary model (as described in chapter 6). These methodological adjustments have improved the validity of the cost-effectiveness model which now represents reality more accurately.

The more appropriate time-dependent Cox model also affected uncertainty. The 95% confidence intervals of the ICERs changed from €10.5 million-€24.0 million per QALY in the model used for the reimbursement dossier to €2.3 million-€5.5 million per QALY and €1.2 million-€4.2 million per QALY in scenario 1 and scenario 2 in chapter 7, respectively. The absolute width of the confidence intervals were much smaller in the updated cost-effectiveness analyses than in the previous model, although the width of the confidence intervals relative to the point estimate were not reduced. Decision makers care about the absolute width of confidence intervals, as this reflects part of the uncertainty of their decisions. As such, the updated cost-effectiveness model reduced the uncertainty around the value of the ICER. Altogether, these improvements did improve the estimates and reduced the uncertainty surrounding them, but they did not change the overall conclusion regarding cost-effectiveness of ERT.

Future research

Cost-effectiveness and displacement costs

Cost-effectiveness is used to maximize health under a given budget constraint. The cost-effectiveness threshold quantifies the societal willingness to pay for one unit of health gain. The current threshold value in the Netherlands of maximally €80,000 per QALY was set arbitrarily, and was not based on empirical evidence. Theoretically, the cost-effectiveness threshold should reflect the opportunity costs of healthcare spending; it assesses whether the health gains of a new intervention exceed the health effects of the interventions that are displaced elsewhere in the healthcare system to compensate for the additional costs of the new technology. A recent study showed that a cost-effectiveness threshold of about £13,000 per QALY resembled the displacement costs in healthcare in England [259]. This threshold is considerably lower than the current threshold range of £20,000-£30,000 per QALY used in reimbursement decisions in England. The study also showed that services most likely to be displaced were found in the respiratory, neurological and mental health healthcare sectors, thus making the opportunity costs of displacement much less anonymous and more concrete. Two Dutch studies recently started to estimate the displacement costs for the Netherlands as well. When displacement costs are quantified for the Netherlands, it will be possible to estimate how much health is forgone by paying for new interventions with ICERS that exceed the cost-effectiveness threshold. However, the concept of displacement does not capture societies' potential additional willingness to pay for treatment of orphan diseases.

Societal preference for rarity

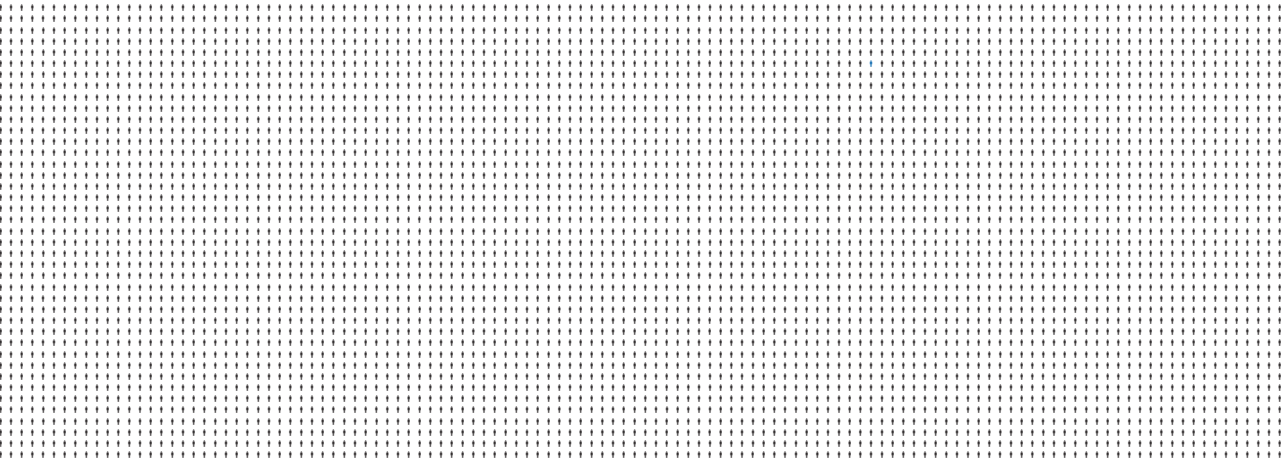
Cost-effectiveness is not the only criterion used in reimbursement decisions. As a result, orphan drugs might still be reimbursed, despite their high cost-effectiveness ratios. If so, transparency on the other criteria that compensate the unfavourable ICER is needed. Rarity in itself could be one of those criteria. The pivotal question that needs to be answered is whether a societal preference for rarity exists [260]. Is society willing to pay extra just because a disease is rare? Theoretical arguments both in favour and against a preference for rarity have been mentioned [66, 261, 262]. From a utilitarian viewpoint it is argued that no theoretical arguments exist for valuing treatments for rare disorders differently [174]. On the other hand, from a rights-based approach it is unethical to deny patients treatment only because their disease is rare [263, 264]. In this respect, the very existence of (EU) orphan drug regulation indicates that EU policy makers treat orphan drugs as a special case [263], as EU regulation states: "*Patients suffering from rare conditions should be entitled to the same quality of treatment as other patients*" [2]. Empirical evidence on whether a preference for rarity exists is mixed [183, 260, 265]. Preferences

can also vary between stakeholders or between countries. Further research is needed to unravel societal preferences.

Multi-criteria decision analyses

Next to rarity, several factors play a role in reimbursement decisions, as has been described in this thesis. The fact that several criteria simultaneously play a role complicates reimbursement decisions. How criteria relate to each other is not clear. Multi-criteria decision analyses (MCDA) is an approach that explicitly incorporates and weighs several criteria [215]. In MCDA, systematic and transparent trade-offs are made between multiple criteria and a weighted composite score is calculated for each treatment alternative. Decision makers can use MCDA as a tool to inform them in their reimbursement decisions. A pilot study applying MCDA to orphan drugs showed that the approach can be useful for comprehensive decision making on orphan drugs [177]. However, to date practical applications of MCDA in orphan drugs have not been published. Several issues have to be overcome before MCDA can be used to inform policy makers in reimbursement decisions. The first issue is to define which criteria should play a role in decision making. Next to rarity, several other factors play a role in reimbursement decisions. A recent systematic literature review found that, besides rarity, the uniqueness of the indication, disease severity, advancement of technology, complexity of manufacturing, unmet medical need, scientific evidence on effectiveness, drug safety, budget impact and cost-effectiveness were used as reimbursement criteria for orphan drugs [176]. Other criteria that have been identified that potentially affect reimbursement decisions on orphan drugs are whether or not alternative treatments exist, social impact of the disease and treatment and whether the treatment has a disease-modifying effect [177, 178]. One of the most heavily debated issues is whether costs should be included as a criterion [218]. When costs are included as a criterion, respondents explicitly trade-off costs against many other criteria in the analyses. A recent literature review showed that 10 out of 23 MCDAs included costs as a criterion [217]. A counterargument to including costs as a criterion is that MCDA creates a new composite measure of benefit, for which the willingness to pay should be determined separately [219]. The second issue is deciding whose weights should be used in an MCDA. As criteria weights vary between different groups of stakeholders, differences in opinion between stakeholders are made explicit. When an MCDA is conducted in a group of patients and physicians, the value of having a treatment for patients for whom no treatment existed in the past is likely to be clearly demonstrated. An MCDA among payers and policy makers is likely to put more emphasis on the cost criterion. MCDA will not solve these differences in opinion between stakeholders. Even if a representative sample of the general population (including all stakeholders) was used in an MCDA, the relative importance of the various criteria would still be a combination of the various opinions of the different stakeholders. Whether

these different opinions should be given the same weight remains open for discussion. Thirdly, performance scores for the various criteria should be adequately scored, which might be challenging for orphan drugs as explained in earlier sections. Fourthly, a choice for a specific methodology needs to be made, as several MCDA techniques exist [266]. Finally, it is yet unclear if policy makers will want to make use of MCDA, as they actually may like the discretion of their deliberate decision making process [57]. MCDA can help decision makers as a tool, but MCDA does not provide a solution to the challenge of estimating opportunity costs in healthcare [218]. In conclusion, further research has to demonstrate whether using MCDA can help policy makers in making reimbursement decisions on orphan drugs.



Summary

Background

A disease is considered rare if the prevalence is less than 5 per 10,000; and diseases with an even lower prevalence (i.e. less than 1 per 50,000 population) are considered ultra-rare. Although a rare disease per definition affects only a small number of individuals, altogether about 30 to 40 million EU citizens suffer from about 7,000 rare diseases. Medical needs of patients are largely unmet because the development of treatments for these diseases has long been neglected. Over the last decades, several regulatory incentives have stimulated interest in developing orphan drugs. The European Medicines Agency approved 63 orphan drugs in the 10 years after the passing of EU orphan drug legislation, but for the vast majority of orphan diseases still no treatment exists. Since R&D costs need to be retained from relatively few patients, prices of orphan drugs are relatively high. As a result, policy makers are faced with difficult reimbursement decisions within a constrained budget, as money spent on one treatment is no longer available for another treatment. This type of decision making can be supported by Health Technology Assessment (HTA), a systematic approach to investigate the clinical, economic, social and ethical consequences of the implementation of an orphan drug.

The orphan disease investigated in this thesis is Pompe disease. Pompe disease is a progressive muscle disorder that belongs to the group lysosomal storage disorders. The disease is caused by a deficiency of the enzyme acid α-glucosidase. As a result, glycogen is not broken down appropriately and accumulates in the lysosomes. The disease has a broad continuous clinical spectrum, ranging from a rapidly progressive infantile form to a more slowly progressive form affecting children and adults. Without specific therapy, classic-infantile patients generally die within the first year of life. Patients with a late-onset form of the disease suffer from progressive muscle weakness and respiratory problems. Most of these patients become dependent on ambulatory and respiratory support; 15 years after diagnosis half of patients has become wheelchair dependent and approximately half of the patients has become dependent on ventilator use. Enzyme replacement therapy (ERT) for Pompe disease became first available in 2006. Conducting HTA of this therapy is confronted with many challenges described in this thesis, which are all, more or less, related to the limited number of patients affected. However, many of the challenges could be addressed because of the availability of a database that Erasmus MC has built over de past decades, including clinical, survival, quality of life and healthcare utilization data, not only from the period after ERT approval, but also from several years before. Furthermore, international collaboration enabled estimation of survival due to ERT.

The aim of this thesis was to provide insight in the various aspects that affect reimbursement decisions of orphan drugs, conduct HTA studies of ERT in Pompe disease and contribute to the decision making process regarding the reimbursement of orphan drugs.

The burden of disease from different perspectives

In the first part of this thesis, the burden of Pompe disease was investigated from multiple perspectives, including a financial and economic perspective, the perspective of the patient, and the perspective of the informal caregiver. **Chapter 2** assessed the budget impact of orphan drugs in the Netherlands and showed that the number of orphan drugs and patients treated increased significantly in the period 2006 to 2012 in the Netherlands. Overall, budget impact increased considerably over this period of six years, both in absolute terms (from €61 million to €260 million) as well as relative to total pharmaceutical spending (from 1.1% to 4.2%). In 2012, 17% of available drugs had an individual budget impact of more than €10 million per year.

Chapter 3 reported on the burden of Pompe disease from a patient's perspective and societal perspective, in terms of quality of life and societal costs in adult Pompe patients receiving supportive care. Quality of life for Pompe patients who only received supportive care was estimated at 0.72; 17% lower than the general Dutch population. A total of 40% of patients had stopped working due to their disease; another 20% had reduced their working hours. Eighty-five percent of patients received informal care. Per patient, annual costs were estimated to be €22,475 (range €0 – €169,539).

Chapter 4 showed that correlations between theoretically related dimensions of two generic quality of life instruments (EQ-5D and SF-6D) that were used to measure the generic health-related quality of life of adult Dutch patients with Pompe disease were moderate to strong. Utility values derived from the two instruments were similar (mean EQ-5D = 0.670; mean SF-6D = 0.699) and strongly correlated. The descriptive system of the SF-6D described health states for Pompe disease more accurately. Discriminative properties were somewhat better for EQ-5D; mean changes and effect sizes were better for SF-6D. In conclusion, both instruments appear to be equally appropriate with respect to assessing utilities in Pompe disease, but neither of them performed excellently.

Chapter 5 examined the impact of Pompe disease from the perspective of the informal caregiver. On average, caregivers (parents, spouses, other family members and friends of the patient) provided 17.7 hours of informal care per week. Half of all caregivers reported mental health problems and problems with daily activities due to providing informal

care. Physical health problems occurred in 40% of caregivers. Caregivers reported deriving personal fulfilment from caregiving and, on average, would become unhappier if someone else were to take over their care tasks.

Chapter 6 presented a conceptual disease model for Pompe disease in adults, structured according to the Wilson-Cleary health outcomes model. The conceptual model described the associations between the biological parameters, physiological parameters, symptoms and functional indicators, health perceptions and finally health-related quality of life. Enzyme activity, muscle strength, respiratory function, fatigue, level of handicap, general health perceptions, mental and physical component scales and utility described these different health concepts for Pompe disease.

