COST-EFFECTIVENESS OF NEONATAL SURGERY
A MATTER OF BALANCE

Marten J. Poley

On the Cover

Johannes Vermeer (1632-1675), Woman Holding a Balance, c. 1664. Oil on canvas. National Gallery of Art, Washington D.C., Widener Collection.
 (Back cover: detail.)

Vermeer's painting we are looking at has long been known as 'The Gold Weigher' or 'Woman Weighing Pearls'. Microscopic analysis, however, has revealed the scales to be empty. However seemingly trivial, this bears importantly on the meaning of the work. For 'Woman Holding a Balance' is overtly allegorical, probably highlighting a virtue. A woman in a fur-trimmed coat—who perhaps is pregnant—stands before a table spread with jewelry. Behind the woman, framing her head, is a large painting of The Last Judgment, which is about the weighing of souls. On the wall in front of the woman is a mirror, symbolizing self-knowledge or vanity. The woman is not weighing jewelry here. She is weighing the meaning of her own actions, choosing between the eternal, spiritual path (the painting on the wall) and the material, sparkling path (the jewels on the table). The composition reinforces this idea: her hand is at the corner of the Last Judgment, and the balance makes the connection to the table of jewels. She waits for the balance pans to settle, caught by the diffuse light from the window, which highlights her white clothes, her serene face, and her hands. The rest of the room is dark, enclosing the woman in her quiet moment of reflection. Vermeer's point may be that we should acknowledge the importance of judgments in weighing our mortal actions in anticipation of the immortal life to come. We are told to live a balanced life.

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COST-EFFECTIVENESS OF NEONATAL SURGERY
A MATTER OF BALANCE

Kosteneffectiviteit van neonatale chirurgie
Een kwestie van balans

THESIS

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Marten Johannes Poleij
born at De Meern

DOCTORAL COMMITTEE

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Copromotor:	Dr. J.J. van Busschbach

If we knew what it was we were doing,
it would not be called research, would it?

Albert Einstein (1879-1955)

PUBLICATIONS

Chapters 2 to 7 are based on the following articles:

Chapter 2
Poley MJ, Stolk EA, Langemeijer RATM, Molenaar JC, Busschbach JJV: The cost-effectiveness of neonatal surgery and subsequent treatment for congenital anorectal malformations. J Pediatr Surg 2001; 36(10): 1471-1478.[a]

Chapter 3
Poley MJ, Stolk EA, Tibboel D, Molenaar JC, Busschbach JJV: The cost-effectiveness of treatment for congenital diaphragmatic hernia. J Pediatr Surg 2002; 37(9): 1245-1252.[b]

Chapter 4
Poley MJ, Stolk EA, Tibboel D, Molenaar JC, Busschbach JJV: Short term and long term health related quality of life after congenital anorectal malformations and congenital diaphragmatic hernia. Arch Dis Child 2004; 89(9): 836-841.[c]

Chapter 5
Poley MJ, Hanekamp MN, Van Heijst AFJ, Michel BC, Rutten FFH, Tibboel D: Cost-effectiveness of neonatal extracorporeal membrane oxygenation in the Netherlands. Submitted for publication.

Chapter 6
Poley MJ, Brouwer WBF, Van Exel NJA, Tibboel D: Informal care for children born with major congenital anomalies: what does it ask and what does it do to parents' health-related quality of life? Submitted for publication.

Chapter 7
Poley MJ, Brouwer WBF, Busschbach JJV, Hazebroek FWJ, Tibboel D, Rutten FFH, Molenaar JC: Cost-effectiveness of neonatal surgery: first skepticized, now increasingly accepted. Submitted for publication.

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Contents

Chapter 1

Introduction

1.1 BACKGROUND AND MOTIVATION

Beginning after the Second World War, neonatal surgery has made enormous progress. Mortality rates for all anomalies belonging to the field, with a few exceptions such as congenital diaphragmatic hernia (CDH), fell from almost 100% to less than 10%. This improvement is testimony to a variety of significant advances for example relating to surgical techniques, neonatal intensive care, respiration techniques, pediatric anesthesiology, pediatric radiology, and prenatal diagnosis. Contemporaneously with these medical advancements came new ethical and economic dilemmas. First, an important ethical question these days is whether anything that is technically possible indeed ought to be done. In cases in which the prognosis for a meaningful life is poor, it may be in the best interest of the child to discontinue treatment, even if this means death. More broadly, a pressing question is whether improved survival does not come at the expense of poor health-related quality of life (HRQoL).[a] Second, another profound change has been the growing economic consequences of health care, in an era where budgetary restrictions are becoming tighter. As in other branches of medicine, medical advancements contributed to increasing costs in neonatal surgery as well. It is against this background of concerns about the HRQoL of the surviving infant and the increasing costs associated with neonatal surgery that information about the cost and effects of neonatal surgery is required. This thesis on the cost-effectiveness of neonatal surgery directly emerges from these concerns.

The relevance of cost-effectiveness information

Today's need for information on the costs and effects of medical services requires a change in attitude from doctors. After all, as Ravitch—one of the pioneers of pediatric surgery—noticed of doctors: "We have all been brought up to ignore the cost of a medication, treatment, or procedure as long as some small likelihood exists that it could be useful or beneficial. If it is better, get it! If it might be helpful, do it!".[1] Despite this strong medical principle, there are several underlying facts that determine why costs should be considered. First, health care costs need to be kept under some form of regulated control, given that the medical market is an imperfect rather than an efficient free market and that we do not wish to give up investing in other highly valued societal priorities. Second, increasing efficiency by eliminating unnecessary, inappropriate, or repetitious care or by streamlining administrative processes will not be enough, unfortunately. However welcome and helpful such efforts are, in the end they will not eliminate the need to choose between treatments and patients.[2,3] So, difficult choices are inescapable, and these choices will affect the content and quality of patient care. By the end of the day, we will not be able to offer some medical

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[a] *Please refer to the Glossary at the end of this book for descriptions of some common terms in the field of cost-effectiveness research as they are used in this thesis. Without pretending to be exhaustive, it explains some of the jargon that the reader will come across throughout this book.*

practices that are known to have favorable effects, but for which the magnitude of the effects is too small to justify the cost. This may be difficult to accept, since it contradicts the wide-spread feeling that a procedure that works and is beneficial must be affordable, a mind set that has been termed 'the efficacy fallacy'.[2]

Despite the uncomfortableness that doctors may feel regarding the situation of scarcity, it is the 'raison d'être' of economics. Economic evaluations of health care are defined as the comparative analyses of alternative courses of action in terms of both their costs and consequences, given the reality of limited resources.[4,5] Put simply, they aim at establishing whether the effects of a given treatment are worth the budget needed, compared to an alternative treatment. It is about getting the optimum benefit for a given set of resources. The value of such evaluations springs from the fact that behind every patient there are other patients and even healthy people (i.e., future patients) waiting who also have a claim to a reasonable amount of scarce health care resources. Or, to quote Williams, one of the founding fathers of health economics: "Anyone who says that no account should be paid to costs is really saying that no account should be paid to the sacrifices imposed on others".[6] All other things being equal, society is better off when resources are used efficiently, as otherwise possible health benefits for society will not be realized. Moreover, resources that are spent on health care cannot be expended on other sectors of society such as education, road safety, or national defense, while people might find that these offer more value for money.

For the case of neonatal surgery, results from cost-effectiveness analyses would make it possible to counteract critiques that have been leveled against the discipline. Neonatal surgery has been criticized with arguments of cost-effectiveness: it has been feared that the high costs of an operation would come with low HRQoL after survival.[7] Extracorporeal membrane oxygenation (ECMO), which is available as a treatment option for acute respiratory failure in selected neonates, is only one but a very typical example. Some 21,000 neonates have been treated worldwide since the initiation of the ECMO procedure.[8] Yet, the benefits of this complicated and potentially hazardous treatment have always been considered controversial—and still are—also in view of the high costs associated with this labor-intensive technique. So, evidence on the cost-effectiveness of neonatal surgery clearly would be welcome. It would enable us to find out what is the most cost-effective strategy for managing a specific condition, and how cost-effective a treatment is in comparison with interventions for other congenital anomalies or interventions outside neonatal surgery.

Current evidence

Nowadays, many medical technologies have been assessed on their cost-effectiveness.[9-12] However, this is not true for neonatal surgery. This lack of evidence was reported by Stolk and colleagues in the year 2000, whose report

provides a good overview of the state of the art at the time that the research presented in this thesis was initiated.[7] Their review of the literature from 1989 to 1998 yielded only two complete economic evaluations. The first economic evaluation documented that, from the point of view of cost-effectiveness, a single-staged approach to Hirschsprung's disease has an advantage over multiple-staged therapy.[13] The second provided evidence of the cost-effectiveness of ECMO in the United Kingdom, as compared to conventional management of severe respiratory failure.[14] Additionally, Stolk and colleagues drew conclusions on current evidence on the two different parts of an economic evaluation, that is, the 'cost side' and the 'effects side'. Studies dealing with the costs of neonatal surgery appeared to adhere to a narrow interpretation of costs. They were limited to health care costs during the initial hospitalization, failing to include costs in the long term as well as costs outside the health care sector. Regarding the effects measures used by studies in the field of neonatal surgery, it was concluded that studies tend to concentrate on survival or disease-specific outcome measures rather than broadly applicable generic HRQoL measures. These findings allowed the authors to conclude that evidence on the cost-effectiveness of neonatal surgery is largely lacking.