Cost-effectiveness of ERT in Pompe disease

In the second part of this thesis, two cost-effectiveness models were presented. **Chapter 7** described the cost-effectiveness of ERT (including supportive therapy) compared to supportive therapy (ST) in adult patients with Pompe disease. Because extrapolation (particularly of effects) is associated with uncertainty, especially when the time horizon is lifetime, we presented two different scenarios. In scenario 1, in which we only include the survival gains in the observed period, we assumed no gains in survival beyond the observed period, as a worse case scenario. In scenario 2, we extrapolated survival gains beyond the observed period. Substantial increases in survival were shown for both scenarios – discounted incremental life years of ERT ranged from 1.9 years (scenario 1) to 5.4 years (scenario 2). Quality of life was also significantly better for patients receiving ERT. Incremental costs primarily consisted of the costs of ERT. Incremental costs per QALY were €3.2 million (scenario 1) and €1.8 million (scenario 2).

Chapter 8 assessed the cost-effectiveness of ERT in patients with classic-infantile Pompe disease. The cost-effectiveness model showed that, on average, ST receiving patients did not survive the first half year of life; whereas the life expectancy in the ERT patients was modelled to be almost 14 years. Lifetime incremental QALYs were 6.8. Incremental costs were estimated to be €7.0 million, which primarily consisted of treatment costs (95%). Incremental costs was €1.0 million per QALY and €0.5 million per life year gained.

Use of HTA in policy making on orphan drugs

The third part of this thesis discussed the use of HTA in decision making on orphan drugs. **Chapter 9** showed the variation of reimbursement status of ERT in Pompe disease between six European countries. Most countries in our study (England, France, Italy, and Belgium)[1] reimbursed ERT for all patients, while Wales reimbursed ERT only for classic-infantile and juvenile patients, but not for adult patients. ERT was not reimbursed in Scotland. More transparency on decision making is needed to determine whether these differences in reimbursement status resulted from differences in the technical assessment of the available evidence or the societal appraisal of the evidence, or both. Transparency can be increased by using an alternative framework of decision-making such as Multi-Criteria Decision Analysis (MCDA), which is a method in which the impact that different criteria have on the decision and their relative importance is made explicit. This can improve transparency, consistency, credibility, and accountability of reimbursement decisions, although it does not solve the willingness-to-pay debate.

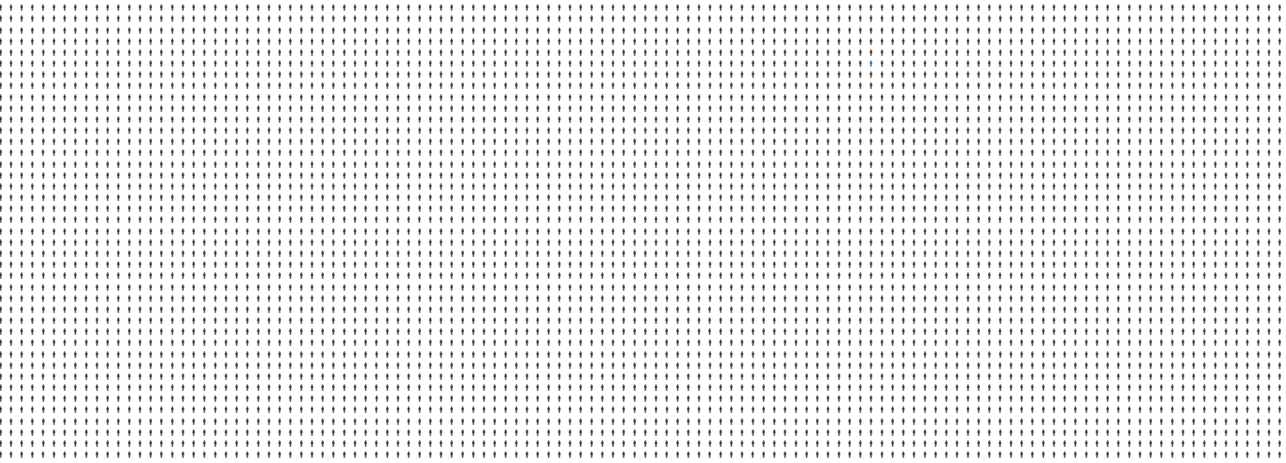
Chapter 10 assessed the applicability of guidelines for pharmacoeconomic research in orphan drugs in general and investigated which criteria are used for reimbursement decisions. Findings from both reimbursement dossiers and interviews indicated that the required level of evidence with respect to effectiveness for orphan drugs does not necessarily have to be lower than for non-orphan drugs. Furthermore, current guidelines for conducting pharmacoeconomic evaluations and budget impact analyses were assumed valid for orphan drugs. In the appraisal process, additional criteria (i.e. limited budget impact, rarity of disease, young age of population, identifiability of named patients and absence of alternative treatments) were used in addition to criteria used for non-orphan drugs (necessity, effectiveness, cost-effectiveness and feasibility).

Discussion

Finally, **chapter 11** described how the preliminary advice not to reimburse ERT for adults with Pompe disease by the Dutch Health Insurance Board in 2012 was perceived from the various perspectives of the patients, physicians, the pharmaceutical company, the general public, policy makers and politicians. It further described how the debate that followed has led to the final decision in favour of reimbursement after reductions in the price of ERT and how it influenced policy making on orphan drugs in the Netherlands in general. Chapter 11 further discussed potential adjustments of current policies

[1] After our study was completed, we learned that Germany also reimbursed ERT in Pompe disease

and regulations regarding market exclusivity, price setting, incentives to stimulate the development of orphan drugs and alternative business models. It finally addressed methodological challenges of doing HTA research in orphan diseases and gives suggestions for future HTA research, such as research on MCDA and opportunity costs of treatments displaced.



Samenvatting

Achtergrond

Een ziekte wordt zeldzaam genoemd als minder dan 5 per 10.000 mensen aan de ziekte lijden en ziektes worden ultra-zeldzaam genoemd als de prevalentie nog lager is (<1 per 50.000). Het aantal mensen dat aan een specifieke zeldzame ziekte lijdt is per definitie beperkt, maar in totaal zijn er 30 tot 40 miljoen mensen in de EU met een zeldzame ziekte. Aan de klinische behoefte van patiënten met zeldzame ziektes wordt slechts beperkt tegemoet gekomen, omdat de interesse voor ontwikkeling van behandelingen voor deze ziektes lange tijd gering was. In de laatste decennia is de ontwikkeling van weesgeneesmiddelen echter gestimuleerd door regelgeving in verschillende landen. In de 10 jaar na de invoering van regelgeving voor weesgeneesmiddelen in de EU zijn er 63 middelen toegelaten tot de markt, alhoewel voor het merendeel van de zeldzame ziekten nog steeds geen behandeling bestaat. Echter, omdat ontwikkelingskosten moeten worden terugverdiend op een relatief klein aantal patiënten zijn de prijzen van weesgeneesmiddelen relatief hoog. Hierdoor worden beleidsmakers geconfronteerd met moeilijke beslissingen over het vergoeden van deze geneesmiddelen bij een vastgesteld budget; uitgaven aan één middel kunnen niet worden uitgegeven aan een andere behandeling. Health Technology Assessment (HTA) is een methodologie om op systematische wijze klinische, economische, maatschappelijke en ethische consequenties van het invoeren van een weesgeneesmiddel te onderzoeken. HTA kan door middel van deze informatie beleidsbeslissingen ondersteunen.

De ziekte van Pompe is de weesziekte die centraal staat in dit proefschrift. De ziekte van Pompe is een progressieve spierziekte die behoort tot de lysosomale stapelingsziekten. De ziekte wordt veroorzaakt door een deficiëntie van het enzym zure alfa-glucosidase. Hierdoor wordt glycogeen niet goed afgebroken en accumuleert het in de lysosomen. De ziekte heeft een breed klinisch spectrum dat loopt van een snel progressieve klassiek infantiele vorm tot een minder progressieve vorm in kinderen en volwassenen. Patiënten met de klassiek infantiele vorm sterven zonder specifieke behandeling doorgaans binnen het eerste levensjaar. Patiënten met een mildere vorm van de ziekte ervaren progressieve spierzwakte en ademhalingsproblemen. Het merendeel van de patiënten wordt rolstoelafhankelijk of gebruikt respiratoire ondersteuning; 15 jaar na diagnose gebruikt de helft van de patiënten een rolstoel en is ongeveer de helft van de patiënten afhankelijk van ademhalingsondersteuning. In 2006 kwam enzymtherapie (ERT) beschikbaar voor de ziekte van Pompe. Er zijn verschillende uitdagingen gemoeid met het uitvoeren van een HTA studie voor deze therapie, die alle min of meer gerelateerd zijn aan het kleine aantal patiënten. Veel vraagstukken over de toepassing van HTA bij weesziekten konden worden onderzocht omdat het Erasmus MC over een rijke database beschikt met klinische data en data over overleving, kwaliteit van leven en zorggebruik,

die niet alleen de periode sinds de goedkeuring van ERT beslaat, maar ook de jaren voorafgaand aan de behandeling. Bovendien was het op basis van internationale samenwerking mogelijk om de overleving van Pompe patiënten te schatten.

Het doel van dit proefschrift is inzicht te geven in de verschillende aspecten die de beslissingen over het vergoeden van weesgeneesmiddelen beïnvloeden, alsmede om HTA studies uit te voeren voor ERT in de ziekte van Pompe, en om bij te dragen aan het besluitvormingsproces inzake weesgeneesmiddelen.

Ziektelast vanuit verschillende perspectieven

In het eerste deel van het proefschrift wordt de ziektelast van de ziekte van Pompe vanuit verschillende perspectieven onderzocht, waaronder een financieel en economisch perspectief, het perspectief van de patiënt en het perspectief van de mantelzorger. **Hoofdstuk 2** behandelt de budgettaire impact van weesgeneesmiddelen in Nederland. Hoofdstuk 2 laat zien dat het aantal weesgeneesmiddelen en het aantal patiënten significant toenam in de periode 2006 tot 2012. In deze periode was er een substantiële stijging van budgetimpact, zowel in absolute termen (van €61 miljoen naar €260 miljoen) als in het relatieve aandeel van totale farmaceutische uitgaven (van 1,1% naar 4,2%). Voor 17% van de beschikbare weesgeneesmiddelen in 2012 was de budgetimpact hoger dan €10 miljoen per jaar.

Hoofdstuk 3 beschrijft de ziektelast van de ziekte van Pompe vanuit het perspectief van de patiënt en het maatschappelijk perspectief, in termen van kwaliteit van leven en maatschappelijke kosten bij volwassen Pompe patiënten die ondersteunende behandeling ontvangen. Kwaliteit van leven voor deze patiënten was 0,72; ofwel 17% lager dan voor de algemene Nederlandse bevolking. Een totaal van 40% van de patiënten moest stoppen met werken en nog eens 20% van de patiënten is minder gaan werken. Van deze patiënten gebruikte 85% mantelzorg. Jaarlijkse kosten waren €22.475 per patiënt (range €0 - €169.539).

Hoofdstuk 4 toont aan dat theoretisch gerelateerde dimensies van twee generieke kwaliteit van leven meetinstrumenten (EQ-5D en SF-6D), die gebruikt werden om de kwaliteit van leven van Pompe patiënten te meten, matig tot sterk correleerden. Utiliteiten die werden verkregen uit beide instrumenten waren ongeveer gelijk (gemiddelde EQ-5D = 0,670; gemiddelde SF-6D = 0,699) en correleerden sterk. De SF-6D beschreef de gezondheidstoestanden voor de ziekte van Pompe beter. Het onderscheidend vermogen van de EQ-5D was iets beter; SF-6D was beter in het meten van gemiddelde verandering en effectgrootte. Concluderend: de instrumenten bleken even geschikt met

betrekking tot het meten van utiliteiten in de ziekte van Pompe, maar geen van beide presteerde uitstekend.

In **hoofdstuk 5** is de impact van de ziekte van Pompe op de mantelzorger onderzocht. Mantelzorgers (ouders, partners, andere familieleden en vrienden van de patiënt) gaven gemiddeld 17,7 uur mantelzorg per week. De helft van de mantelzorgers gaf aan mentale gezondheidsproblemen en problemen met dagelijkse activiteiten te ondervinden vanwege het geven van mantelzorg. Het geven van mantelzorg leidde tot fysieke klachten bij 40% van de mantelzorgers. Desondanks meldden mantelzorgers voldoening te krijgen uit het geven van mantelzorg en, gemiddeld gezien, minder gelukkig zouden worden als iemand anders de zorg van hen zou overnemen.

Hoofdstuk 6 presenteert een conceptueel ziektemodel voor volwassen Pompe patiënten, dat is opgezet volgens het Wilson-Cleary model. In het conceptuele model worden de relaties beschreven tussen biologische parameters, fysiologische parameters, symptomen en functionele indicatoren, gezondheidspercepties en uiteindelijk gezondheidsgerelateerde kwaliteit van leven. Voor de ziekte van Pompe werden deze concepten geoperationaliseerd door enzymactiviteit, spierkracht en respiratoir functioneren, vermoeidheid, niveau van handicap, algemene gezondheidsperceptie, mentale en fysieke componenten schalen en utiliteiten.

Kosteneffectiviteit van ERT in de ziekte van Pompe

In het tweede deel van het proefschrift worden twee kosteneffectiviteitsmodellen gepresenteerd. **Hoofdstuk 7** beschrijft de kosteneffectiviteit van ERT (inclusief ondersteunende behandeling) in vergelijking tot ondersteunende behandeling (ST) bij volwassen patiënten met de ziekte van Pompe. Vanwege de onzekerheid die bestaat omtrent extrapolatie (met name van effecten), vooral als de tijdshorizon levenslang is, worden twee scenario's gepresenteerd. In scenario 1, waarin uitsluitend de overlevingswinsten van de geobserveerde periode worden opgenomen, zijn geen winsten in overleving na de geobserveerde periode gemodelleerd, als een ongunstig scenario. In scenario 2 worden wel overlevingswinsten geëxtrapoleerd na de geobserveerde periode. Voor beide scenario's werden substantiële winsten in overleving aangetoond: verdisconteerde winst in overleving door ERT varieerde van 1,9 jaar (scenario 1) tot 5,4 jaar (scenario 2). Daarnaast was ook kwaliteit van leven significant beter voor patiënten die ERT ontvingen. Incrementele kosten bestonden voornamelijk uit kosten van ERT. Incrementele kosten per QALY waren €3,2 miljoen (scenario 1) en €1,8 miljoen (scenario 2).

In **hoofdstuk 8** is de kosteneffectiviteit van ERT in patiënten met de klassiek-infantiele vorm van de ziekte van Pompe onderzocht. Het kosteneffectiviteitsmodel laat zien

dat de gemiddelde patiënt die ST ontving het eerste half jaar niet overleefde, terwijl de gemodelleerde levensverwachting van patiënten die met ERT behandeld werden bijna 14 jaar was. Bij een levenslange tijdshorizon werden 6,8 QALYs gewonnen door ERT. Incrementele kosten waren €7,0 miljoen, en bestonden voornamelijk (95%) uit behandelkosten. De incrementele kosten waren €1,0 miljoen per QALY en €0,5 miljoen per gewonnen levensjaar.

Gebruik van HTA in beleid voor weesgeneesmiddelen

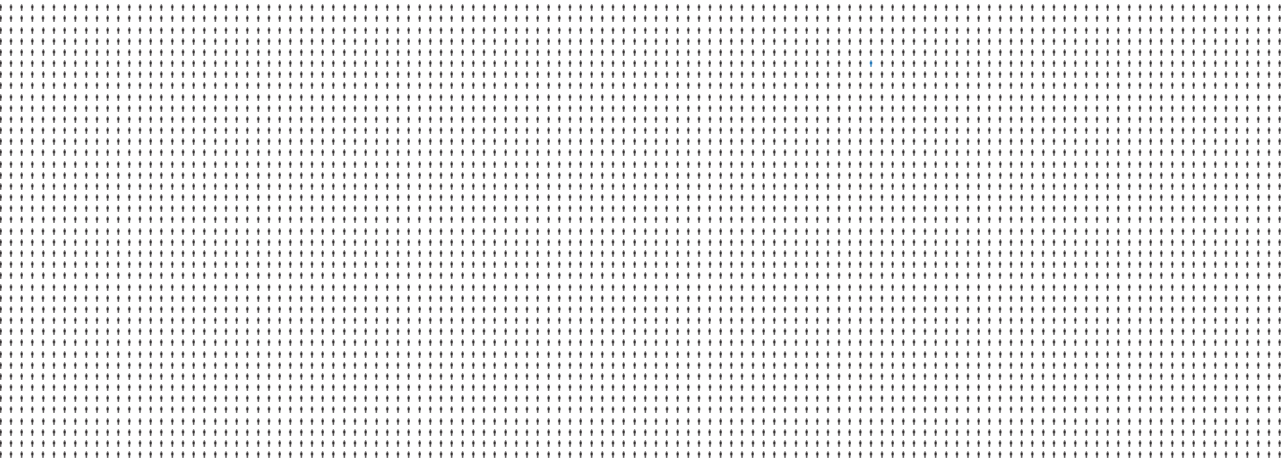
In het derde deel van het proefschrift is het gebruik van HTA in besluitvorming over weesgeneesmiddelen bestudeerd. **Hoofdstuk 9** toont de variatie tussen zes Europese landen in de beslissingen om ERT in de ziekte van Pompe al dan niet te vergoeden. In de meeste landen in onze studie (Engeland, Frankrijk, Italië en België)[2] werd ERT vergoed voor alle patiënten, terwijl in Wales ERT uitsluitend werd vergoed voor klassiek-infantiele en juveniele patiënten maar niet voor volwassen patiënten. ERT werd niet vergoed in Schotland. Meer transparantie in de besluitvorming is nodig om te bepalen of de verschillen in vergoeding het resultaat zijn van verschillen in de technische beoordeling van het beschikbare bewijs of in de maatschappelijke waardering van het bewijs, of beide. Transparantie kan worden verhoogd door het gebruik van een alternatieve aanpak, zoals Multi-Criteria Decision Making (MCDA), een methode waarmee de impact van verschillende criteria en hun relatieve gewicht expliciet gemaakt wordt. Hierdoor kan de transparantie, consistentie, geloofwaardigheid en verantwoording van vergoedingsbeslissingen verbeteren. Het lost echter het vraagstuk over de bereidheid tot betalen niet op.

De toepasbaarheid van richtlijnen voor farmacoeconomisch onderzoek op weesgeneesmiddelen en de criteria die worden gebruikt voor vergoedingsbeslissingen zijn onderzocht in **hoofdstuk 10**. Interviews en vergoedingsdossiers laten zien dat het vereiste bewijs voor de effectiviteit niet noodzakelijkerwijs lager hoeft te zijn voor weesgeneesmiddelen dan voor niet-weesgeneesmiddelen. Bovendien werden de huidige farmacoeconomische richtlijnen en de richtlijnen voor budgetimpact studies ook op weesgeneesmiddelen van toepassing geacht. In de maatschappelijke afweging van bewijs werden additionele criteria gebruikt (beperkte budgetimpact, zeldzaamheid van de ziekte, lage leeftijd van de populatie, identificeerbaarheid van patiënten, en afwezigheid van alternatieve behandelingen) in aanvulling op de reguliere criteria voor niet-weesgeneesmiddelen (noodzakelijkheid, effectiviteit, kosteneffectiviteit en uitvoerbaarheid).

[2] Nadat onze studie was afgerond bleek dat ERT ook in Duitsland vergoed wordt

Discussie

Ten slotte beschrijft **hoofdstuk 11** verschillende perspectieven van patiënten, artsen, farmaceutische industrie, algemeen publiek, beleidsmakers en politici op het voorlopige advies uit 2012 van het Zorginstituut om te stoppen met vergoeding van ERT in de ziekte van Pompe. Beschreven wordt hoe het daaropvolgende debat uiteindelijk leidde tot de beslissing om ERT wel te vergoeden (na een prijsonderhandeling over ERT) en hoe dit het beleid voor weesgeneesmiddelen in het algemeen heeft beïnvloed. In hoofdstuk 11 worden ook verschillende aanpassingen in huidig beleid en regelgeving voor weesgeneesmiddelen besproken met betrekking tot marktexclusiviteit, prijsstelling, prikkels om de ontwikkeling van weesgeneesmiddelen te stimuleren en alternatieve verdienmodellen. Ten slotte worden methodologische uitdagingen voor HTA research in weesgeneesmiddelen besproken en suggesties gegeven voor toekomstig HTA onderzoek, zoals verder onderzoek naar MCDA en verdringingseffecten.



PhD Portfolio,
List of publications,
About the author

PhD Portfolio

PhD candidate: Tim A. Kanters

Institute: institute of Health Policy & Management,
Erasmus University Rotterdam, the Netherlands

PhD period: 2008-2016

Promotors: Prof.dr. M.P.M.H. Rutten-van Mölken
Prof.dr. A.T. van der Ploeg

Copromotor: Dr. L. Hakkaart-van Roijen

PhD Training

Speaking skills for staff C1. Erasmus University Rotterdam. 2016.

Q-methodology. International Society for the Scientific Study of Subjectivity. 2013.

Repeated measurements. Netherlands Institute for Health Sciences. 2012.

Survival analyses. Netherlands Institute for Health Sciences. 2010.

Academic writing in English. Leiden University. 2010.

Advanced modelling methods for health economic evaluations. University York. 2009.

Prognosis research. Netherlands Institute for Health Sciences. 2009.

Teaching

Pharmaceutical Pricing and Market Access, Master program Health Economics Policy & Law, Erasmus University Rotterdam. Co-coordinator & Tutor. 2014-2016.

Health Technology Assessment, Master program Health Economics Policy & Law, Erasmus University Rotterdam. Instructor computer lab. 2014-2016.

Bachelor theses, Bachelor program Health Sciences 3rd year, Erasmus University Rotterdam. Supervisor and co-evaluator. 2012-2016.

Quantitative research in healthcare, Bachelor program Health Sciences 2nd year, Erasmus University Rotterdam. Tutor. 2009-2016.

Master theses, Master program Health Economics Policy & Law, Erasmus University Rotterdam. Supervisor and co-evaluator. 2013-2015.

Statistics B, Pre-master program Health Economics Policy & Law, Erasmus University Rotterdam. Tutor. 2013-2014.

Health Economics, NIHES Summer School, Erasmus University Rotterdam. Instructor computer lab. 2012-2014.

Methods & Techniques 1, Bachelor program Health Sciences 1st year, Erasmus University Rotterdam. Tutor. 2012-2013.

Startweek, Bachelor program Health Sciences 1st year, Erasmus University Rotterdam. Tutor. 2010.

Podium presentations

Standard costs in the Netherlands: Dutch costing manual. 8. Dggö Jahrestagung 2016: Berlin, Germany. 2016.

Priority Setting and Orphan Drugs. Prioriteringskonferens 2015: Norrköpping, Sweden. 2015.

Budget impact of orphan drugs in NL. Orphan Drug Summit 5th edition: Copenhagen, Denmark. 2015.

Cost-effectiveness of Enzyme Replacement Therapy with alglucosidase alfa in classic-infantile patients with Pompe disease [Discussed]. LolaHESG 2013: Nunspeet, the Netherlands. 2013.

A conceptual disease model for Pompe disease: the backbone for an economic evaluation of an orphan drug. ISPOR 13th annual European congress: Prague, Czech Republic. 2010.

Prevention and risk equalization: A different prevention paradox? 8th European Conference on Health Economics: Helsinki, Finland. 2010.

Cost-effectiveness research under policy rule for orphan drugs [presentation in Dutch: Doelmatigheidsonderzoek in kader van beleidsregel weesgeneesmiddelen]. Symposium Weesgeneesmiddelen: Houten, Nederland. 2009.

Cost-effectiveness research under policy rule for orphan drugs [presentation in Dutch: Doelmatigheidsonderzoek in kader van beleidsregel weesgeneesmiddelen]. Stuurgroep Weesgeneesmiddelen: Utrecht, Nederland. 2009.

Poster presentations

Cost-effectiveness of omalizumab in Chronic Spontaneous Urticaria in the Netherlands. ISPOR 18th annual European congress: Milan, Italy. 2015.

Budget impact of orphan drugs in the Netherlands in the period 2006-2012. ISPOR 17th annual European congress: Amsterdam, the Netherlands. 2014.

Cost-effectiveness of enzyme replacement therapy in patients with classic-infantile Pompe disease. ISPOR 16th annual European congress: Dublin, Ireland. 2013.

Factors predicting reimbursement decisions on orphan drugs in eight countries. ISPOR 15th annual European congress: Berlin, Germany. 2012.

Comparison of EQ-5D and SF-6D utilities in Pompe disease. ISPOR 14th annual European congress: Madrid, Spain. 2011.

Burden of illness of Pompe disease not treated with Enzyme Replacement Therapy. 8th European Conference on Health Economics: Helsinki, Finland. 2010.

Publications in this thesis

Kanters TA, Hakkaart L, Rutten-van Mölken MPMH, Redekop WK (2015) Access to orphan drugs in western Europe: can more systematic policymaking really help to avoid different decisions about the same drug? *Expert Rev Pharmacoecon Outcomes Res* 15(4):557-559

Kanters TA, Redekop WK, Kruijshaar ME, Van der Ploeg AT, Rutten-van Mölken MPMH, Hakkaart L (2015) Comparison of EQ-5D and SF-6D utilities in Pompe disease. *Qual Life Res* 24:837-844

Kanters TA, Redekop WK, Rutten-van Mölken MPMH, Kruijshaar ME, Güngör D, Van der Ploeg AT, Hakkaart L (2015) A conceptual disease model for adult Pompe disease. *Orphanet J Rare Dis* 10:112

Kanters TA, Steenhoek A, Hakkaart L (2014) Orphan drugs expenditure in the Netherlands in the period 2006-2012. *Orphanet J Rare Dis* 9:154

Kanters TA, Hoogenboom-Plug I, Rutten-van Mölken MPMH, Redekop WK, Van der Ploeg AT, Hakkaart L (2014) Cost-effectiveness of enzyme replacement therapy with alglucosidase alfa in classic-infantile patients with Pompe disease. *Orphanet J Rare Dis* 9:75

Kanters TA, Van der Ploeg AT, Brouwer WBF, Hakkaart L (2013) The impact of informal care for patients with Pompe disease: An application of the CarerQol instrument. *Mol Genet Metab* 110:281-286

Kanters TA, Hagemans MLC, Van der Beek NAME, Rutten, FFH, Van der Ploeg AT, Hakkaart L (2011) Burden of illness of Pompe disease in patients only receiving supportive care. *J Inherit Metab Dis* 34:1045-1052

Kanters TA, Van der Ploeg, AT, Kruijshaar ME, Rizopoulos D, Redekop WK, Rutten-van Mölken MPMH, Hakkaart L. Cost-effectiveness of enzyme replacement therapy in adult Pompe disease, *Submitted*

Kanters TA, Hollak CEM, Van der Ploeg AT, Rutten-van Mölken MPMH, Hakkaart L. Evaluation of orphan drugs in the Netherlands: can HTA offer guidance to healthcare policy? *Submitted*