Stolk and co-workers explain that this evidence gap might be caused by clinicians' long tradition of using disease-specific symptoms, whereas measuring outcomes suitable for economic evaluation is relatively new. Another explanation they put forward is the difficulty in long-term tracking of the patients and the problem that most generic HRQoL measures are not applicable in children yet. Next to these reasons, one can speculate on other reasons. Many surgical interventions do not lend themselves easily to clinical trials. Historically, surgeons have been free to develop new operations and treatments, whereas high-standard clinical research has been largely absent. Also in pediatric surgery, progress has relied primarily on the diffusion of innovations as reported in case series in the literature. There is a paucity of rigorously designed prospective studies in the literature, which may be explained by, inter alia, problems associated with inadequate patient numbers and rare conditions.[15-18] Note that major congenital anomalies occur infrequently, with incidences of the different anomalies varying between 1 per 3,000 and 1 per 15,000 live births. Even large pediatric surgical centers only see an average of 10 to 20 patients per year for each of the main surgical index diagnoses. The lack of formal clinical assessments is a factor likely to hinder the development of cost-effectiveness studies, because data needed for cost-effectiveness studies are often collected in conjunction with other primary data. As a consequence, claims of new surgical procedures are quite often being labeled as cost-effective without an actual economic analysis being conducted, just like it is the case with surgery in general.[19]

To conclude so far: very little has been written on the cost-effectiveness of neonatal surgery. The number of published studies is so small that this conclusion remains valid even if it is taken into consideration that neonatal surgery is a

relatively small discipline and that resources for cost-effectiveness research have themselves to be prioritized.

What does it take to determine the cost-effectiveness of neonatal surgery? What is needed in a cost-effectiveness study, is information on both costs and effects. Costs and effects are preferably analyzed from a societal perspective.[4,5] This implies that all costs and effects of a studied intervention should be taken into account, irrespective of to whom they accrue. So if costs and effects occur to 'significant others' than the patient, such as the parents in the case of neonatal surgery, these should also be taken into account. Another requirement for a solid cost-effectiveness evaluation is that the follow-up period is long enough to capture all costs and effects.

Costs. As mentioned above, studies dealing with the costs of neonatal surgery often only focus on health care costs during the initial hospitalization. This observation, for that matter, applies equally to the field of economic evaluation in general. Undoubtedly, the so-called direct medical costs are often the most important, comprising a large proportion of the total costs. Yet, a wide range of other cost categories can have a strong influence on cost-effectiveness ratios. Among these other costs are direct non-healthcare costs, such as out-of-pocket expenses and time costs, indirect healthcare costs, and indirect non-healthcare costs. The latter two categories will now be described in some more detail, as they are relevant for neonatal surgery.

Indirect healthcare costs comprise future costs in added life-years. We may distinguish between costs of treating clinically related diseases and costs of treating other, unrelated diseases. For example, a patient who has recovered from a life-threatening heart disease may still make costs of cardiovascular maintenance therapy, but can also incur costs of cancer in future life-years. Much controversy has surrounded the inclusion of unrelated costs. Most guidelines for economic evaluations published throughout the world (such as guidelines from the Netherlands,[20] Canada,[21,22] Australia,[23] the United Kingdom,[24] Norway,[25] and Spain[26]) recommend that they should not be included. In the literature, there is a vigorous debate between proponents[27,28] and opponents[29] of including future costs for unrelated diseases, and, between these two poles of thought, a camp that leaves it to the discretion of the researchers.[5,30] The debate has not only theoretical importance, but also important practical consequences, since including future (un-)related health care costs can have a large impact on cost-effectiveness ratios of life-saving treatments,[31,32] which treatments in neonatal surgery often are. The most common practice seems to be to restrict health care costs in added life-years (if included at all) to related costs.

The second cost category that is frequently ignored are indirect non-healthcare costs.[33] These are usually restricted to productivity costs, which may be defined as costs associated with production loss and replacement caused by illness,

disability, and death of productive persons, both paid and unpaid.[34] Which method to use for measuring these costs (the so-called friction cost or the human capital cost approach) has long been a subject of debate,[35-38] and is still not settled.[39,40] Productivity costs can be substantial, especially when the human capital approach is followed.

Both these cost categories—i.e., indirect healthcare costs and indirect non-healthcare costs—can have a large impact on cost-effectiveness ratios. This is undeniably also true for cost-effectiveness ratios of neonatal surgery. Exactly these often ignored cost categories are potentially major drivers of the results in neonatal surgery.

Effects. In neonatal surgery, avoided mortality has been a widely accepted measure of success since many years. Furthermore, the emphasis has been on the immediate outcome of surgery. More often than not, the immediate outcome is satisfactory in all respects, with alleviation of the symptoms, cure of the primary pathology, and a rapid return to a normal pattern of life. As a consequence, little thought has been given to the possibility that at a later stage problems may develop.[41] Of course, on the face of it, certain surgical diseases of the neonate seem unlikely to require any form of long-term follow-up (such as umbilical hernia, acute appendicitis, or circumcision), whereas others seem to call for ongoing follow-up (such as esophageal atresia, Hirschsprung's disease, etc.). Similarly, within a specific diagnosis there can be a group that does well and a group that does badly. A good example is the difference in outcome between 'low' and 'high' congenital anorectal malformations (ARM). Yet, research to support these perceptions is highly needed. This type of research is not only necessary when performing cost-effectiveness analyses, but will also help to predict the outcome and as such can be used to inform the parents about the prospects for their child.

It should be emphasized here that it is essential to carefully distinguish between different types of outcome measures.[42,43] For example, the prevalence of symptoms does not of itself account for the relevance of these symptoms to the patient. One study for example found that fecal incontinence and constipation had almost no effect on the generic HRQoL of patients with ARM or Hirschsprung's disease.[44] Another study showed that adolescents with Hirschsprung's disease had more severe levels of fecal incontinence, but no more psychopathology nor psychosocial dysfunction than healthy controls.[45] So, to gain a full understanding of the long-term outcomes of neonatal surgical diseases, it is important to include various outcome measures, such as measures of symptomatology and HRQoL.

As said above, the time horizon should be sufficiently long to capture all significant effects. This is especially relevant for the case of neonatal surgery. After all, many of the most important outcomes, such as language or cognitive abilities, educational attainment, and adult employment status, are

developmentally programmed to occur years if not decades after the intervention.[46] To take just one example, it requires a follow-up of more than two decades to see whether early surgery for undescended testes has a favorable effect on fertility.

The position of the parents. A consequence of taking a societal perspective is that the position of the parents should not be ignored in cost-effectiveness studies of neonatal surgery. Major health problems in infants affect the whole family. In a small-scale study from Norway for example, 59% of the parents of children with 'low' ARM and 23% of the parents of children with Hirschsprung's disease reported that their child's malformation had a negative influence on their marital relationship and family life. Fifty-three percent of the parents of children with a 'low' ARM recalled that they became isolated from their family, friends, and social activities.[47]

Again it is important to precisely distinguish between different outcome measures. To assess the effects of providing so-called 'informal care' to children suffering from congenital anomalies, there are various options, such as measuring general effects on the caregivers' wellbeing, marital and life satisfaction, broadly-defined quality of life, burden of informal care, or HRQoL. Earlier studies in children with a chronic illness or disability mainly focused on the burden that informal caregiving may cause. Hassink et al. for example investigated stress in parents of children with ARM and found that especially the parents of older boys who were incontinent for feces experienced stress when caring for their child.[48] Such studies also demonstrated that impacts on the family differ according to the type of condition.[49,50] Yet, present understanding of the effects of caregiving on parents' multidimensional HRQoL is still rudimentary in neonatal surgery. It is exactly this outcome measure however that seems to have great value to inform cost-effectiveness analysis. HRQoL represents an overall outcome measure, comprises a valuation of some type, may be measured by using instruments similar to the ones used to assess patients' HRQoL, and closely matches the main goal of health care (i.e., to preserve or restore health). Despite these appealing features, the full potential and limitations of the HRQoL outcome measure in parents are not yet fully understood.

Like the effects on the parents, the costs of providing informal care are presently often ignored in economic evaluations.[33,51] Yet, it is increasingly being acknowledged that a child with a chronic health condition requires additional caregiver time.[52] Studies in parents of children with atopic dermatitis, children with cystic fibrosis, and gastrostomy-dependent children showed that caregiving takes up significant amounts of time, reducing the time available for other activities such as work or recreation, and that it may be associated with high out-of-pocket expenses.[53-55] However, evidence in neonatal surgery is largely lacking. Obviously, the costs that fall to the caregivers, such as transportation costs

incurred in visiting health care providers and costs associated with production losses, should no longer be ignored.

Further research on the process of informal caregiving is clearly warranted. It can lead to better informing caregivers and preparing them for their roles. Moreover, creating understanding of the impact of informal caregiving can help health care professionals in exploring the need for support programs where these do not exist yet and in identifying those caregivers that are most likely to be in need of emotional and social support.