Other scientific publications

Kanters TA, Wolff C, Boyson D, Kouakam C, Dinh T, Hakkaart L, Rutten-van Mölken MPMH (2016) Cost comparison of two implantable cardiac monitors in two different settings: Reveal XT in a catheterization laboratory vs. Reveal LINQ in a procedure room. *Europace* 18:919-924

Güngör D, Kruijshaar ME, Plug I, Rizopoulos D, **Kanters TA**, Wens SCA, Reuser AJJ, Van Doorn PA, Van der Ploeg AT (2016) Quality of life and participation in daily life of adults with Pompe disease receiving enzyme replacement therapy: 10 years of international follow-up. *J Inherit Metab Dis* 39(2):253-260

Kanters TA, De Sonneville-Koedoot C, Redekop WK, Hakkaart L (2013) Systematic review of available evidence on 11 high-priced inpatient orphan drugs. *Orphanet J Rare Dis* 8:124

Kanters TA, Brouwer WBF, Van Vliet RCJA, Van Baal PHM, Polder JJ (2013) A new prevention paradox: The trade-off between reducing incentives for risk selection and increasing the incentives for prevention for health insurers. *Soc Sci Med* 76:150-158

Other professional publications

Riemsma R, Büyükkaramikli N, **Kanters T**, Armstrong N, Leadley R, Fayter D, Stirk L, Worthy G, Al M, Kleijnen J (2016) Grazoprevir-elbasvir for treating chronic hepatitis C; A Single Technology Assessment. York, United Kingdom: Kleijnen Systematic Reviews Ltd

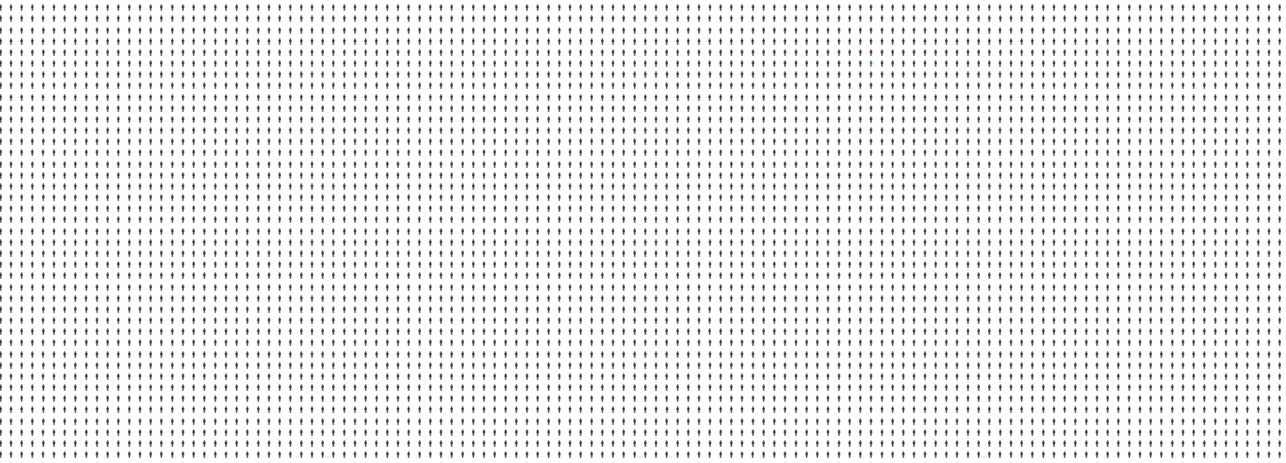
Hakkaart-van Roijen L, Van der Linden N, Bouwmans C, **Kanters T**, Tan SS (2015) Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Diemen, the Netherlands: Zorginstituut Nederland

Riemsma R, Büyükkaramikli N, Corro Ramos I, Armstrong N, Blommestein H, Westwood M, Portegijs P, **Kanters T**, Worthy G, Ross J, Al M, Severens JL, Kleijnen J (2015) Asfotase alfa for treating paediatric-onset hypophosphatasia: a Highly Specialised Technology Evaluation. York, United Kingdom: Kleijnen Systematic Reviews Ltd

Kanters TA, Van der Ploeg AT, Rutten-van Mölken MPMH, Hakkaart L (2013) Vergoeding duur middel vraagt breder fundament. *Medisch Contact* 68:2150-2153

About the author

Tim Kanters (1983) was born in Utrecht. In 2002, he graduated from the St. Bonifatius College, Utrecht. In 2007, he obtained his Master's degree in Economics & Geography at the University of Utrecht and obtained his Master's degree in Health Economics at Erasmus University Rotterdam in 2008. That same year, he started as a junior researcher at Erasmus University Rotterdam, at the Department of Health Policy & Management (iBMG). His work focussed on HTA research on orphan drugs. The economic evaluation of enzyme replacement therapy in Pompe disease was the main topic of his PhD thesis. In addition, he worked on the economic evaluation of three other rare diseases and on a study on the applicability of HTA guidelines in orphan drugs financed by ZonMw. Besides his work on rare diseases, he worked on several projects, such as the 2015 update of the Dutch costing manual.



Dankwoord

Aan de totstandkoming van dit proefschrift hebben velen, direct of indirect, bijgedragen. Ik wil iedereen hiervoor hartelijk bedanken. Een aantal personen wil ik in het bijzonder noemen.

Leona, bedankt voor je begeleiding, voor het lezen van talloze stukken, het vergezellen bij afspraken en de gezelligheid in de afgelopen acht jaar. Ik heb bovendien veel geleerd van het schrijven van subsidievoorstellen en van alle andere projecten waar we samen op werk(t)en. De grote mate van vertrouwen en vrijheid die je me daarbij geeft, waardeer ik zeer.

Maureen, jouw scherpe blik heeft mijn proefschrift vele malen beter gemaakt. Bedankt daarvoor. Jouw commentaar, variërend van details tot hoofdlijnen, is nauwkeurig en zet aan tot nadenken. Je inspireert en motiveert tot gedegen onderzoek door de lat hoog te leggen. Ik ben blij jou als promotor te hebben.

Ans en andere collega's van het Centrum voor Lysosomale en Metabole Ziekten, bedankt voor het verzamelen van de data, het gebruik van jullie dataset en de praktische hulp daarbij, en jullie gastvrijheid als ik op het Erasmus MC was om zelf data in te voeren. Ans, in de vele discussies die wij hebben gehad leken onze verschillende achtergronden nog wel eens te botsen, maar deze hebben uiteindelijk bijgedragen aan het expliciteren van de verschillende perspectieven en hebben het proefschrift verbeterd. Bedankt daarvoor. Michelle en Iris, bedankt voor het kritisch lezen van de verschillende artikelen. Jan-Dietert, bedankt voor al je hulp vanuit de apotheek.

De leden van de promotiecommissie wil ik hartelijk bedanken voor het beoordelen van mijn proefschrift.

Frans, alhoewel Maureen mijn 1e promotor is, was jij mijn eerste promotor. Bedankt voor je input destijds. Ken, bedankt voor alle keren dat ik bij je kon binnenlopen met mijn vragen, ook al had je geen formele rol in mijn promotie. Ik heb veel van je geleerd.

De collega's van het iBMG maken het werk nog leuker. Het is een voorrecht om van collega's je vrienden te kunnen maken. Apo, Hedwig, Igna, Laura, Matthijs, Pieter en Saskia, fijn dat we nu als collectief gepromoveerd zijn! Mijn kamergenoten van de afgelopen jaren wil ik bedanken voor hun interesse, gerelateerd aan dit proefschrift of juist niet. Menno, ik hoop dat ook jij je proefschrift snel kan afronden. Annemieke, jouw vrolijkheid fleurt onze kamer op. Sas, helaas promoveren we niet op dezelfde dag, maar het scheelt niet veel. Het is fijn om, naast de laatste stappen van een promotietraject, ook een kamer met jou te delen. Bedankt dat je er altijd bent.

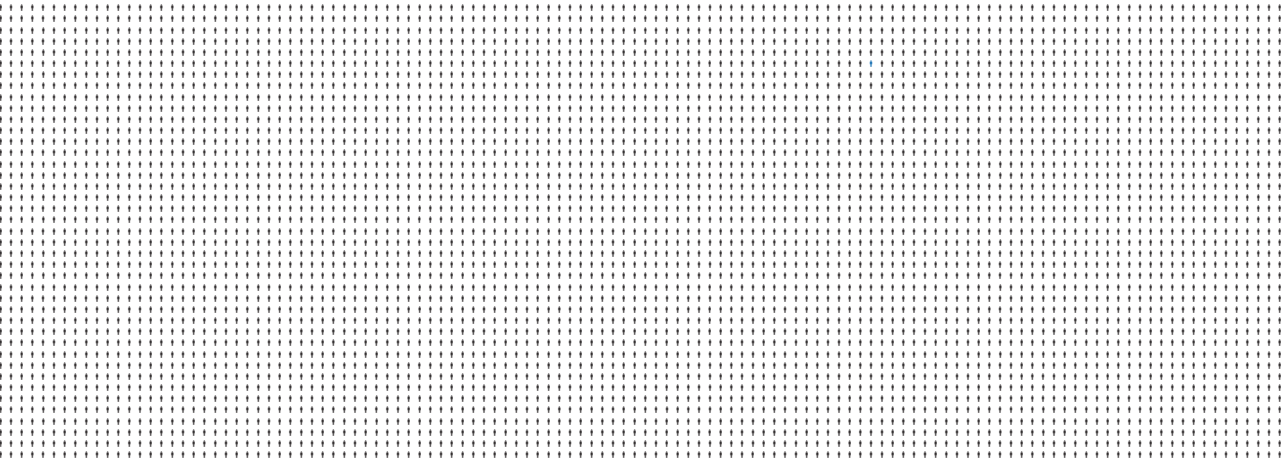
Willem, je bent een vriend voor het leven. Bedankt voor je humor, interesse en je vriendschap. David, Maarten, Marc, Paul en Steven, bedankt voor jullie belangstelling en voor al het plezier dat we al zo lang samen maken. Het voelt vertrouwd bij jullie, ook als we elkaar al langere tijd niet hebben gezien. De jongens van de Sporting selectie weten hoeveel tijd, pijn en moeite het kost om te promoveren. De afleiding die het voetbal geeft blijkt telkens weer onmisbaar.

Mijn paranimfen Paul en Matthijs. Paul, ik ben blij dat je achter me staat, niet alleen vandaag. Je bent een vriend waar ik op kan bouwen. Matthijs, ik ben zo blij dat je weer terug bent op de EUR. Bedankt voor al je adviezen, humor, en de gezellige autoritten.

Jaap en Tiny, Menno en Eelker, bedankt voor jullie belangstelling in mijn proefschrift. Jeanne en Jan, Toon en Beer, bedankt voor jullie interesse en dat ik altijd welkom ben bij jullie. Mari, ik vind het geweldig om samen met jou dingen te ondernemen, op Sporting en daarbuiten. Ik geniet ervan dat jij en ik dezelfde humor hebben. Ik word blij van je oprechte enthousiasme. Danny, je bent een aanwinst voor onze familie.

H&D, jullie betrokkenheid en interesse in mijn promotieonderzoek en daarbuiten waardeer ik enorm. Het is fijn dat ik met jullie, al dan niet inhoudelijk, over mijn werk kan praten, en dat jullie ook begrijpen dat ik soms juist over iets anders wil praten. Mijn dank voor jullie onvoorwaardelijke steun en liefde is niet in woorden te beschrijven, laat staan uit te spreken.

Lieve Femke, dagelijks reizen naar Rotterdam leverde niet alleen dit proefschrift op, maar ook onze eerste ontmoeting. Toen gingen we samen de poortjes door, nu reizen we samen de wereld over. Ik kijk uit naar alles dat we samen nog gaan beleven. Jij maakt me gelukkig.