The limits of the cost-effectiveness argument

The above could rightly be interpreted as a plea for the cost-effectiveness argument. Nevertheless, this introduction should not end before having stated the boundaries of this argument. To put it briefly: cost-effectiveness must not be the only factor determining where money goes. Economic evaluations can only be an aid to decision making processes, in which they constitute but one argument among others. Experience indeed shows that health policies in practice are not based on cost-effectiveness grounds exclusively. Examples from the Netherlands from outside the discipline of neonatal surgery demonstrate that arguments other than cost-effectiveness also have a major role, even when the cost-effectiveness data leave nothing to doubt. Note, for example, that a heated debate has arisen over the possible reimbursement of Viagra (sildenafil), whereas therapies such as heart transplantation and lung transplantation are paid for collectively without much debate.[56] Yet, Viagra has been proven to be highly cost-effective (costs of £ 3,639, or € 5,279, per quality-adjusted life year (QALY) gained),[57] a much better cost-effectiveness than that of heart transplantation (costs of € 32,627 per QALY gained)[58] or lung transplantation (costs of € 75,781 per QALY gained).[59]

More generally, much debate has revolved around economic evaluations of health care. This debate centered on the outcome measure 'quality-adjusted life years' (QALYs), which are life years 'corrected' for the quality of life in those years. It has been argued that the use of cost-effectiveness analysis (in the sense of QALY maximization) may lead to health care policies that are inequitable, that is, unfair distribution of health care. Some, for example, contend that we should strive for saving as many lives as possible, not QALYs. Others have been concerned about discrimination against persons who have diseases that are 'inefficient to treat'. Some authors, most notably Harris,[60,61] claim that each patient helped should count equally, no matter how much he or she can be helped for a certain amount of money. Especially interesting, and indeed relevant, is the question of whether QALYs should count the same regardless of to whom they go, be it the very sick or the not so sick for example. Evidence is growing that people are not indifferent as to which patients receive the QALYs.

A point worth making here is that economic evaluations do not by definition conflict with equity. This is because such evaluations themselves are underlied by

particular equity principles, which can be utilitarian or egalitarian. First, cost-effectiveness analysis contains a preference for the 'greater outcome', in terms of (quality-adjusted) life years. It operates under the normative assumption that it is best to maximize the total benefit per dollar spent. In this respect, cost-effectiveness analysis is based on a utilitarian equity principle. Second, the worth of a specific life relative to others is entirely ignored: a QALY is a QALY no matter to whom it accrues—be it a Prime Minister, a drunk driver, or a vagrant. In this sense, cost-effectiveness analysis stands for an egalitarian equity principle (or, as others have said: in this sense, cost-effectiveness analysis is philosophically neutral).[62] Despite these equity assumptions already implicit in economic evaluations, it is increasingly recognized that cost-effectiveness analyses probably do not sufficiently take account of society's preferences for equity.[63] Yet, how exactly to consider equity when prioritizing health care programs for resource allocation, is a question that has been tackled by many authors but with no conclusive answers. Nevertheless, given their high impact, it would be of interest to analyze how equity considerations would work out for the case of neonatal surgery, or, in other words, whether or not they add weight to the outcomes of cost-effectiveness analyses of neonatal surgery.

These issues have received hardly any attention so far in the literature on neonatal surgery. Yet, it is beyond a doubt that they are potentially important. This is because, during the last several decades when cost-effectiveness analyses became more common, it has been widely felt that one of the equity dimensions that may not be sufficiently accounted for in such analyses, is the age of the patient—a characteristic clearly relevant to the case of newborns. Although some studies found no such evidence, most studies consulting the public presented evidence that a life saved, QALYs gained, or a year of perfect life are valued more when they occur to the young than to the old.[64-71] The reasons usually put forward to justify the preference for the young include that they did not yet have their 'fair innings', that a healthy start in life is a good investment for the future, that the young are more productive or have more future productive capacity, and more intangible aspects of personality. Interestingly, reasons like these would perhaps suggest that, while the young are generally preferred over the older, newborns should nevertheless not be given priority over slightly older children. Finally, for the case of neonatal surgery, another element to be considered is that ethical considerations on the level of individual medical decision making may be extra important, relative to equity and efficiency arguments at the budget level. When faced with a child with serious birth defects, the team of medical professionals is confronted with many ethical dilemmas such as whether the condition should indeed be treated, a decision making process in which the parents have an essential say and which often begins before the child's birth.[72-74] These decisions in the individual care plan, often involving life-and-death decisions, may in a sense overshadow factors relevant at the societal level.

1.2 OBJECTIVES

This study's main objective is to collect evidence on the cost-effectiveness of neonatal surgery and to place this evidence in its proper context. The explicit intention is to include a large group of newborns and, since treatment may have impacts on cost and outcomes basically over a patient's life time, to adopt a long-term horizon. Also, it is intended to consider a wide range of relevant costs and effects, not only those occurring to the children themselves but also those to the parents. First and foremost, this main objective is effected through comprehensive economic evaluations of the treatments for two prevalent diagnostic groups, i.e., ARM and CDH. These evaluations are supplemented by an in-depth analysis of the HRQoL of survivors of ARM and CDH. Moreover, this study seeks to provide evidence on the cost-effectiveness of neonatal ECMO, an intervention the cost-effectiveness of which probably has been questioned more than that of any other intervention in neonatal surgery. Furthermore, this thesis aims to describe the situation the parents may find themselves in after the birth of a child with ARM or CDH, to provide evidence of the impact on the caregivers' HRQoL, and to give insight in some basic determinants of this impact. A final objective of the study is to generate insights into how cost-effectiveness interacts with other relevant determinants of how much priority should be given to neonatal surgery.

Besides its aim to present evidence on the cost-effectiveness of neonatal surgery, this thesis can serve as an introduction into cost-effectiveness analyses to pediatric surgeons. Although the number of people acquainted with the principles of cost-effectiveness analysis is growing, misunderstandings are still around. This study attempts to clear up the main misapprehensions. First, cost-effectiveness is not identical to cost-saving. Yet, Luks and colleagues in their study into laparoscopic surgery for example, claimed to analyze cost-effectiveness, but really only included costs.[75] Lönnqvist made statements on the cost-effectiveness of inhaled nitric oxide based on costs alone.[76] This thesis provides yet another example that economic evaluation is as much about effects as it is about costs. Second, this thesis can help to improve understanding of the difference between several outcome measures, another area of all too frequent confusion. Only one example is the study of Baeten and co-workers into dynamic (electrically stimulated) graciloplasty for the treatment of fecal incontinence.[77] The authors correctly conclude that the technique was effective in achieving continence. The data do not, however, support their statement that dynamic graciloplasty improves quality of life, since this was not measured. The literature contains more examples of studies (e.g., on Hirschsprung's disease and omphalocele) that said to study quality of life—or at least draw conclusions on quality of life—but in fact studied biological and physiological factors, symptoms, or aspects of functioning.[78-80] As a note, these observations do not intend to disapprove the quality of these studies or the relevance of their results. What they do intend to

say is that the research literature would benefit from a clearer distinction between different types of outcomes.

1.3 OUTLINE OF THESIS CONTENTS

The contents of this thesis can be summarized as follows. Chapter 2 presents a full economic evaluation of neonatal surgery and subsequent treatment for ARM. Using the technique of cost-utility analysis, the costs and effects of treating patients with ARM are compared to 'no treatment', that is, the natural course of the disease. Following this, Chapter 3 contains a cost-utility analysis of treatment for CDH, closely resembling the methods used in Chapter 2. Chapter 4 is dedicated to the short-term and long-term HRQoL of survivors of ARM and CDH. The patients or their parents are administered symptom checklists and generic HRQoL instruments to find out how the patients are doing compared to the general population. Chapter 5 covers the cost-effectiveness of neonatal ECMO in the Netherlands. A national population of 244 consecutive ECMO-treated newborns with a diagnosis of CDH or meconium aspiration syndrome are compared to a historical control group that would have been eligible for ECMO, were it available at the time. Chapter 6 goes on to consider the position of the parents of children who as newborns underwent treatment for ARM or CDH. It is investigated what it takes to care for these children and whether caregiving has an effect on the parents' HRQoL. In Chapter 7, we explain the relevance of cost-effectiveness analyses in neonatal surgery, examine the state of the art in this area, and place the results of such studies in a wider context. Finally, Chapter 8 draws together the results presented in the various chapters. We will discuss the significance of the results viewed from the perspectives of, respectively, the child and his or her parents, the pediatric specialist, society and its agents (the decision makers), and the health economics researcher.

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Chapter 2

THE COST-EFFECTIVENESS OF TREATMENT FOR CONGENITAL ANORECTAL MALFORMATIONS

ABSTRACT

Background/ Purpose: The progress made in all fields of medicine, including neonatal surgery, has contributed to the rise in healthcare costs. Although neonatal surgery may provide survival gains, these could be at the expense of worse quality of life caused by impairment after surgery. For example, congenital anorectal malformations (ARM) are complex anomalies, and the surgical techniques available have their limitations in achieving continence. It therefore seems justifiable to consider what the effects of treatment are in relation to the costs. Evidence of the cost-effectiveness of neonatal surgery, however, is lacking.

Methods: We analyzed both direct and indirect, medical and nonmedical costs in patients who had undergone treatment for ARM. Quality-adjusted life years (QALYs) were measured using the EuroQol EQ-5D questionnaire. Descriptive quality-of-life data were collected using a disease-specific questionnaire and a medical consumption questionnaire.

Results: Mean costs of treatment are calculated at Euro € 31,593. Treated ARM patients suffer stool difficulties and their medical consumption is relatively high. The EQ-5D, however, shows that the quality of life of ARM patients is only slightly lower than that of the general population (0.88 *v* 0.93). Treatment results in a gain of 12.7 QALYs. Costs per QALY of treatment for ARM amount to € 2,482.

Conclusions: Treatment for ARM has a favorable cost-effectiveness ratio compared with other evaluated healthcare programs. Bearing in mind the increasing political interest in evidence-based and cost-effective medicine, the results are encouraging.

2.1 INTRODUCTION

Continuing increases in healthcare costs imply that the costs of innovative healthcare interventions, such as developments in neonatal surgery, should be assessed. Given that financial resources for healthcare are limited, information on the cost-effectiveness of neonatal surgery is welcome, both from a scientific and a strategic point of view. Evidence of the cost-effectiveness of neonatal surgery, however, is lacking.[1] The current study aims to provide evidence of the cost-effectiveness of treatment for congenital anorectal malformations (ARM).

Two main types of ARM can be distinguished. In a 'low' malformation, the anus is visible in the perineum, but abnormal (narrow or ectopic). A 'high' malformation is characterized by the absence of an anal opening in the perineum. In these cases the anorectum usually opens into the urethra (in boys) or into the vagina (in girls). Treatment depends on the type of anorectal malformation. A 'low' ARM can be treated with definitive surgery in the perineum. For a 'high' ARM, the preferred technique is a posterior sagittal anorectoplasty (PSARP),[2,3] mostly preceded by a protecting colostomy. If surgery is successful, the colostomy will be closed a few weeks after the reconstruction. In almost every case it is necessary to dilate the neoanus after surgery. In the long term, most ARM patients have to cope with fecal incontinence or obstipation, sometimes in combination with urinary incontinence. Depending on the degree of incontinence, it is probable that the anorectum has to be emptied using enemas to achieve pseudocontinence. Patients might experience emotional and social problems, even after successful surgical reconstruction. Moreover, little is known about the patients' sexual functions. Quality of life of ARM patients, therefore is a subject of concern.[4-8]

2.2 MATERIALS AND METHODS

We performed a retrospective study in patients who underwent treatment for ARM in the Sophia Children's Hospital in Rotterdam. Patients included were treated after the year 1969. Patients born after the year 1996 were excluded. To examine to what extent incontinence and other disease-specific symptoms were the result of the ARM, we recruited a control group of children who visited the day-care department in 1998 for minor day-case surgery. The data have been collected in the years 1997, 1998, and 1999.

The study was carried out from a societal perspective, which means that all costs and effects were considered, regardless of who pays or who benefits. This is the preferred perspective in cost-effectiveness analyses.[9] Because of the expected impact of ARM on quality of life, we used the technique of cost-utility analysis. Accordingly, the outcomes are presented in costs per quality-adjusted life-year (QALY). Both costs and effects basically were analyzed in a lifelong setting,

whereas the chronic nature of ARM necessitates a long follow-up period. In past studies, this frequently has been disregarded.[1,10] In this study, the follow-up period is assumed to be sufficiently long enough to detect the relevant (late) economic and clinical outcomes.

Treatment comparator

In an economic evaluation of healthcare programs, treatments or diagnoses are compared with one or more alternatives. For ARM, however, there is no realistic alternative treatment. Therefore, the costs and effects had to be compared with 'no treatment', although this option, in reality, is hypothetical. 'No treatment' implies that all diagnoses or treatments are withheld, hence, no costs are generated. Obviously, life expectancy and quality of life of patients not receiving treatment is unknown. We assumed that patients with a 'high' ARM (50% of all patients) would die shortly after birth because they are unable to defecate. Patients with a 'low' malformation do not die if they do not receive treatment. We assumed that these patients have the same life expectancy as treated ARM patients, but with a substantially lower quality of life, for example, suffering from serious obstipation and incontinence. On the basis of the study of Takayanagi and Suruga[11] we estimated the utility of this hypothetical health state at 0.5. In the sensitivity analysis, we analyzed to what extent this assumption might have influenced our results.

Costs

Identification of the costs. Because this study was conducted from a societal perspective, costs incurred inside and outside the healthcare sector were included. A second distinction was made between direct and indirect costs.

Measurement of the costs. Direct medical costs comprise the healthcare costs incurred between the child's birth and the end of the hospital admission during which the definitive surgical correction of the anorectum takes place, or, when applicable, the end of the hospital admission during which the colostomy is closed. These costs are calculated only for patients born between 1993 and 1996, because computerized data on previous patients were lacking. Data on the volumes were available in an electronic hospital database. To calculate cost prices we included information from the financial accounts of the hospital.

Direct nonmedical costs comprise costs incurred outside the healthcare sector that accrue to patients and their families while receiving healthcare. We limited these costs to transportation costs, which can be estimated on the basis of frequency, distance, and mode of transportation. Costs that can be attributed to ARM were calculated by defining the difference between the frequency of visits to healthcare providers of ARM patients (notably derived from questionnaires) and that of the general population (based on national statistics[12]). Because of insufficient data, we were not able to take into account visits to alternative healers and to the pharmacy.

Indirect medical costs are the healthcare costs made after the period that refers to the direct medical costs. We excluded future healthcare costs of unrelated diseases. In this study, costs of related diseases are calculated by defining the difference between the costs of the healthcare consumption of ARM patients (derived from a medical consumption questionnaire) and the healthcare consumption of the general population.[12]

Indirect nonmedical costs are costs associated with production loss and replacement caused by illness, disability, and death of productive persons, both paid and unpaid.[13] Note that in this study of treatment costs of a condition that arises in childhood, the greatest proportion of productivity changes may fall to the parents or caregivers of the patient. From a societal perspective, these costs are as relevant as patient costs. We measured productivity losses in both caregivers and patients with a preliminary version of the 'Health and Labor Questionnaire'.[14]

Valuation of the costs. Because tariffs are not accurate measures of costs,[9] we set out to calculate the real direct medical costs. There are approximately 2 approaches for calculating cost prices, i.e., 'top down' and 'bottom up'. In top down costing, the total costs of a unit are apportioned to different categories of patients. Bottom up costing measures the resource items specific to individual patients.[15] In this study, we adopted a combination of these 2 methods. The cost price of a hospitalization day is largely calculated using the top down method and, therefore, refers to all patients of the pediatric surgery department. If necessary, we made corrections for our particular patient group. Tariffs (determined by a central body on medical fees in 1998) were taken as 'cost prices' of laboratory tests, because these tariffs are based on a nationwide investigation into real cost prices. The combination of methods also was used to calculate cost prices of diagnostic radiology and nuclear medicine, surgeries, intercollegial consultations, and visits to the outpatient department.

Estimates of the distance of the patient's house to the healthcare provider and the mode of transportation are required to determine the direct nonmedical costs. Because no empirical data were available, we used an established estimate,[16] which gives the mean distances to an academic hospital, a general practitioner, and a physiotherapist as 24.3, 1.1, and 1.1 km, respectively. A cost price of 0.18 Euro (€) per kilometer was adopted. Costs of round trips to a hospital, a general practitioner, and a physiotherapist are thus € 8.61, € 0.39, and € 0.40, respectively.

The indirect medical costs were determined largely on the basis of Rutten et al.,[16] i.e., € 325 for a hospitalization day and € 57 for a visit to the outpatient department. Additionally, we made use of tariffs, i.e., € 17 for a consultation with a general practitioner and with a physiotherapist. Market prices were taken as cost prices of aids for defecation and diapers.

Indirect nonmedical costs were measured using the friction cost method.[17] Besides production losses regarding paid work, losses in the following unpaid activities were also included: household work, shopping, and odd jobs.[14] The value of this work was estimated by taking the wage rate of a professional housekeeper[13] (€ 7.94 per hour). Currently, it is not clear whether a friction period exists regarding unpaid work.[18] We chose to consider these costs for 1 year. Lost hours on activities other than the above-mentioned unpaid activities, such as sleeping, education, and leisure time, were considered as changes in quality of life.

Effects

Identification of the effects. We calculated both the life expectancy and the health-related quality of life of the ARM patients.

Measurement of the effects. Given the chronic but nonlethal character of the anorectal malformation, we assumed that patients who survived the first few years would have a normal life expectancy (75.4 years at birth[19]). The life span of the deceased patients also was determined. On the basis of these data the mean life expectancy was calculated. Descriptive quality-of-life data were collected using a disease-specific questionnaire. A symptom score of the most relevant clinical items was constructed, ranging from 0 to 12 (maximum amount of stool difficulties). Reference scores were derived from the control group. Medical consumption also was considered an indication of the quality of life. Reference scores on medical consumption were derived from national statistics.[12]

Valuation of the effects. Quality of life was valued using the generic EuroQol EQ-5D questionnaire.[20] Patients were asked to classify themselves on 5 dimensions of health (each with 3 levels of dysfunction): mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. This 'descriptive system' generates 243 theoretically possible health states. Building on work in England that elicited valuations for a subset of health states from a general population sample, Dolan[21] published a value set for all the possible health states generated by EQ-5D using modeling techniques. This resulted in an index that assigned a value 1 for normal health and 0 for the value of death. On the basis of the EQ-5D index and the aforementioned life expectancy, we were able to calculate the QALY gains.

Patients younger than 16 years did not fill in the EQ-5D and the medical consumption questionnaire themselves. Their parents were used as proxies. The disease-specific questionnaire was self-administered from the age of 12 years.

Cost-effectiveness

Finally, incremental costs per QALY of treatment for ARM compared with 'no treatment' were calculated. Both future costs and future effects were discounted (to the child's date of birth) at 5% per year to reflect that in general, individuals and society have a positive rate of time preference. This means that people prefer

desirable consequences, such as effects, to occur earlier in life and undesirable consequences, such as costs, to occur later.[9]

2.3 RESULTS

Responders

Of the 526 patients who underwent treatment for ARM, 473 (90%) could be traced. Fifty-four of these (11%) had died, and 8 patients (1.7%) were mentally disabled. The remaining 411 were sent questionnaires. The response rate was 69% (n = 283). Boys comprised a larger proportion (59%). The mean age of the responders was 15.1 years, the youngest 1 year, and the oldest 51 years. The nonresponders did not differ from the responders in terms of sex or age. The children in the patient group did not differ from the general population in regard to participation in education, attending a special school or educational level. Adult patients did not differ from the general population in regard to completed education, having a partner, and number of children. The results indicate that ARM patients differed from the general population in that fewer ARM patients lived alone.

Questionnaires were sent to (the caregivers of) 72 children in the control group and returned by 53 (74%). These children were aged between 1 and 17 years (mean, 7.4 years).