References

1. Joppi R, Bertele' V, Garattini S. (2013) Orphan drugs, orphan diseases. The first decade of orphan drug legislation in the EU. *Eur J Clin Pharmacol.* 69:1009-1024.
2. European Commission. (2000) Regulation (EC) no 141/2000 of the European parliament and of the council of 16 December 1999 on orphan medicinal products. *Off J Eur Comm.* L18/1:1-5.
3. Richter T, Nestler-Parr S, Babela R, Khan ZM, Tesoro T, et al. (2015) Rare disease terminology and definitions - A systematic global review: Report of the ISPOR rare disease special interest group. *Value Health.* 18:906-914.
4. Gammie T, Lu CY, Babar ZU. (2015) Access to orphan drugs: A comprehensive review of legislations, regulations and policies in 35 countries. *PloS One.* 10:e0140002.
5. Franco P. (2013) Orphan drugs: The regulatory environment. *Drug Discov Today.* 18:163-172.
6. Wellman-Labadie O, Zhou Y. (2010) The US orphan drug act: Rare disease research stimulator or commercial opportunity? *Health Policy.* 95:216-228.
7. Dolgin E. (2010) Big pharma moves from 'blockbusters' to 'niche busters'. *Nat Med.* 16:837-837.
8. Phillips MI. (2013) Big pharma's new model in orphan drugs and rare diseases. *Exp Opin Orphan Drugs.* 1:1-3.
9. Wästfelt M, Fadeel B, Henter J. (2006) A journey of hope: Lessons learned from studies on rare diseases and orphan drugs. *J Intern Med.* 260:1-10.
10. Wilcken B. (2001) Rare diseases and the assessment of intervention: What sorts of clinical trials can we use? *J Inherit Metab Dis.* 24:291-298.
11. Luisetti M, Campo I, Scabini R, Zorzetto M, Kadija Z, et al. (2010) The problems of clinical trials and registries in rare diseases. *Respir Med.* 104:S42-S44.
12. Buckley BM. (2008) Clinical trials of orphan medicines. *Lancet.* 371:2051-2055.
13. Picavet E, Cassiman D, Hollak CE, Maertens JA, Simoens S. (2013) Clinical evidence for orphan medicinal products - a cause for concern? *Orphanet J Rare Dis.* 8:
14. Thadhani R (2006) Formal trials versus observational studies. In: Mehta A, Beck M & Sunder-Plassmann G (Eds.) *Fabry disease: Perspectives from 5 years of FOS.* Oxford, United Kingdom: Oxford PharmaGenesis.
15. Kishnani PS, Corzo D, Nicolino M, Byrne B, Mandel H, et al. (2007) Recombinant human acid α-glucosidase: Major clinical benefits in infantile-onset Pompe disease. *Neurology.* 68:99-109.
16. Luisetti M, Balfour-Lynn IM, Johnson SR, Miravitlles M, Strange C, et al. (2012) Perspectives for improving the evaluation and access of therapies for rare lung diseases in Europe. *Respir Med.* 106:759-768.
17. Forrest CB, Bartek RJ, Rubinstein Y, Groft SC. (2011) The case for a global rare-diseases registry. *Lancet.* 377:1057-1059.
18. Vegter S, Rozenbaum MH, Postema R, Tolley K, Postma MJ. (2010) Review of regulatory recommendations for orphan drug submissions in the Netherlands and Scotland: Focus on the underlying pharmacoeconomic evaluations. *Clin Ther.* 32:1651-1661.
19. De Varax A, Letellier M, Börtlein G. (2004) *Study on orphan drugs. Phase I: Overviews of the conditions for marketing orphan drugs in Europe*. Paris, France: Alcimed.
20. Gregson N, Sparrowhawk K, Mauskopf J, Paul J. (2005) A guide to drug discovery: Pricing medicines: Theory and practice, challenges and opportunities. *Nat Rev Drug Discov.* 4:121-130.
21. Schey C, Milanova T, Hutchings A. (2011) Estimating the budget impact of orphan medicines in Europe: 2010-2020. *Orphanet J Rare Dis.* 6:62.
22. Denis A, Mergaert L, Fostier C, Cleemput I, Simoens S. (2010) Budget impact analysis of orphan drugs in Belgium: Estimates from 2008 to 2013. *J Med Econ.* 13:295-301.

23. Divino V, DeKoven M, Kim T, Kleinrock M, Wade RL, Kaura S. (2015) The budget impact of orphan drugs in the US and Canada: A 2007-2013 Midas sales data analysis. *Value Health.* 18:A666.
24. Divino V, DeKoven M, Kleinrock M, Wade RL, Kim T, Kaura S. (2016) Pharmaceutical expenditure on drugs for rare diseases in Canada: A historical (2007–13) and prospective (2014–18) MIDAS sales data analysis. *Orphanet J Rare Dis.* 11:1.
25. Hutchings A, Schey C, Dutton R, Achana F, Antonov K. (2014) Estimating the budget impact of orphan drugs in Sweden and France 2013-2020. *Orphanet J Rare Dis.* 9:22.
26. Van der Ploeg AT, Reuser AJJ. (2008) Pompe's disease. *Lancet.* 372:1342-1353.
27. Pompe JC. (1932) Concerning idiopathic hypertrophy of the heart [in Dutch: Over idiopathische hypertrofie van het hart]. *Ned Tijdsch Geneesk.* 76:304-311.
28. Hers HG. (1963) A-glucosidase deficiency in generalized glycogen-storage disease (Pompe's disease). *Biochem J.* 86:11.
29. De Duve C, Pressman BC, Gianetto R, Wattiaux R, Appelmans F. (1955) Tissue fractionation studies. 6. Intracellular distribution patterns of enzymes in rat-liver tissue. *Biochem J.* 60:604-617.
30. Ausems MGEM, Verbiest J, Hermans MMP, Kroos MA, Beemer FA, et al. (1999) Frequency of glycogen storage disease type II in the Netherlands: Implications for diagnosis and genetic counselling. *Eur J Hum Genet.* 7:713-716.
31. Güngör D, Reuser AJJ. (2013) How to describe the clinical spectrum in Pompe disease? *Am J Med Genet.* 161:399-400.
32. Van den Hout HMP, Hop W, Van Diggelen OP, Smeitink JAM, Smit GPA, et al. (2003) The natural course of infantile Pompe's disease: 20 original cases compared with 133 cases from the literature. *Pediatrics.* 112:332-340.
33. Kishnani PS, Hwu WL, Mandel H, Nicolino M, Yong F, Corzo D. (2006) A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. *J Pediatr.* 148:671-676. e2.
34. Hagemans MLC, Winkel LPF, Hop WCJ, Reuser AJJ, Van Doorn PA, Van der Ploeg AT. (2005) Disease severity in children and adults with Pompe disease related to age and disease duration. *Neurology.* 64:2139-2141.
35. Hagemans MLC, Winkel LPF, Van Doorn PA, Hop WJC, Loonen MCB, et al. (2005) Clinical manifestation and natural course of late-onset Pompe's disease in 54 Dutch patients. *Brain.* 128:671-677.
36. Winkel LPF, Hagemans MLC, Van Doorn PA, Loonen MCB, Hop WJC, et al. (2005) The natural course of non–classic Pompe's disease; a review of 225 published cases. *J Neurol.* 252:875-884.
37. Hagemans MLC, Janssens A, Winkel LPF, Sieradzan KA, Reuser AJJ, et al. (2004) Late-onset Pompe disease primarily affects quality of life in physical health domains. *Neurology.* 63:1688-1692.
38. Güngör D, De Vries JM, Hop WCJ, Reuser AJJ, Van Doorn PA, et al. (2011) Survival and associated factors in 268 adults with Pompe disease prior to treatment with enzyme replacement therapy. *Orphanet J Rare Dis.* 6:34.
39. Hagemans MLC, Laforet P, Hop WJC, Merkies ISJ, Van Doorn PA, et al. (2007) Impact of late-onset Pompe disease on participation in daily life activities: Evaluation of the Rotterdam Handicap Scale. *Neuromuscular Disorders.* 17:537-543.
40. Kornfeld S. (1986) Trafficking of lysosomal enzymes in normal and disease states. *J Clin Invest.* 77:1-6.
41. Van der Ploeg AT, Bolhuis PA, Wolterman RA, Visser JW, Loonen MCB, et al. (1988) Prospect for enzyme therapy in glycogenosis II variants: A study on cultured muscle cells. *J Neurol.* 235:392-396.

42. Hoefsloot LH, Hoogeveen-Westerveld M, Kroos MA, Van Beeumen J, Reuser AJ, Oostra BA. (1988) Primary structure and processing of lysosomal alpha-glucosidase; homology with the intestinal sucrase-isomaltase complex. *Embo J.* 7:1697-1704.
43. Bijvoet AG, Van Hirtum H, Kroos MA, Van de Kamp EH, Schoneveld O, et al. (1999) Human acid alpha-glucosidase from rabbit milk has therapeutic effect in mice with glycogen storage disease type II. *Hum Mol Genet.* 8:2145-2153.
44. Van den Hout JMP, Reuser AJJ, De Klerk JBC, Arts WF, Smeitink JAM, Van der Ploeg AT. (2001) Enzyme therapy for Pompe disease with recombinant human α-glucosidase from rabbit milk. *J Inherit Metab Dis.* 24:266-274.
45. Kishnani PS, Corzo D, Leslie ND, Gruskin D, Van der Ploeg A, et al. (2009) Early treatment with alglucosidase alfa prolongs long-term survival of infants with Pompe disease. *Pediatr Res.* 66:329-335.
46. Van der Ploeg AT, Clemens PR, Corzo D, Escolar DM, Florence J, et al. (2010) A randomized study of alglucosidase alfa in late-onset Pompe's disease. *N Engl J Med.* 362:1396-1406.
47. De Vries JM, Van der Beek NAME, Hop WCJ, Karstens FPJ, Wokke JH, et al. (2012) Effect of enzyme therapy and prognostic factors in 69 adults with Pompe disease: An open-label single-center study. *Orphanet J Rare Dis.* 7:73.
48. Güngör D, Kruijshaar ME, Plug I, Rizopoulos D, Kanters TA, et al. (2016) Quality of life and participation in daily life of adults with Pompe disease receiving enzyme replacement therapy: 10 years of international follow-up. *J Inherit Metab Dis.* 39:253-260.
49. Güngör D, Kruijshaar ME, Plug I, D'Agostino RB, Hagemans MLC, et al. (2013) Impact of enzyme replacement therapy on survival in adults with Pompe disease: Results from a prospective international observational study. *Orphanet J Rare Dis.* 8:49.
50. Schoser B, Laforêt P, Kruijshaar ME, Toscano A, Van Doorn PA, Van der Ploeg AT. (2015) 208th ENMC international workshop: Formation of a European network to develop a European data sharing model and treatment guidelines for Pompe disease. Naarden, the Netherlands, 26–28 September 2014. *Neuromuscul Disord.* 25:674-678.
51. College voor zorgverzekeringen. (2012) *Advice on alglucosidase alfa (myozyme®) in the indication 'Pompe disease' [in Dutch: Advies alglucosidase alfa (myozyme®) bij de indicatie 'ziekte van Pompe']*. Diemen, the Netherlands: College voor zorgverzekeringen.
52. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW: 2015. *Methods for the economic evaluation of health care programmes*. Oxford, United Kingdom: Oxford University Press;
53. Draborg E, Gyrd-Hansen D, Bo Poulsen P, Horder M. (2005) International comparison of the definition and the practical application of health technology assessment. *Int J Technol Assess Health Care.* 21:89-95.
54. Zwaap J, Knies S, Van der Meijden C, Staal P, Van der Heiden L. (2015) *Cost-effectiveness in practice [in Dutch: Kosteneffectiviteit in de praktijk]* No. 2015076142. Diemen, the Netherlands: Zorginstituut Nederland.
55. Van de Wetering EJ, Stolk EA, Van Exel NJA, Brouwer WBF. (2013) Balancing equity and efficiency in the Dutch basic benefits package using the principle of proportional shortfall. *Eur J Health Econ.* 14:107-115.
56. Franken M, Le Polain M, Cleemput I, Koopmanschap M. (2012) Similarities and differences between five European drug reimbursement systems. *Int J Technol Assess Health Care.* 28:349-357.
57. Franken M, Stolk E, Scharringhausen T, de Boer A, Koopmanschap M. (2015) A comparative study of the role of disease severity in drug reimbursement decision making in four European countries. *Health Policy.* 119:195-202.

58. College voor zorgverzekeringen. (2013) *Management of the basic benefit package in practice part 3 [in Dutch: Pakketbeheer in de praktijk (deel 3)]*. Diemen, the Netherlands: College voor zorgverzekeringen.
59. Staal PC, Heymans J, Ligtenberg G, Derksen JTM, Couwenbergh BTLE. (2015) *Assessment current medical science and practice [in Dutch: Beoordeling stand van wetenschap en praktijk]* No. 2014116583. Diemen, the Netherlands: Zorginstituut Nederland.
60. Le Polain M, Franken M, Koopmanschap MA, Cleemput I. (2010) *Drug reimbursement systems: International comparison and policy recommendations* No. 147C. Brussels, Belgium: Belgian Health Care Knowledge Centre (KCE).
61. Nederlandse Zorgautoriteit. (2006) *Policy rule CI-1133: Orphan drugs in university hospitals [in Dutch: Beleidsregel CI-1133: Weesgeneesmiddelen in academische ziekenhuizen]* No. CI-1133. Utrecht, the Netherlands: Nederlandse Zorgautoriteit.
62. College voor zorgverzekeringen. (2012) *Advice on alglucosidase alfa (myozyme®) in the indication 'Pompe disease': Draft [in Dutch: Advies alglucosidase alfa (myozyme®) bij de indicatie 'ziekte van Pompe' concept]* No. 2012035967). Diemen, the Netherlands: College voor zorgverzekeringen.
63. Schippers EI. (2013) *Position on Pompe and Fabry [in Dutch: Standpunt Pompe en Fabry]* No. 155165-111008-GMT. The Hague, the Netherlands: Ministry of Health.
64. Burls A, Austin D, Moore D. (2005) Commissioning for rare diseases: View from the frontline. *Bmj.* 331:1019-1021.
65. Sheldon T. (2012) Dutch doctors call for EU evaluation of cost effectiveness of high cost orphan drugs. *Bmj.* 345:e5461.
66. Hughes DA, Tunnage B, Yeo ST. (2005) Drugs for exceptionally rare diseases: Do they deserve special status for funding? *Qjm.* 98:829-836.
67. Cohen J, Stolk E, Niezen M. (2007) The increasingly complex fourth hurdle for pharmaceuticals. *Pharmacoeconomics.* 25:727-734.
68. Mauskopf JA, Sullivan SD, Annemans L, Caro J, Mullins CD, et al. (2007) Principles of good practice for budget impact analysis: Report of the ISPOR task force on good research practices - budget impact analysis. *Value Health.* 10:336-347.
69. Orofino J, Soto J, Casado MA, Oyagüez I. (2010) Global spending on orphan drugs in France, Germany, the UK, Italy and Spain during 2007. *Appl Health Econ Health Policy.* 8:301-315.
70. College voor zorgverzekeringen. (2013). *GIP database [in Dutch: GIP databank].* Retrieved 04/30, 2014, from www.gipdatabank.nl
71. Stichting Farmaceutische Kengetallen. (2010) *Monitor expensive drugs 2008: Costs of expensive and orphan drugs in hospitals [in Dutch: Monitor dure geneesmiddelen 2008: Kosten van dure- en weesgeneesmiddelen in het ziekenhuis]*. The Hague, the Netherlands: Stichting Farmaceutische Kengetallen.
72. FarmInform. (2013) *MAT turnover development on the basis of euro AIP* FarmInform.
73. Hirschhorn R, & Reuser AJJ (2001) Glycogen storage disease type II: Acid alpha-glucosidase (acid maltase) deficiency. In: Scriver CR, Beaudet AL, Sly W & Valle D (Eds.) *The metabolic and molecular bases of inherited disease.* 8th ed., pp. 3389-3420. New York, United States: New York: McGraw Hill.
74. Laforet P, Nicolino M, Eymard B, Puech JP, Caillaud C, et al. (2000) Juvenile and adult-onset acid maltase deficiency in France. *Neurology.* 55:1122-1128.
75. Martiniuk F, Chen A, Mack A, Arvanitopoulos E, Chen Y, et al. (1998) Carrier frequency for glycogen storage disease type II in New York and estimates of affected individuals born with the disease. *Am J Med Genet.* 79:69-72.

76. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. (1999) Prevalence of lysosomal storage disorders. *Jama.* 281:249-254.
77. Van den Hout H, Reuser AJJ, Vulto AG, Loonen MCB, Cromme-Dijkhuis A, Van der Ploeg AT. (2000) Recombinant human [alpha]-glucosidase from rabbit milk in Pompe patients. *Lancet.* 356:397-398.
78. Barton NW, Brady RO, Dambrosia JM, Di Bisceglie AM, Doppelt SH, et al. (1991) Replacement therapy for inherited enzyme deficiency—macrophage-targeted glucocerebrosidase for Gaucher's disease. *N Engl J Med.* 324:1464-1470.
79. Eng CM, Guffon N, Wilcox WR, Germain DP, Lee P, et al. (2001) Safety and efficacy of recombinant human α-galactosidase A replacement therapy in Fabry's disease. *N Engl J Med.* 345:9-16.
80. Schiffmann R, Kopp JB, Austin III HA, Sabnis S, Moore DF, et al. (2001) Enzyme replacement therapy in Fabry disease. *Jama.* 285:2743-2749.
81. Kakkis ED, Muenzer J, Tiller GE, Waber L, Belmont J, et al. (2001) Enzyme-replacement therapy in Mucopolysaccharidosis I. *N Engl J Med.* 344:182-188.
82. Harmatz P, Whitley CB, Waber L, Pais R, Steiner R, et al. (2004) Enzyme replacement therapy in Mucopolysaccharidosis VI (maroteaux-lamy syndrome). *J Pediatr.* 144:574-580.
83. Drummond MF, Wilson DA, Kanavos P, Ubel P, Rovira J. (2007) Assessing the economic challenges posed by orphan drugs. *Int J Technol Assess Health Care.* 23:36-42.
84. Oostenbrink JB, Bouwmans CAM, Koopmanschap MA, Rutten FFH. (2004) *Manual for costing studies: Methods and standard unit costs for economic evaluations in health care [in Dutch: Handleiding voor kostenonderzoek: Methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg]*. Amstelveen, the Netherlands: College voor zorgverzekeringen.
85. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL: 2005. *Methods for the economic evaluation of health care programmes*. Oxford, United Kingdom: Oxford University Press.
86. College voor zorgverzekeringen. (2009) *Pharmacotherapeutic compass [in Dutch: Farmacotherapeutisch kompas]*. Diemen, the Netherlands: College voor zorgverzekeringen.
87. Hoogendoorn EJI, Feenstra TL, Rutten-van Mölken M. (2005) *Inventarisation healthcare usage and costs of asthma and COPD in the Netherlands [in Dutch: Inventarisatie van het gebruik en de kosten van zorg voor astma en COPD in Nederland]*. Bilthoven, the Netherlands: Rijksinstituut voor Volksgezondheid en Milieu RIVM.
88. Koopmanschap MA, Rutten FFH, Van Ineveld BM, Van Roijen L. (1995) The friction cost method for measuring indirect costs of disease. *J Health Econ.* 14:171-189.
89. Van den Hout WB. (2010) The value of productivity: Human-capital versus friction-cost method. *Ann Rheum Dis.* 69:i89-i91.
90. Lamers LM, McDonnell J, Stalmeier PFM, Krabbe PFM, Busschbach JJV. (2006) The Dutch tariff: Results and arguments for an effective design for national EQ-5D valuation studies. *Health Econ.* 15:1121-1132.
91. Stolk EA, Krabbe P, Busschbach J. (2009). Using the internet to collect EQ-5D norm scores: A valid alternative. *Proceedings of the Plenary Meeting of the EuroQoL Group, the Hague,* Kijkduin - the Hague, the Netherlands. pp. 153-165.
92. Kobelt G, Berg J, Lindgren P. (2006) Costs and quality of life in multiple sclerosis in the Netherlands. *Eur J Health Econ.* 7:55-64.
93. Franke LC, Ament A, Laar M, Boonen A, Severens JL. (2009) Cost-of-illness of rheumatoid arthritis and ankylosing spondylitis. *Clin Exp Rheumatol.* 27:118-123.

94. Ouyang L, Grosse SD, Kenneson A. (2008) Health care utilization and expenditures for children and young adults with muscular dystrophy in a privately insured population. *J Child Neurol.* 23:883-888.
95. Drummond M, Manca A, Sculpher M. (2005) Increasing the generalizability of economic evaluations: Recommendations for the design, analysis, and reporting of studies. *Int J Technol Assess Health Care.* 21:165-171.
96. Grutters JPC, Joore MA, Van der Horst F, Verschuure H, Dreschler WA, Anteunis LJC. (2007) Choosing between measures: Comparison of EQ-5D, HUI2 and HUI3 in persons with hearing complaints. *Qual Life Res.* 16:1439-1449.
97. Haffner ME. (2006) Adopting orphan drugs - two dozen years of treating rare diseases. *N Engl J Med.* 354:445-447.
98. Van der Beek NAME, Van Capelle CI, Van der Velden-Van Etten, K.I., Hop WCJ, Van den Berg B, et al. (2011) Rate of progression and predictive factors for pulmonary outcome in children and adults with Pompe disease. *Mol Genet Metab.* 104:129-136.
99. Müller-Felber W, Horvath R, Gempel K, Podskarbi T, Shin Y, et al. (2007) Late onset Pompe disease: Clinical and neurophysiological spectrum of 38 patients including long-term follow-up in 18 patients. *Neuromuscular Disord.* 17:698-706.
100. Van der Beek NAME, De Vries JM, Hagemans MLC, Hop WCJ, Kroos MA, et al. (2012) Clinical features and predictors for disease natural progression in adults with Pompe disease: A nationwide prospective observational study. *Orphanet J Rare Dis.* 7:88.
101. Van der Beek NAME, Hagemans MLC, Reuser AJJ, Hop WCJ, Van der Ploeg AT, et al. (2009) Rate of disease progression during long-term follow-up of patients with late-onset Pompe disease. *Neuromuscular Disord.* 19:113-117.
102. Kanters TA, Hagemans MLC, Van der Beek NAME, Rutten FFH, Van der Ploeg AT, Hakkaart L. (2011) Burden of illness of Pompe disease in patients only receiving supportive care. *J Inherit Metab Dis.* 34:1045-1052.
103. Lamers LM, Bouwmans CAM, Van Straten A, Donker MCH, Hakkaart L. (2006) Comparison of EQ-5D and SF-6D utilities in mental health patients. *Health Econ.* 15:1229-1236.
104. Joore M, Brunenberg D, Nelemans P, Wouters E, Kuijpers P, et al. (2010) The impact of differences in EQ-5D and SF-6D utility scores on the acceptability of cost–utility ratios: Results across five trial-based cost–utility studies. *Value Health.* 13:222-229.
105. Sach TH, Barton GR, Jenkinson C, Doherty M, Avery AJ, Muir KR. (2009) Comparing cost-utility estimates: Does the choice of EQ-5D or SF-6D matter? *Med Care.* 47:889-894.
106. Brooks R. (1996) EuroQol: The current state of play. *Health Policy.* 37:53-72.
107. Brazier J, Roberts J, Deverill M. (2002) The estimation of a preference-based measure of health from the SF-36. *J Health Econ.* 21:271-292.
108. Dolan P. (1997) Modeling valuations for EuroQol health states. *Med Care.* 35:1095-1108.
109. Brazier J, Tsuchiya A, Roberts J, Busschbach J. (2004) A comparison of the EQ-5D and the SF-6D across seven patient groups. *Health Econ.* 13:873-884.
110. Stavem K, Frøland SS, Hellum KB. (2005) Comparison of preference-based utilities of the 15D, EQ-5D and SF-6D in patients with HIV/AIDS. *Qual Life Res.* 14:971-980.
111. Szende A, Leidy NK, Ståhl E, Svensson K. (2009) Estimating health utilities in patients with asthma and COPD: Evidence on the performance of EQ-5D and SF-6D. *Qual Life Res.* 18:267-272.
112. Marra CA, Woolcott JC, Kopec JA, Shojania K, Offer R, et al. (2005) A comparison of generic, indirect utility measures (the HUI2, HUI3, SF-6D, and the EQ-5D) and disease-specific instruments (the RAQoL and the HAQ) in rheumatoid arthritis. *Soc Sci Med.* 60:1571-1582.

113. Fisk JD, Brown MG, Sketris IS, Metz LM, Murray TJ, Stadnyk KJ. (2005) A comparison of health utility measures for the evaluation of multiple sclerosis treatments. *J Neurol Neurosurg Psychiatry.* 76:58-63.
114. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. (1993) Lung volumes and forced ventilatory flows. Report working party standardization of lung function tests, European community for steel and coal. Official statement of the European respiratory society. *Eur Respir J Suppl.* 16:5-40.
115. Medical Research Council: 1986. *Aids to the examination of the peripheral nervous system*. London, United Kingdom: Tindall.
116. Field AP: 2009. *Discovering statistics using SPSS*. London, United Kingdom: SAGE publications Ltd.
117. Streiner DL, Norman GR: 2008. *Health measurement scales*. Oxford, United Kingdom: Oxford University Press.
118. Ghislandi S, Apolone G, Garattini L, Ghislandi I. (2002) Is EQ-5D a valid measure of HRQoL in patients with movement disorders? *Eur J Health Econ.* 3:125-130.
119. Janssen MF, Birnie E, Haagsma JA, Bonsel GJ. (2008) Comparing the standard EQ-5D three-level system with a five-level version. *Value Health.* 11:275-284.
120. McTaggart-Cowan HM, Marra CA, Yang Y, Brazier JE, Kopec JA, et al. (2008) The validity of generic and condition-specific preference-based instruments: The ability to discriminate asthma control status. *Qual Life Res.* 17:453-462.
121. Khanna D, Furst DE, Wong WK, Tsevat J, Clements PJ, et al. (2007) Reliability, validity, and minimally important differences of the SF-6D in systemic sclerosis. *Qual Life Res.* 16:1083-1092.
122. Brouwer WBF, Van Exel NJA, Van den Berg B, Van den Bos GAM, Koopmanschap MA. (2005) Process utility from providing informal care: The benefit of caring. *Health Policy.* 74:85-99.
123. Serrano-Aguilar PG, Lopez-Bastida J, Yanes-Lopeza V. (2006) Impact on health-related quality of life and perceived burden of informal caregivers of individuals with Alzheimer's disease. *Neuroepidemiology.* 27:136-142.
124. Brouwer WBF, Van Exel N, Van de Berg B, Dinant HJ, Koopmanschap MA, Van den Bos GAM. (2004) Burden of caregiving: Evidence of objective burden, subjective burden, and quality of life impacts on informal caregivers of patients with rheumatoid arthritis. *Arthrit Car Res.* 51:570-577.
125. Jönsson AC, Lindgren I, Hallström B, Norrving B, Lindgren A. (2005) Determinants of quality of life in stroke survivors and their informal caregivers. *Stroke.* 36:803-808.
126. Khan F, Pallant J, Brand C. (2007) Caregiver strain and factors associated with caregiver self-efficacy and quality of life in a community cohort with multiple sclerosis. *Disabil Rehabil.* 29:1241-1250.
127. Bobinac A, Van Exel NJA, Rutten FFH, Brouwer WBF. (2010) Caring for and caring about: Disentangling the caregiver effect and the family effect. *J Health Econ.* 29:549-556.
128. Schulz R, Sherwood PR. (2008) Physical and mental health effects of family caregiving. *J Soc Work Educ.* 44:105-113.
129. Schulz R, Beach SR. (1999) Caregiving as a risk factor for mortality: The caregiver health effects study. *Jama.* 282:2215-2219.
130. Koopmanschap MA, Van Exel N, Van den Berg B, Brouwer WBF. (2008) An overview of methods and applications to value informal care in economic evaluations of healthcare. *Pharmacoeconomics.* 26:269-280.
131. Kishnani PS, Howell RR. (2004) Pompe disease in infants and children. *J Pediatr.* 144:S35-S43.
132. Brouwer WBF, Van Exel NJA, Van Gorp B, Redekop WK. (2006) The CarerQol instrument: A new instrument to measure care-related quality of life of informal caregivers for use in economic evaluations. *Qual Life Res.* 15:1005-1021.