Costs

Direct medical costs. *Table 2.1* presents the prices of the most important units that pertain to these costs. *Table 2.2* shows that the mean direct medical costs of treatment are substantial (€ 22,082). The period in which direct medical costs are made lasts 0.6 years in patients with a 'low' malformation and 1.7 years in patients with a 'high' malformation.

Direct nonmedical costs. The transportation costs amount to € 343 up to the age of 45 years.

Indirect medical costs. Almost half of the patients (49%) appear to use some aids for defecation or diapers. Mean costs that are attributable to ARM are calculated at € 11,818 up to the age of 45 years (without discounting). On the basis of the difference in medical consumption between ARM patients and the general population (*Table 2.3*), we were able to estimate the other indirect medical costs, excluding future health care costs of unrelated diseases. As *Table 2.4* shows, these costs are considerable, although sometimes also savings in future costs occur.

Table 2.1 Costs (in the Year 1998) of Units Pertaining to the Direct Medical Costs of ARM

Hospital days (75.8% of the total direct medical costs)	
Medium care	€ 405
Intensive care	€ 772
Day care	€ 322
Laboratory tests[*] (3.8% of the total direct medical costs)	
12 tests: mean cost price (SD)[†]	€ 2.19 (€ 0.58)
Cross-reactivity test	€ 5.22
Blood group ABO and Rh factor	€ 3.24
Urine culture	€ 16.06
Postnatal chromosome culture	€ 499.16
Diagnostic radiology and nuclear medicine (3.5% of the total direct medical costs)	
Echography kidneys and bladder	€ 79.17
Echography lumbar spine	€ 95.11
Echography heart	€ 85.94
Abdominal X-ray (2 directions)	€ 39.83
Lumbosacral spine (2 directions)	€ 42.47
Voiding cystography	€ 106.95
X-colon/videodefecography	€ 72.59
Renography	€ 238.42
Surgeries[‡] (16.2% of the total direct medical costs)	
Colostomy	€ 1,029
Colostomy closure	€ 971
Colostomy closure, dilatation, and electrostimulation	€ 1,145
Posterior sagittal anorectoplasty	€ 3,292
Anoplasty (cut back)	€ 624
Scopy of urethra/bladder	€ 589
Scopy of urethra/bladder, electrostimulation, and manometry	€ 1,024
Scopy of vagina	€ 589
Dilatation[§]	€ 24
Manometry[§]	€ 143
Video-urodynamic study[§]	€ 152
Intercollegial consultations (0.1% of the total direct medical costs)	
Cardiology[‖]	€ 18.82
Visits to the outpatient department (0.7% of the total direct medical costs)	
Surgery	€ 59.53

[*] *Tariffs instead of cost prices.*
[†] *Twelve different 'general' tests, such as pH, sodium, and hemoglobin.*
[‡] *Not all combinations can be enumerated here. Rare surgical interventions and those that resemble others are not mentioned.*
[§] *Outpatient. Costs of the outpatient department included.*
[‖] *Additional echocardiography not included.*

Table 2.2 Direct Medical Costs of One Treatment for ARM

	No.	Mean	Median	Standard Deviation
All patients	63	€ 22,082	€ 18,205	€ 18,225
Patients with a high malformation	33*	€ 29,822	€ 29,504	€ 13,336
Patients with a low malformation	25*	€ 15,654	€ 8,636	€ 20,493
Boys	40	€ 18,342	€ 14,233	€ 15,091
Girls	23	€ 28,587	€ 26,797	€ 21,509

* *The type of malformation could not be determined in 5 deceased patients.*

Indirect nonmedical costs. In ARM patients, there appear to be no productivity losses caused by mortality. Patients are rarely unable to perform paid work because of ARM. Although reduced productivity while undertaking paid work cannot be disregarded entirely, it can be concluded that the influence of ARM in this respect is small.

We anticipated that a greater proportion of the productivity changes might fall to the caregivers instead of the patients, but this does not seem to have been the case despite 47% of the female caregivers and 31% of the male caregivers expressing the view that their child needed more attention than other children of the same age. *Table 2.5* summarizes the results.

Total costs of treatment for ARM amount to € 31,593 (€ 45,660 without discounting). The discounted costs comprise direct medical costs (70%), direct nonmedical costs (1%), indirect medical costs (25%), and indirect nonmedical costs (4%).

Table 2.3 Medical Consumption of ARM Patients Compared with the General Population

	Age			
	ARM Patients		General Population	
	0-19 yr	20-44 yr	0-19 yr	20-44 yr
Last year (mean):				
Days of hospitalization*	0.6†	1.5	0.4	0.5
Consultations with a specialist‡	2.1§	1.8	1.4	1.5
Consultations with a general practitioner‖	2.3	3.2	3.0	4.1
Consultations with a physiotherapist‡	1.8	1.4	1.0	2.4
Consultations with an alternative healer¶	0.2	0.7	Unknown	Unknown
Last 14 days:				
Persons with prescribed medication (%)**	17.7	18.7	9.0	10.2

* *Admissions for childbirth are not included.*
† *Patients aged from 4 to 19 years.*
‡ *Consultations during hospitalization are not included.*
§ *Patients aged from 2 to 19 years.*
‖ *Consultations by telephone are included.*
¶ *'Alternative' practicing GPs are not included.*
** *Contraceptive pills and medication during hospitalization are not included.*

Table 2.4 Mean Indirect Medical Costs of One Treatment for ARM

Costs of hospital admissions	€ 9,180
Costs of consultations with a specialist	€ 1,194
Costs of consultations with a general practitioner	- € 542
Costs of consultations with a physiotherapist	- € 118
Costs of aids for defecation and diapers	€ 11,818
Total costs up to the age of 45	€ 21,532
Total costs up to the age of 45, discounted	€ 7,791

Effects

Life expectancy. Of the 473 traced patients, 54 (11%) patients had died with a mean life span of 1.4 years (median, 23 days). We assumed that the survivors will have a normal life expectancy of 75.4 years. Accordingly, the mean life expectancy of the ARM patients amounts to 67.0 years.

Health state description. The analysis of the disease-specific questionnaire proves that ARM patients suffer stool difficulties. Dirty pants, lack of urge sensation, inability to recognize the type of defecation, inability to hold defecation, and urinary incontinence are problems that are reported more frequently in ARM patients than in the general population. Furthermore, ARM patients more often use aids for defecation and diapers. This results in a higher symptom score for ARM patients (mean score, 3.5) than for the control group (mean score, 1.4). As a consequence of these stool difficulties, social and sexual problems also are more frequently reported in ARM patients than in the general population.

It appears from the medical consumption questionnaire that ARM patients, in childhood as well as in adulthood, are more often admitted to a hospital, more often consult with a specialist (not during hospitalization), and more often receive medication. However, ARM patients consult with a general practitioner less frequently than the general population.

Health state valuation. Patients from 5 to 15 years scored 0.89 and adults scored 0.88 on the EQ-5D index. Both values are significantly lower than the reference scores for the general population (0.93 both in adults[22] and in children[23]). The mean quality of life of all patients is 0.88. Given the life expectancy of 67.0 years, treating ARM produces 59.0 (67.0 x 0.88) QALYs, whereas 'no treatment' produces 16.7 QALYs (50% of patients live to 67.0 years with a quality of life of 0.5). Treatment for ARM compared with 'no treatment' thus results in a gain of 42.2 QALYs. When discounted at 5% per year, the QALY gain is 12.7.

Table 2.5 Productivity Losses in the Parents/Caregivers of 115 ARM Patients

	Female Caregivers	Male Caregivers*	Total Per Child
Paid work			
Caregivers having paid work	49%†	96%‡	
Mean number of hours paid work per week	9.7§	39.0	
Caregivers who gave up paid work for taking care of their child(-ren)	45%	2%	
Mean number of hours paid work given up per week for taking care of their child(-ren)	11.6	0.3	
Caregivers who gave up paid work for taking care of their child(-ren) as a consequence of the ARM	12%	1%	
Mean number of hours paid work given up per week for taking care of their child(-ren) as a consequence of the ARM	2.4	0.2	
Productivity losses during the friction period	€ 401	€ 30	€ 420
Unpaid work‖			
Mean number of hours spent on unpaid work per week	29.3	10.2	
Mean number of hours less to spend on unpaid work per week as a consequence of the ARM and taking care	1.4	1.1	
Productivity losses during one year after the child's birth	€ 565	€ 445	€ 957
Total productivity losses			€ 1,377

* *One percent of these caregivers is female. Children of these caregivers have two female caregivers.*
† *Only in caregivers aged from 25 to 34 significantly lower than in the general population (P = 0.003).*
‡ *In no age class different from the general population at the 0.05 level.*
§ *As in all following numbers in this table: this is the mean of all (female or male) caregivers, thus including those who do not have paid work, did not give up paid work, etc.*
‖ *Household work, shopping, and odd jobs.*

Cost-effectiveness and sensitivity analysis

Costs per QALY for the treatment of ARM compared with 'no treatment' amount to € 2,482 (€ 1,082 without discounting). Finally, we performed a sensitivity analysis to determine to what extent our assumption on the patients' quality of life in the 'no treatment' scenario (0.5) influenced these results. Values between 0.6 and 0.4 are seen as a plausible range (0.5 ± 20%). This results in a more conservative estimate of € 2,696 costs per QALY and a less conservative estimate of € 2,300 costs per QALY (both discounted).

2.4 Discussion

We analyzed the cost-effectiveness of treatment for ARM. The costs appear to be substantial, especially the direct medical costs. Considerable stool difficulties

occur in ARM patients. Taking medical consumption as an indication of quality of life, the quality of life of ARM patients is lower than that of the general population. Nevertheless, the EQ-5D results show that the impact of stool difficulties on the overall quality of life is limited. Given the concerns about the quality of life of ARM patients mentioned above, this finding is encouraging. Cost-effectiveness (cost per QALY of € 2,482) is good.

We were interested to know whether the type of malformation (high or low) and the mode of treatment affect the long-term consequences of ARM. However, it was only possible to elicit this information for patients born between 1993 and 1996 (who constitute less than one seventh of all responders). To retrieve this information for older patients would require in-depth, time-consuming research, given the long time interval and the lack of computerized data. With the exception of the direct medical costs (*Table 2.2*), we were, therefore, unable to make this distinction for all costs and effects. Our knowledge of the impact of the type of malformation and the mode of treatment is, therefore, restricted to the first few years after birth. No conclusions can be made currently on the effect on long-term costs and effects and on cost-effectiveness.

To determine direct medical costs, we adopted a combination of top down and bottom up calculations. It can be disputed whether the efforts required to apply time-consuming bottom up methods for all cost items are in proportion to the influence on the comparison between treatment and no treatment. We verified in advance whether abandoning precise bottom up methods would crucially affect the outcomes, and, when in doubt, we selected the bottom up technique. We, therefore, expect that the outcomes will not change substantially when all costs are calculated using precise bottom up methods.

Economic analyses always are partly based on assumptions. As far as possible we chose solutions that were more likely to overestimate the costs of treatment, so we consider it to be unlikely that we have presented a too favorable picture of cost-effectiveness. This applies to all 4 cost categories.

The skew of the distribution of the direct medical costs is striking (*Table 2.2*). This can be explained partly by 3 'outliers' who spent respectively 128, 46, and 30 days in the intensive care department. Obviously, a certain spread in the costs is foreseeable because of 'regular' complications. However, when taking this into account, part of this spread could probably be attributed to comorbidity. Therefore, the costs that can be attributed to the treatment of ARM are likely to be overestimated. This observation is not only valid in these 3 apparent 'outliers' but also in other patients. These questions also apply to the indirect medical costs. As mentioned previously, it was our intention to exclude future healthcare costs of unrelated diseases, but costs of comorbidity inevitably enter into the calculations. It is particularly difficult to understand the higher number of nights spent in hospital by patients aged 20 years and older as a consequence of ARM.

This again implies that the cost-effectiveness ratio is likely to be a conservative estimate that possibly underestimates the cost-effectiveness of treatment for ARM.

The study had an adequate response rate (69%), considering the long period between the treatment and the date of the investigation. It is unlikely that the nonresponse influenced the calculated treatment costs because, from a medical point of view, the severity of the malformation does not noticeably differ between nonresponders and responders. However, we cannot be certain that the quality of life of the nonresponders does not differ from the responders. Because we followed our initial contact with a telephone reminder, we had some opportunity to investigate the reasons for nonresponse, but the results were ambiguous. Some nonresponders seemed to indicate that they had a lower quality of life, citing reasons for nonresponse as 'various health problems', 'nonacceptance', 'avoidance', and 'behavioral and family problems'. Other nonresponders, however, suggested that quality of life was underestimated. Some stated that they were not participating in the investigation because they had no health problems. Although no firm conclusions can be drawn, it seems likely that the quality of life of the nonresponders did not differ considerably from the responders.

Remarkably, the results suggest that quality of life of ARM patients does not differ greatly from the general population. The mean EQ-5D index score for their health state is 0.88 compared with 0.93 in the general population. On the basis of the literature, we expected a more severe impairment of quality of life.[4-8] It could of course be argued that the EQ-5D is not sufficiently sensitive to detect stool difficulties. However, former research in this patient group confirmed the sensitivity of the EQ-5D to clinical differences in all age groups where it was administered (i.e., from 5 years on).[23]

Because of difficulties that small children have with notions of abstract concepts and language, we used the parents as proxies to answer the disease-specific questionnaire and the EQ-5D. We are conscious of the variety of factors that can influence a parent's rating of his or her child's quality of life and the equivocal findings reported in the literature.[24-29] Nevertheless, recent research findings in children[30-36] seem to suggest that a parent is able to report appropriate information regarding his or her child's quality of life, especially when observable, concrete questions are asked (e.g., about mobility, usual activities). Furthermore, when the parent and the child disagree about the child's quality of life, the parent tends to rate the child as having a poorer quality of life than the child does him or herself. In this investigation, such a tendency would result in a more conservative estimate of cost-effectiveness. Moreover, we also compared the proxy version of the EQ-5D in these patients with another proxy questionnaire, the TACQOL, whose validity in children has been confirmed previously.[37] The EQ-5D showed good validity from 5 years and over.[23] We consider, therefore, that the favorable

cost-effectiveness ratio found in this study has not been hampered by methodologic flaws surrounding quality of life measurement in children.

We realized that the birth of a child with a congenital anomaly might influence the quality of life of his or her parents or caregivers. This issue also needs to be addressed from a societal perspective. However, Brouwer et al.[13] and Busschbach et al.[38] argue that such changes should be incorporated as a separate item in the analysis, rather than as a part of the measure of the patient's quality of life. Our views on changes in the caregivers' quality of life will, however, be covered separately in Chapter 6.

Treatment for ARM has a favorable cost-effectiveness ratio compared with other evaluated healthcare programs that society in the Netherlands considers to be acceptable expenditure of scarce means. These include heart transplantation (costs per QALY of € 32,627),[39] liver transplantation (costs per QALY between € 31,311 and € 38,118),[40] or lung transplantation (costs per QALY of € 75,781).[41] Taking into account the increasing political interest in evidence-based and cost-effective medicine, the results are reassuring. Our study provides a strong argument for giving priority to treatment for ARM in discussions about the allocation of health care resources.

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Chapter 3

The Cost-Effectiveness of Treatment for Congenital Diaphragmatic Hernia

ABSTRACT

Background/ Purpose: The cost-effectiveness of medical interventions is becoming an important issue for decision makers. Until recently, evidence of the cost-effectiveness of neonatal surgery was largely lacking. We analyzed the cost-effectiveness of neonatal surgery and subsequent treatment for congenital diaphragmatic hernia (CDH).

Methods: Both costs incurred inside and outside the health care sector (e.g., out-of-pocket expenses and productivity losses) were included. Quality-adjusted life years (QALYs) were measured using the EuroQol EQ-5D questionnaire. Descriptive quality-of-life data were collected using a disease-specific questionnaire. Both costs and effects basically were measured in a life-time setting.

Results: Total costs of treatment average € 42,658, mainly consisting of costs of the initial hospitalization. Productivity losses in both the patients and their caregivers appear to be minor. Treated CDH patients, even adults, suffer from respiratory difficulties and stomach aches. According to the EQ-5D, however, their quality of life does not differ from the general population, suggesting that these symptoms barely affect overall quality of life. Treatment results in a gain of 17.5 QALYs. Costs per QALY amount to € 2,434.

Conclusions: Treatment for CDH has favorable cost-effectiveness. Considering the growing importance of cost-effective medicine, these are important and encouraging results. Health economics outlines the inevitability of making choices that directly affect patient care and places relative values on different health care programs. The results of this study provide convincing evidence that treatment for CDH is indeed cost effective.

3.1 INTRODUCTION

In a recent article published in this journal, we emphasized the importance of health economics.[1] We are faced with a continuing dilemma that the supply of care never will be able to meet the growing demand for care. We cannot afford all the treatments patients might desire, not even only those treatments that have proven effectiveness. Administrative efficiencies (for example, negotiating better prices for equipment or reducing paperwork) and removing waste (like harmful practices and practices in which harm equals the benefits but have costs) will not eliminate the need to choose between treatments. Therefore, difficult choices seem to be inescapable, and these choices will affect patient care.[2,3] Economic evaluations are appropriate tools to define the relationship between costs and effects of medical interventions, highlighting those interventions that society considers acceptable expenditure of scarce resources.

Until recently, evidence of the cost-effectiveness of neonatal surgery was lacking.[1] Now, however, the first data on the cost-effectiveness of neonatal surgery have become available. In Chapter 2, we analyzed the cost-effectiveness of treatment for congenital anorectal malformations (ARM) and concluded that treatment for ARM has a favorable cost-effectiveness ratio.[4] We realize, however, that this evidence is limited in the sense that only one particular malformation, characterized by high morbidity into adulthood and low mortality, was studied. Therefore, we set out to analyze the cost-effectiveness of treatment for another malformation that belongs to the field of neonatal surgery and, to a large extent, represents the opposite end of the spectrum in terms of mortality and morbidity. Accordingly, in this chapter we present our results on patients with congenital diaphragmatic hernia (CDH).

CDH consists of a combination of pulmonary hypoplasia, abnormal pulmonary vascular growth, and a defect in the diaphragm. Despite the many advances in prenatal diagnosis, ventilation techniques, and neonatal intensive care, the mortality rate still remains around 40%, although recently better survival rates have been published.[5-7] This is in sharp contrast with the decreasing mortality rate (around 10%) seen in many other major congenital anomalies within the field of neonatal surgery. Considering the high mortality rate, it is hardly surprising that most studies have concentrated on mortality rates. In recent times, however, morbidity and the quality of life of CDH patients are becoming increasingly relevant as survival rates improve, partly because of high technology procedures with inherent morbidity such as fetal surgery and extracorporeal membrane oxygenation (ECMO) in selected cases. In general, the prognosis and quality of life of survivors appears to be good. CDH patients can nevertheless be faced with a range of problems, such as gastroesophageal reflux, airway obstruction and increased airway responsiveness, growth failure and feeding problems, and neurodevelopmental delays resulting from perinatal asphyxia.[8-11]

3.2 MATERIALS AND METHODS

There is a close relationship between this study on the cost-effectiveness of treatment for CDH and our study in ARM patients. For the purpose of comparability, the methodologies of both studies were replicated as far as it was possible. We, therefore, have restricted ourselves to a brief description of our methodology, except for discrepancies between the 2 studies. For a more detailed description, please refer to Chapter 2.