133. Hoefman RJ, Van Exel NJA, Looren de Jong S, Redekop WK, Brouwer WBF. (2011) A new test of the construct validity of the CarerQol instrument: Measuring the impact of informal care giving. *Qual Life Res.* 20:875-887.
134. Hoefman RJ, Van Exel NJA, Foets M, Brouwer WBF. (2011) Sustained informal care: The feasibility, construct validity and test-retest reliability of the CarerQol-instrument to measure the impact of informal care in long-term care. *Aging Ment Health.* 15:1018-1027.
135. Van Exel NJA, Scholte op Reimer WJM, Brouwer WBF, Van den Berg B, Koopmanschap MA, Van den Bos GAM. (2004) Instruments for assessing the burden of informal caregiving for stroke patients in clinical practice: A comparison of CSI, CRA, SCQ and self-rated burden. *Clin Rehabil.* 18:203-214.
136. Hoefman RJ (2009) Providers of informal care [in Dutch: Aanbieders van mantelzorg]. In: De Boer A, Broese van Groenou M & Timmermans J (Eds.) *Informal care: An overview of the support from and to informal caregivers in 2007 [in Dutch: Mantelzorg: Een overzicht van de steun van en aan mantelzorgers in 2007].* pp. 29-44. The Hague, the Netherlands: Sociaal en Cultureel Planbureau.
137. Veenhoven R. (2011). *Happiness in Netherlands, world database of happiness.* Retrieved Jan/18, 2012, from http://worlddatabaseofhappiness.eur.nl
138. Pangalila RF, Van den Bos GAM, Stam HJ, Van Exel NJA, Brouwer WBF, Roebroeck ME. (2011) Subjective caregiver burden of parents of adults with Duchenne muscular dystrophy. *Disabil Rehabil.* 1-9.
139. Garau M, Mestre-Ferrandiz J. (2009) Access mechanisms for orphan drugs: A comparative study of selected European countries. *OHE Briefing.* 52:1-30.
140. Wilson IB, Cleary PD. (1995) Linking clinical variables with health-related quality of life. *Jama.* 273:59-65.
141. Engel AG, Gomez MR. (1970) Acid maltase levels in muscle in heterozygous acid maltase deficiency and in non-weak and neuromuscular disease controls. *J Neurol Neurosurg Psychiatry.* 33:801-804.
142. Rosenow EC, Engel AG. (1978) Acid maltase deficiency in adults presenting as respiratory failure. *Am J Med.* 64:485-491.
143. Roberts M, Russell LB, Paltiel AD, Chambers M, McEwan P, Krahn M. (2012) Conceptualizing a model: A report of the ISPOR-SMDM modeling good research practices task force-2. *Med Decis Making.* 32:678-689.
144. Wooldridge J.M.: 2002. *Econometric analysis of cross section and panel data*. Cambridge, United States: The MIT Press;
145. Wokke JHJ, Escolar DM, Pestronk A, Jaffe KM, Carter GT, et al. (2008) Clinical features of late-onset pompe disease: A prospective cohort study. *Muscle Nerve.* 38:1236-1245.
146. Hagemans MLC, Van Schie SPM, Janssens ACJW, Van Doorn PA, Reuser AJJ, Van der Ploeg AT. (2007) Fatigue: An important feature of late-onset Pompe disease. *J Neurol.* 254:941-945.
147. De Vries JM, Hagemans MLC, Bussmann JBJ, Van der Ploeg AT, Van Doorn PA. (2010) Fatigue in neuromuscular disorders: Focus on Guillain–Barré syndrome and Pompe disease. *Cell Mol Life Sci.* 67:701-713.
148. Mellies U, Lofaso F. (2009) Pompe disease: A neuromuscular disease with respiratory muscle involvement. *Respir Med.* 103:477-484.
149. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. (1989) The fatigue severity scale: Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol.* 46:1121-1123.
150. Merkies ISJ, Schmitz PIM, Van der Meché FGA, Samijn J, Van Doorn PA. (2002) Psychometric evaluation of a new handicap scale in immune-mediated polyneuropathies. *Muscle Nerve.* 25:370-377.

151. EuroQol Group. (1990) EuroQol: A new facility for the measurement of health-related quality of life. *Health Policy.* 16:199-208.
152. Ware JE, Kosinski M: 2001. *SF-36 physical & mental health summary scales: A manual for users of version 1*. Lincoln, United States: QualityMetric Incorporated.
153. Ware JE, Sherbourne CD. (1992) The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Med Care.* 30:473-483.
154. Herzog A, Hartung R, Reuser AJJ, Hermanns P, Runz H, et al. (2012) A cross-sectional single-centre study on the spectrum of Pompe disease, German patients: Molecular analysis of the GAA gene, manifestation and genotype-phenotype correlations. *Orphanet J Rare Dis.* 7:35.
155. Güngör D, De Vries JM, Brusse E, Kruijshaar ME, Hop WCJ, et al. (2013) Enzyme replacement therapy and fatigue in adults with Pompe disease. *Mol Genet Metab.* 109:174-178.
156. Güngör D, Kruijshaar ME, Plug I, Rizopoulos D, Kanters TA, et al. (2013) Quality of life and participation in the daily life activities of adults with Pompe disease receiving enzyme replacement therapy: 10 years of international follow-up. In: Güngör D (Ed.) *Survival, quality of life and effects of enzyme replacement therapy in adults with Pompe disease.* pp. 111-123. Enschede, the Netherlands: Ipskamp Drukkers.
157. Toscano A, Schoser B. (2013) Enzyme replacement therapy in late-onset Pompe disease: A systematic literature review. *J Neurol.* 260:951-959.
158. Davis S, Stevenson M, Tappenden P, Wailoo A. (2014) *NICE DSU technical support document 15: Cost-effectiveness modelling using patient-level simulation* No. 15. Sheffield, United Kingdom: University of Sheffield.
159. Centraal Bureau voor de Statistiek. (2011). *Life expectancy; age and gender [in Dutch: Levensverwachting; geslacht en leeftijd].* Retrieved 04/10, 2013, from http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=37450&D1=0&D2=a&D3=0-91&D4=l&HDR=T,G1&STB=G2,G3&VW=T
160. Kanters TA, Redekop WK, Rutten-Van Mölken MPMH, Kruijshaar ME, Güngör D, et al. (2015) A conceptual disease model for adult Pompe disease. *Orphanet J Rare Dis.* 10:112.
161. Hakkaart-van Roijen L, Van der Linden N, Bouwmans CAM, Kanters TA, Tan SS. (2015) *Costing manual: Methodology of costing research and reference prices for economic evaluations in healthcare [in Dutch: Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg]*. Diemen, the Netherlands: Zorginstituut Nederland.
162. Hoefman RJ, van Exel J, Brouwer W. (2013) How to include informal care in economic evaluations. *Pharmacoeconomics.* 31:1105-1119.
163. Vemer P, Goossens LMA, Rutten-van Mölken MPMH. (2014) Not simply more of the same: Distinguishing between patient heterogeneity and parameter uncertainty. *Med Decis Making.* 34:1048-1058.
164. College voor zorgverzekeringen. (2006) *Guidelines for pharmacoeconomic research, updated version [in Dutch: Richtlijnen voor farmaco-economisch onderzoek, geactualiseerde versie]*. Diemen, the Netherlands: College voor zorgverzekeringen.
165. R Development Core Team: 2006. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing.
166. Rombach SM, Hollak CEM, Linthorst GE, Dijkgraaf MGW. (2013) Cost-effectiveness of enzyme replacement therapy for Fabry disease. *Orphanet J Rare Dis.* 8:29.
167. Zorginstituut Nederland. (2015) *Advice nivolumab (opdivo) [in Dutch: Pakketadvies nivolumab (opdivo)]* No. 2015145637. Diemen, the Netherlands: Zorginstituut Nederland.
168. Zorginstituut Nederland. (2015) *Pharmacoeconomic report for pertuzumab (perjeta ®) for the treatment metastatic breast cancer [in Dutch: Farmaco-economisch (FE) rapport voor pertuzumab*

(perjeta ®) bij de behandeling van gemetastaseerde borstkanker] No. 2014141237. Diemen, the Netherlands: Zorginstituut Nederland.

169. Kamphoven, J. H. J. (2004). Pompe's disease: The mouse model in the development of enzyme therapy. Erasmus Universiteit Rotterdam, Rotterdam, the Netherlands.
170. Moore DF, Ries M, Forget EL, Schiffmann R. (2007) Enzyme replacement therapy in orphan and ultra-orphan diseases. *Pharmacoeconomics.* 25:201-208.
171. Schuller Y, Hollak CEM, Biegstraaten M. (2015) The quality of economic evaluations of ultra-orphan drugs in Europe - a systematic review. *Orphanet J Rare Dis.* 10:92.
172. Grimes DA, Schulz KF. (2002) Bias and causal associations in observational research. *Lancet.* 359:248-252.
173. The Cochrane Collaboration: 2011. *Cochrane handbook for systematic reviews of interventions.* The Cochrane Collaboration;
174. McCabe C, Claxton K, Tsuchiya A. (2005) Orphan drugs and the NHS: Should we value rarity? *Bmj.* 331:1016-1019.
175. Drummond M, Evans B, LeLorier J, Karakiewicz P, Martin D, et al. (2009) Evidence and values: Requirements for public reimbursement of drugs for rare diseases - a case study in oncology. *Can J Clin Pharmacol.* 16:e273-e281.
176. Kolasa K, Zwolinski KM, Kalo Z, Hermanowski T. (2016) Potential impact of the implementation of multiple-criteria decision analysis (MCDA) on the Polish pricing and reimbursement process of orphan drugs. *Orphanet J Rare Dis.* 11:1.
177. Sussex J, Rollet P, Garau M, Schmitt C, Kent A, Hutchings A. (2013) A pilot study of multicriteria decision analysis for valuing orphan medicines. *Value Health.* 16:1163-1169.
178. Hughes-Wilson W, Palma A, Schuurman A, Simoens S. (2012) Paying for the orphan drug system: Break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments? *Orphanet J Rare Dis.* 7:74.
179. Hutton J, Trueman P, Henshall C. (2007) Coverage with evidence development: An examination of conceptual and policy issues. *Int J Technol Assess Health Care.* 23:425-432.
180. Nicolino M, Byrne B, Wraith JE, Leslie N, Mandel H, et al. (2009) Clinical outcomes after long-term treatment with alglucosidase alfa in infants and children with advanced Pompe disease. *Genet Med.* 11:210-219.
181. Latimer NR. (2013) Survival analysis for economic evaluations alongside clinical Trials - Extrapolation with patient-level data inconsistencies, limitations, and a practical guide. *Med Decis Making.* 33:743-754.
182. Ungar WJ. (2011) Challenges in health state valuation in paediatric economic evaluation. *Pharmacoeconomics.* 29:641-652.
183. Desser AS, Gyrd-Hansen D, Olsen JA, Grepperud S, Kristiansen IS. (2010) Societal views on orphan drugs: Cross sectional survey of Norwegians aged 40 to 67. *Bmj.* 341:c4715.
184. Scottish Medicines Consortium. (2007) *Alglucosidase alfa 50mg powder for concentrate for solution for infusion (myozyme) no. (352/07).* Glasgow, Scotland: Scottish Medicines Consortium.
185. All Wales Medicines Strategy Group. (2006) *Use of alglucosidase alfa (myozyme) within NHS Wales*. Wales: All Wales Medicines Strategy Group.
186. National Specialised Commissioning Advisory Group. (2008) *Policy on the funding of enzyme replacement therapy and substrate reduction therapy*. United Kingdom: National Health Services.
187. Transparency Committee. (2013) *Myozyme 50mg, powder for concentrate for solution for infusion*. France: Haute Authorité de Santé.