The data were collected in 1997, 1998, and 1999. Patients included underwent treatment for CDH in the Sophia Children's Hospital in Rotterdam after 1969. In principle, all patients until 1986 were treated by emergency surgery to close the diaphragmatic defect, followed by preoperative stabilization and delayed repair from that time onward.[12] ECMO was applied in the hospital from January 1992. Treatment of pulmonary hypertension with inhaled nitric oxide was not available during the study period. Patients born after 1996 were excluded to ensure a minimal follow-up period. Two patients were excluded because their CDH was not diagnosed during the neonatal period. To examine to what extent respiratory difficulties, stomach aches, and other disease-specific symptoms really are consequences of CDH, we recruited a control group of children who visited the day care department in 1998 for minor day-case surgery.

As with our study on ARM, the current study was carried out from a societal perspective using the technique of cost-utility analysis. Accordingly, the outcomes are presented in costs per quality-adjusted life year (QALY).[13] Both costs and effects basically were analyzed in a life-time setting.

Treatment comparator

In economic evaluations of health care programs, treatments or diagnoses are compared with one or more alternatives. Ideally, the alternative is the most cost-effective alternative treatment. More often, the studied program is compared with the most common treatment (i.e., the existing, local practice). For CDH, however, there is no realistic alternative. Therefore, the costs and effects had to be compared with 'no treatment'. In this scenario, all diagnoses or treatments are withheld; hence, no costs are generated. Furthermore, we assumed that in this scenario, the inability to obtain sufficient oxygen uptake because of the underlying lung anomalies would bring about death shortly after birth.

Costs

Identification, measurement, and valuation of the costs. Direct medical costs make up the health care cost incurred between the child's birth and the end of the hospital admission during which the defect in the diaphragm was closed. These costs were calculated only for patients born between 1993 and 1996, because computerized data on previous patients were lacking. Consistent with the methods outlined in Chapter 2 we calculated real costs of hospital days,

laboratory tests, diagnostic radiology, surgeries, intercollegial consultations, and visits to the outpatient department. There is, however, one difference with our previous study. Costs of ECMO were calculated as part of the direct medical costs. These costs, i.e., the additional costs over the costs of a 'standard' day in an intensive care unit, were taken from a large Dutch survey on ECMO in neonates.[14]

Direct nonmedical costs are costs incurred outside the health care sector that accrue to patients and their families while receiving health care. These costs were limited to transportation costs regarding visits to health care providers.

Indirect medical costs are the health care costs made after the period that refers to the direct medical costs. Costs of hospital admissions, visits to the outpatient department, consultations with a general practitioner, and consultations with a physiotherapist are all part of these costs. No reliable data were available on costs of visits to alternative healers, use of medication outside the hospital, and use of medicinal oxygen at home. We excluded future health care costs of unrelated diseases.

Indirect nonmedical costs are costs associated with production loss and replacement owing to illness, disability, and death of productive persons, both paid and unpaid.[15] As we adopted a societal perspective, both productivity changes in patients and in their parents or caregivers were included.

Effects

Identification, measurement, and valuation of the effects. We repeated the methodology outlined in the previous chapter regarding the effects.[4] In summary, we calculated both the life expectancy and the health-related quality of life. We assumed that patients who survived the first few years would have a normal life expectancy (75.4 years at birth[16]). The life span of the deceased patients also was determined. On the basis of these data, the mean life expectancy was calculated. Using the EQ-5D questionnaire,[17] we were then able to calculate the QALY gains. Descriptive quality-of-life data were collected using a disease-specific questionnaire that aimed to measure respiratory difficulties, stomach aches, and other disease-specific symptoms. A symptom score of the most relevant clinical items was constructed, ranging from 0 to 45 (maximum number of symptoms). Medical consumption also was considered an indication of the quality of life.

Generally, patients younger than 16 years did not fill in the questionnaires themselves. Their parents were used as proxies. The disease-specific questionnaire was the only exception. Here, the age limit was put at 12 years.

Cost-effectiveness

Incremental costs per QALY of treatment for CDH compared with 'no treatment' were calculated. Both future costs and future effects were discounted (to the

child's date of birth) at 5% per year. Additionally, we calculated the outcome applying a discount rate of 0%.

3.3 RESULTS

Responders

Of the 285 patients who underwent treatment for CDH, 261 (92%) patients could be traced. Eighty-six of these 261 patients (33%) had died, and 7 patients (2.7%) were mentally disabled. The remaining 168 were sent questionnaires containing questions on social and demographic characteristics, the costs of treatment (with the exception of the direct medical costs), and its effects (the prevalence of symptoms, the medical consumption, and the overall quality of life). The response rate was 67% (n = 112). Female patients constituted almost half of the responders (46%). The mean age of the responders was 14.8 years (range, 1 to 42). The nonresponders did not differ from the responders in terms of sex or age. The children in the patient group did not differ from their contemporaries in the general population in regard to participation in education, attending a special school, or educational level. There is no indication that adult patients differ from the general population in regard to completed education, having a partner, and number of children. Finally, fewer CDH patients were living alone than population standards predict (significant at the 0.05 level).

Questionnaires were sent to (the caregivers of) 72 children belonging to the control group and returned by 53 (74%). These children were aged between 1 and 17 years (mean, 7.4 years).

Costs

Direct medical costs. *Table 3.1* presents the costs of the most important units that pertain to the health care costs between the child's birth and the end of the hospital admission during which the defect in the diaphragm was closed (the first admission in 95% of the patients). This period lasts, on average, 91 days in the survivors (median, 33 days), as against 7 days in the deceased (median, 2 days). *Table 3.2* shows that the mean direct medical costs are considerable (€ 33,080; 1 Euro = 0.87 US dollar). The distribution of these costs appears to be skew. Fifty-eight percent of the costs are spent on the 21% most expensive patients. The average periods of intensive care and medium care are 24 days (median, 14 days) and 4 days (median, 0 days), respectively. The difference between the survivors and the deceased (significant at the 0.05 level) and that between patients treated with ECMO and patients not treated with ECMO (not significant at the 0.05 level) also are shown.

Direct nonmedical costs. The transportation costs amount to € 356 up to the age of 45 years.

Table 3.1 Costs (in the Year 1998) of Units Pertaining to the Direct Medical Costs of CDH

Hospital days (86.4% of the total direct medical costs)	
Medium care	€ 476
Intensive care	€ 1,036
Additional costs of ECMO*	€ 9,400
Laboratory tests† (5.1% of the total direct medical costs)	
12 tests: mean cost price (SD)‡	€ 2.24 (€ 0.47)
Blood gas	€ 10.35
Calcium	€ 3.11
C-reactive protein	€ 4.90
Magnesium	€ 6.24
Cross-reactivity test	€ 5.22
Blood group ABO and Rh factor	€ 3.24
Bacteriological culture	€ 16.06
Postnatal chromosome culture	€ 499.16
Prenatal chromosome culture	€ 494.62
Diagnostic radiology§ (3.7% of the total direct medical costs)	
Echography abdomen	€ 95.11
Echography kidneys and bladder	€ 79.17
Echography heart	€ 85.94
Echography skull	€ 85.63
Abdominal X-ray (1 direction)	€ 38.09
Thoracic X-ray	€ 34.80
X-ray stomach/duodenum/oesophagus (barium swallow)	€ 100.22
Surgeries (4.7% of the total direct medical costs)	
Hernia repair (using a Gore-Tex patch)	€ 1,959
Central line insertion (Broviac catheter)	€ 608
Nissen fundoplication	€ 2,046
Intercollegial consultations (0.0% of the total direct medical costs)	
Cardiology‖	€ 18.82
Neonatology	€ 25.09
Neurology	€ 25.09
Visits to the outpatient department (0.0% of the total direct medical costs)	
Surgery	€ 59.53
Lung diseases	€ 96.06
Pediatrics	€ 64.69

* *Additional costs of a complete ECMO treatment over the costs of a 'standard' day in an intensive care unit.*
† *Tariffs instead of cost prices.*
‡ *Twelve different 'general' tests, such as kalium, glucose, and hemoglobin.*
§ *Not all interventions can be enumerated here. Some interventions that resemble others are not mentioned. As in the other categories, this enumeration does not imply that each action is carried out for each patient.*
‖ *Additional echocardiography not included.*

Indirect medical costs. We were able to estimate the indirect medical costs on the basis of the difference between CDH patients and the general population in medical consumption after the hospital admission during which the defect in the

diaphragm was closed (*Table 3.3*). Using cost prices of € 325 per hospitalization day, € 57 for a visit to the outpatient department, and using a tariff of € 17 for both a consultation with a general practitioner and a consultation with a physiotherapist,[4] mean indirect medical costs are calculated at € 8,470 (*Table 3.4*). Note that for some aspects, treatment for CDH produces financial savings.

Indirect nonmedical costs. In CDH patients, there appear to be no productivity losses owing to mortality. Besides mortality, illness and disability also may cause productivity losses. Adult patients and the general population, however, appeared not to differ in having paid work, corrected for differences in sex and age. For example, 67% of all male CDH patients between 16 and 24 years of age do not have paid work compared with 59% of their contemporaries in the general population. Of all patients that are currently without paid work (i.e., 49% of all patients aged 16 years and older), none attributed their unemployment to CDH. Although reduced productivity while undertaking paid work (for example because of concentration disorders) cannot be disregarded entirely, the available data suggest that the influence of CDH in this respect also is small.