188. Agenzia Italiano Del Farmaco. (2006) Reimbursement and pricing of the specialized medicine for human use «Myozyme» (recombinant human a-glucosidase acid) authorized by the centralized European procedure by European commission (determination/C n. 111/06) [in Italian: Regime di rimborsabilita' e prezzo di vendita della specialita' medicinale per uso umano «Myozyme» (a-glucosidasi acida umana ricombinante), autorizzata con procedura centralizzata europea dalla commissione europea. (determinazione/C n. 111/06)]. *Gazetta Ufficiale.* 273.
189. Denis A, Simoens S, Fostier C, Mergaert L, Cleemput I. (2009) *Policy for rare diseases and orphan drugs [in Dutch: Beleid voor zeldzame ziekten en weesgeneesmiddelen]* No. 112A. Brussels, Belgium: Federaal Kenniscentrum voor de Gezondheidszorg.
190. Kanters TA, Redekop WK, Hakkaart L. (2012) Factors predicting reimbursement decisions on orphan drugs in eight countries. *Value Health.* 15:A308.
191. Winkel LPF, Van den Hout JMP, Kamphoven JHJ, Disseldorp JAM, Remmerswaal M, et al. (2004) Enzyme replacement therapy in late-onset Pompe's disease: A three-year follow-up. *Ann Neurol.* 55:495-502.
192. Williams A. (1997) Intergenerational equity: An exploration of the 'fair innings' argument. *Health Econ.* 6:117-132.
193. McKie J, Richardson J. (2003) The rule of rescue. *Soc Sci Med.* 56:2407-2419.
194. Bobinac A, van Exel NJA, Rutten FFH, Brouwer WBF. (2012) Inquiry into the relationship between equity weights and the value of the QALY. *Value Health.* 15:1119-1126.
195. Mirelman A, Mentzakis E, Kinter E, Paolucci F, Fordham R, et al. (2012) Decision-making criteria among national policymakers in five countries: A discrete choice experiment eliciting relative preferences for equity and efficiency. *Value Health.* 15:534-539.
196. Dear JW, Lilitkarntakul P, Webb DJ. (2006) Are rare diseases still orphans or happily adopted? The challenges of developing and using orphan medicinal products. *Br J Clin Pharmacol.* 62:264-271.
197. European Commission. (2014). *Community register of medicinal products.* Retrieved 9/9, 2014, from http://ec.europa.eu/health/documents/community-register/html/
198. Kanters TA, Steenhoek A, Hakkaart L. (2014) Orphan drugs expenditure in the Netherlands in the period 2006-2012. *Orphanet J Rare Dis.* 9:154.
199. Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. (2006) Good practice guidelines for decision-analytic modelling in health technology assessment. *Pharmacoeconomics.* 24:355-371.
200. Ministry of Health, Welfare and Sport, College voor zorgverzekeringen. (2010) *Dutch assessment procedures for the reimbursement of outpatient medicines*. Diemen, the Netherlands: College voor zorgverzekeringen.
201. Stolk EA, van Donselaar G, Brouwer WBF, Busschbach JJV. (2004) Reconciliation of economic concerns and health policy. *PharmacoEconomics.* 22:1097-1107.
202. Zorginstituut Nederland. (2015) *Package management orphan drugs [in Dutch: Pakketbeheer weesgeneesmiddelen]* No. 2015010627. Diemen, the Netherlands: Zorginstituut Nederland.
203. Kwaliteitsinstituut voor de Gezondheidszorg CBO. (2007) *Evidence-based guideline development; manual for working group members [in Dutch: Evidence-based richtlijnontwikkeling; handleiding voor werkgroepleden]*. Utrecht, the Netherlands: Kwaliteitsinstituut voor de Gezondheidszorg CBO.
204. College voor zorgverzekeringen. (2012) *Advice on agalsidase alfa (replagal®) agalsidase beta (fabrazyme®) in the indication 'Fabry disease' [in Dutch: Advies agalsidase alfa (replagal®) agalsidase beta (fabrazyme®) bij de indicatie 'ziekte van Fabry']*. Diemen, the Netherlands: College voor zorgverzekeringen.

205. European Parliament and Council of the European Union. (2014) Regulation (EU) no 536/2014 of the European parliament and of the council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing directive 2001/20/EC. *Off J Eur Union.* L(158):1-76.
206. Simoens S, Cassiman D, Dooms M, Picavet E. (2012) Orphan drugs for rare diseases. *Drugs.* 72:1437-1443.
207. Kanters TA, De Sonneville-Koedoot C, Redekop WK, Hakkaart L. (2013) Systematic review of available evidence on 11 high-priced inpatient orphan drugs. *Orphanet J Rare Dis.* 8:124.
208. Rosenberg-Yunger ZRS, Daar AS, Thorsteinsdóttir H, Martin DK. (2011) Priority setting for orphan drugs: An international comparison. *Health Policy.* 100:25-34.
209. National Institute for Health and Care Excellence. (2013) *Interim process and methods of the highly specialised technologies programme*. United Kingdom: National Institute for Health and Care Excellence.
210. All Wales Medicines Strategy Group. (2015) *Process for appraising orphan and ultra-orphan medicines and medicines developed specifically for rare diseases. Effective from September 2015*. Wales: All Wales Medicines Strategy Group.
211. Picavet E, Cassiman D, Simoens S. (2014) Reimbursement of orphan drugs in Belgium: What (else) matters? *Orphanet J Rare Dis.* 9:139.
212. Gabler NB, Duan N, Vohra S, Kravitz RL. (2011) N-of-1 trials in the medical literature: A systematic review. *Med Care.* 49:761-768.
213. Griggs RC, Batshaw M, Dunkle M, Gopal-Srivastava R, Kaye E, et al. (2009) Clinical research for rare disease: Opportunities, challenges, and solutions. *Mol Genet Metab.* 96:20-26.
214. Dupont AG, Van Wilder PB. (2011) Access to orphan drugs despite poor quality of clinical evidence. *Br J Clin Pharmacol.* 71:488-496.
215. Baltussen R, Niessen L. (2006) Priority setting of health interventions: The need for multi-criteria decision analysis. *Cost Eff Resour Alloc.* 4:14.
216. Thokala P, Devlin N, Marsh K, Baltussen R, Boysen M, et al. (2016) Multiple criteria decision analysis for health care decision Making - An introduction: Report 1 of the ISPOR MCDA emerging good practices task force. *Value Health.* 19:1-13.
217. Marsh K, Lanitis T, Neasham D, Orfanos P, Caro J. (2014) Assessing the value of healthcare interventions using multi-criteria decision analysis: A review of the literature. *Pharmacoeconomics.* 32:345-365.
218. Marsh K, IJzerman M, Thokala P, Baltussen R, Boysen M, et al. (2016) Multiple criteria decision analysis for health care decision Making - Emerging good practices: Report 2 of the ISPOR MCDA emerging good practices task force. *Value Health.* 19:125-137.
219. Claxton K, Sculpher M, Palmer S, Culyer AJ. (2015) Causes for concern: Is NICE failing to uphold its responsibilities to all NHS patients? *Health Econ.* 24:1-7.
220. Rinaldi A. (2005) Adopting an orphan. *EMBO Rep.* 6:507-510.
221. Haffner ME, Torrent-Farnell J, Maher PD. (2008) Does orphan drug legislation really answer the needs of patients? *Lancet.* 371:2041-2044.
222. Meekings KN, Williams CSM, Arrowsmith JE. (2012) Orphan drug development: An economically viable strategy for biopharma R&D. *Drug Discov Today.* 17:660-664.
223. Beutler E. (2006) Lysosomal storage diseases: Natural history and ethical and economic aspects. *Mol Genet Metab.* 88:208-215.
224. Van Capelle CI, Van der Beek NAME, Hagemans MLC, Arts WFM, Hop WCJ, et al. (2010) Effect of enzyme therapy in juvenile patients with Pompe disease: A three-year open-label study. *Neuromuscul Disord.* 20:775-782.

225. Zorginstituut Nederland. (2016) *Advice on eculizumab (soliris®) for the treatment of PNH-patients [in Dutch: Pakketadvies eculizumab (soliris®) bij behandeling van PNH-patiënten]* No. 2016034722. Diemen, the Netherlands: Zorginstituut Nederland.
226. Onakpoya IJ, Spencer EA, Thompson MJ, Heneghan CJ. (2015) Effectiveness, safety and costs of orphan drugs: An evidence-based review. *BMJ Open.* 5:e007199.
227. Michel M, Toumi M. (2012) Access to orphan drugs in Europe: Current and future issues. *Expert Rev Pharmacoecon Outcomes Res.* 12:23-29.
228. Blackstone EA, Fuhr JP. (2010) Biosimilars and innovation: An analysis of the possibility of increased competition in biopharmaceuticals. *Future Med Chem.* 2:1641-1649.
229. Roger SD, Goldsmith D. (2008) Biosimilars: It's not as simple as cost alone. *J Clin Pharm Ther.* 33:459-464.
230. Simoens S. (2011) Pricing and reimbursement of orphan drugs: The need for more transparency. *Orphanet J Rare Dis.* 6:42.
231. Blackstone EA, Fuhr JP. (2012) Innovation and competition: Will biosimilars succeed? *Biotechnol Healthc.* 9:24-27.
232. Therapeutic Goods Administration. (2015) *Orphan drugs program: Discussion paper*. Symonston, Australia: Commonwealth of Australia.
233. Pharmac. (2014) *High cost medicines for rare disorders: Discussion document and a request for your input*. Wellington, New Zealand: Pharmac.
234. O'Sullivan BP, Orenstein DM, Milla CE. (2013) Pricing for orphan drugs: Will the market bear what society cannot? *Jama.* 310:1343-1344.
235. Van Dussen L, Biegstraaten M, Hollak CEM, Dijkgraaf MGW. (2014) Cost-effectiveness of enzyme replacement therapy for type 1 Gaucher disease. *Orphanet J Rare Dis.* 9:51.
236. Picavet E, Cassiman D, Simoens S. (2013) Do ultra-orphan medicinal products warrant ultra-high prices? A review. *Orphan Drugs Res Rev.* 3:23-31.
237. Côté A, Keating B. (2012) What is wrong with orphan drug policies? *Value Health.* 15:1185-1191.
238. Rollet P, Lemoine A, Dunoyer M. (2013) Sustainable rare diseases business and drug access: No time for misconceptions. *Orphanet J Rare Dis.* 8:109.
239. Thamer M, Brennan N, Semansky R. (1998) A cross-national comparison of orphan drug policies: Implications for the U.S. orphan drug act. *J Health Polit Policy Law.* 23:265-290.
240. Hemphill TA. (2010) Extraordinary pricing of orphan drugs: Is it a socially responsible strategy for the US pharmaceutical industry? *J Bus Ethics.* 94:225-242.
241. Picavet E, Dooms M, Cassiman D, Simoens S. (2011) Drugs for rare diseases: Influence of orphan designation status on price. *Appl Health Econ Health Policy.* 9:275-279.
242. Ferner RE, Hughes DA. (2010) The problem of orphan drugs. *Bmj.* 341:c6456.
243. Murphy SM, Puwanant A, Griggs RC. (2012) Unintended effects of orphan product designation for rare neurological diseases. *Ann Neurol.* 72:481-490.
244. Picavet E, Morel T, Cassiman D, Simoens S. (2014) Shining a light in the black box of orphan drug pricing. *Orphanet J Rare Dis.* 9:62.
245. Simoens S, Cassiman D, Picavet E, Dooms M. (2011) Are some orphan drugs for rare diseases too expensive? A study of purchase versus compounding costs. *Drug Ther Perspect.* 27:24-26.
246. Banerjee A, Hollis A, Pogge T. (2010) The health impact fund: Incentives for improving access to medicines. *Lancet.* 375:166-169.
247. Putzeist M, Mantel-Teeuwisse AK, Gispen-de Wied CC, Hoes AW, Leufkens HGM, de Vrueh RLA. (2013) Drug development for exceptionally rare metabolic diseases: Challenging but not impossible. *Orphanet J Rare Dis.* 8:179.

248. Van Weely S, & Leufkens HGM (2004) Orphan diseases. In: Kaplan W, & Laing R (Eds.) *Priority medicines for Europe and the world: A public health approach to innovation*. Geneva, Switzerland: World Health Organization.
249. McCabe C, Tsuchiya A, Claxton K, Raftery J. (2006) Orphan drugs revisited. *Qjm.* 99:341-345.
250. Thorat C, Xu K, Freeman SN, Bonnel RA, Joseph F, et al. (2012) What the orphan drug act has done lately for children with rare diseases: A 10-year analysis. *Pediatrics.* 129:516-521.
251. Carlson MDA, Morrison RS. (2009) Study design, precision, and validity in observational studies. *J Palliat Med.* 12:77-82.
252. Psaty BM, Koepsell TD, Lin D, Weiss NS, Siscovick DS, et al. (1999) Assessment and control for confounding by indication in observational studies. *J Am Geriatr Soc.* 47:749-754.
253. Marko NF, Weil RJ. (2010) The role of observational investigations in comparative effectiveness research. *Value Health.* 13:989-997.
254. Schneeweiss S, Gagne JJ, Glynn RJ, Ruhl M, Rassen JA. (2011) Assessing the comparative effectiveness of newly marketed medications: Methodological challenges and implications for drug development. *Clin Pharmacol Ther.* 90:777-790.
255. Berger ML, Mamdani M, Atkins D, Johnson ML. (2009) Good research practices for comparative effectiveness research: Defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources: The ISPOR good research practices for retrospective database analysis task force Report - Part I. *Value Health.* 12:1044-1052.
256. Hoogendoorn M, Oppe M, Stolk E, Boland M, Goossens L, Rutten-van Mölken M. (2016). Exploring the impact of adding a respiratory dimension to the current EQ-5D descriptive system. *European Respiratory Society, International Congress London 2016,* London, United Kingdom.
257. Suissa S. (2007) Immortal time bias in observational studies of drug effects. *Pharmacoepidemiol Drug Saf.* 16:241-249.
258. Lévesque LE, Hanley JA, Kezouh A, Suissa S. (2010) Problem of immortal time bias in cohort studies: Example using statins for preventing progression of diabetes. *Bmj.* 340:b5087.
259. Claxton K, Martin S, Soares M, Rice N, Spackman E, et al. (2015) Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. *Health Technol Assess.* 19:1-542.
260. Drummond M, Towse A. (2014) Orphan drugs policies: A suitable case for treatment. *Eur J Health Econ.* 15:335-340.
261. Paulden M, Stafinski T, Menon D, McCabe C. (2015) Value-based reimbursement decisions for orphan drugs: A scoping review and decision framework. *Pharmacoeconomics.* 33:255-269.
262. Gericke CA, Riesberg A, Busse R. (2005) Ethical issues in funding orphan drug research and development. *J Med Ethics.* 31:164-168.
263. Hyry HI, Stern AD, Cox TM, Roos JC. (2014) Limits on use of health economic assessments for rare diseases. *Qjm.* 107:241-245.
264. Picavet E, Dooms M, Cassiman D, Simoens S. (2012) Orphan drugs for rare diseases: Grounds for special status. *Drug Dev Res.* 73:115-119.
265. Mentzakis E, Stefanowska P, Hurley J. (2010) A discrete choice experiment investigating preferences for funding drugs used to treat orphan diseases: An exploratory study. *Health Econ Pol Law.* 6:405.
266. Thokala P, Duenas A. (2012) Multiple criteria decision analysis for health technology assessment. *Value Health.* 15:1172-1181.