Table 3.2 Direct Medical Costs of One Treatment for CDH

	No.	Mean	Median	Standard Deviation
All patients	38	€ 33,080	€ 21,256	€ 39,356
Survivors	24	€ 45,164	€ 26,164	€ 44,343
Deceased patients	14	€ 12,365	€ 3,120	€ 14,068
Patients treated with ECMO	8	€ 35,718	€ 31,506	€ 19,943
Patients not treated with ECMO	30	€ 32,376	€ 18,898	€ 43,333

Table 3.3 Medical Consumption of CDH Patients Compared with the General Population

	CDH Patients		General Population	
	0-19 yr	20-44 yr	0-19 yr	20-44 yr
Last year (mean):				
Days of hospitalization*	2.2†	1.0	0.4	0.5
Consultations with a specialist‡	0.7†	1.4	1.4	1.5
Consultations with a general practitioner§	2.2	3.5	3.0	4.1
Consultations with a physiotherapist‡	3.7	4.0	1.0	2.4
Consultations with an alternative healer‖	0.7	2.5	Unknown	Unknown
Last 14 days:				
Persons with prescribed medication (%)¶	8.1	40.9	9.0	10.2

* *Admissions for childbirth are not included.*
† *Patients aged from 4 to 19 years.*
‡ *Consultations during hospitalization are not included.*
§ *Consultations by telephone are included.*
‖ *'Alternative' practicing GPs are not included.*
¶ *Contraceptive pills and medication during hospitalization are not included.*

Table 3.4 Mean Indirect Medical Costs of One Treatment for CDH

Costs of hospital admissions	€ 12,542
Costs of consultations with a specialist	- € 99
Costs of consultations with a general practitioner	- € 322
Costs of consultations with a physiotherapist	€ 1,017
Total costs up to the age of 45	€ 13,138
Total costs up to the age of 45, discounted	€ 8,470

We had expected that a greater proportion of the productivity changes might fall to the caregivers instead of the patients. However, only 24% of the female caregivers and 13% of the male caregivers expressed the view that their child required more attention than other children of the same age. Only 7% of the female caregivers and none of the male caregivers had given up paid work to take care of their child as a direct consequence of the CDH. Total productivity losses in the caregivers appeared to be minor (*Table 3.5*).

Table 3.5 Productivity Losses in the Parents/Caregivers of 46 CDH Patients

	Female Caregivers	Male Caregivers	Total Per Child
Paid work			
Caregivers having paid work	51%*	97%*	
Mean number of hours paid work per week	11.0†	39.3	
Caregivers who gave up paid work for taking care of their child(-ren)	48%	7%	
Mean number of hours paid work given up per week for taking care of their child(-ren)	11.5	1.0	
Caregivers who gave up paid work for taking care of their child(-ren) as a consequence of the CDH	7%	0%	
Mean number of hours paid work given up per week for taking care of their child(-ren) as a consequence of the CDH	1.0	0.0	
Productivity losses during the friction period	€ 161	€ 0	€ 154
Unpaid work‡			
Mean number of hours spent on unpaid work per week	29.6	12.4	
Mean number of hours less to spend on unpaid work per week as a consequence of the CDH and taking care	1.0	0.6	
Productivity losses during one year after the child's birth	€ 400	€ 238	€ 598
Total productivity losses			€ 752

* *In no age class different from the general population at the 0.05 level.*
† *As in all following numbers in this table: this is the mean of all (female or male) caregivers, thus, including those who do not have paid work, did not give up paid work, etc.*
‡ *Household work, shopping, and odd jobs.*

Total costs of treatment for CDH amount to € 42,658 (€ 47,495 without discounting). The discounted costs comprise direct medical costs (78%), direct nonmedical costs (1%), indirect medical costs (20%), and indirect nonmedical costs (2%).

Effects

Life expectancy. Of the 261 traced patients, 86 (33%) patients had died with a mean life span of 1.5 years (median, 3 days). We assumed that the survivors will have a normal life expectancy of 75.4 years. Accordingly, the mean life expectancy of all patients, including the deceased, amounts to 51.1 years.

Health state description. The prevalence of symptoms in CDH patients will be presented extensively in Chapter 4. To summarize, the disease-specific symptoms are not unique to CDH patients but almost all symptoms are more frequently reported in CDH patients than in the general population. Statistically significant differences were found between CDH patients and the controls concerning coughing up sputum when waking up, shortness of breath when performing heavy physical activities, experiencing constraints as a result of respiratory problems, suffering from hiccupping (because of its intensity or duration), heartburn, and stomach aches. This results in a significantly higher symptom score for CDH patients under the age of 19 (n = 81; mean age, 10.3; mean symptom score, 6.8) than for their contemporaries in the control group (n = 53; mean age, 7.4; mean symptom score, 4.9).

It appears from the medical consumption questionnaire that, compared with the general population, a significantly larger proportion of the CDH patients under the age of 20 was admitted to a hospital (17% *v* 4%) and consulted a physiotherapist (13% *v* 7%) during the last 12 months. A significantly larger proportion of the older CDH patients (between 20 and 45 years of age) than the general population consulted a general practitioner during the last 12 months (96% *v* 74%) and used prescribed medication during the last 14 days (41% *v* 10%).

Health state valuation. Patients from 5 to 15 years scored 0.92, and adults scored 0.91 on the EQ-5D index. Both values do not significantly differ from the reference scores for the general population (0.93 both in adults[18] and in children[19]). The mean quality of life of all patients is 0.91. Given the life expectancy of 51.1 years, treating CDH produces 46.5 (51.1 x 0.91) QALYs. As said before, we assumed that 'no treatment' would bring about death shortly after birth. In this case, the number of QALYs equals zero. Treatment for CDH compared with 'no treatment' thus results in a gain of 46.5 QALYs. When discounted at 5% per year, the QALY gain is 17.5.

Cost-effectiveness

Costs per QALY of treatment for CDH compared with 'no treatment' amount to € 2,434 (€ 1,022 without discounting).

3.4 Discussion

The cost-effectiveness ratio amounts to € 2,434 (costs per QALY), which indicates good cost-effectiveness. We conclude that, although CDH patients might fall into the costliest category of all hospitalized patients, the effects of treatment are worth the costs. Only minor social and demographic differences were found between CDH survivors and the general population. The costs of treatment are substantial (€ 42,658), mainly consisting of costs of the initial hospitalization. To the best of our knowledge, complete direct medical costs of treatment for CDH (i.e., not only those of ECMO), including all presenting patients, have not been calculated previously. For example, some studies did not include the full range of costs,[20,21] because the research questions made it unnecessary to include, for example, costs of surgeries and hospital overhead costs. The methods of the few other studies reported in the literature are either not sufficiently refined for calculating real economic costs[22,23] or unclear.[24] With the exception of the research of Waitzman et al.,[22] no attempts have been made to consider other cost categories that should also be taken into account from a societal perspective. Up to adulthood, CDH patients to some degree, suffer from disease-specific symptoms such as pulmonary problems and stomach aches. Previous studies have suggested that this is the case.[8-11,25] Taking medical consumption as an indication of quality of life, the quality of life of CDH patients seems lower than that of the general population. Despite these findings, the EQ-5D shows that the overall quality of life of CDH patients does not differ from the general population. This outcome is in line with our introductory remark that, in general, CDH survivors can expect good survival.

Direct medical costs could be calculated only for 38 patients born in a rather short period (between 1993 and 1996). No conclusions are drawn on patients born in other periods. Our results are likely to be representative for most patients born in that era. Of course, we cannot be sure that the same results apply to previous or future patients. For example, treatment patterns may change in the future. However, some parts of the calculations, such as the large share of the costs of hospital days in the total direct medical costs, are likely to show similar results. Many of the reflections on the cost calculations in our study in ARM patients[4] also apply to the current study. For example, we chose solutions that were more likely to overestimate the costs of treatment. We therefore consider it unlikely that we have presented a too favorable picture of cost-effectiveness. One particular caveat should be made, however, on the cost calculations in this study, i.e., the costs of ECMO were taken from a large Dutch survey on ECMO in neonates.[14] It is unlikely, however, that this would lead to substantial bias, because both our study and the ECMO survey were performed in patients at the Sophia Children's Hospital, and in both studies the cost calculations were largely based on the same financial accounts. Moreover, only 21% of the patients in this study underwent ECMO treatment, and the costs of ECMO comprised only 6% of all direct medical costs.

Regarding the treatment of CDH patients, ECMO is the subject for debate. The current study brings us to the following reflections about ECMO. The average costs of a treatment including ECMO (€ 35,718) appear not to be much more than the costs of a treatment without ECMO (€ 32,376; *Table 3.2*). One possible explanation is that there is an interaction between the use of ECMO and the total length of stay in a neonatal intensive care unit. A few findings suggest that ECMO might shorten the length of stay in patients with severe respiratory illness (i.e., not only CDH patients).[26-29] This will have a negative influence on overall direct medical costs. Because of the small patient numbers (caused by the lack of computerized data), we could not test this assumption in this study. However, there might be a more likely explanation. Six of the 8 patients that underwent ECMO treatment died, in comparison with 27% of the others. The small patient numbers may have impeded representative survival rates. In larger study groups, survival rates in ECMO patients and thus direct medical costs are likely to be higher. This would be more in line with other studies that found that the use of ECMO in CDH patients is likely to increase the initial hospitalization costs (or charges).[14,23] Furthermore, the application of ECMO gives rise to additional questions. ECMO is widely believed to improve survival rates in neonates with severe respiratory failure. At the same time, however, this technique increases the importance of studies on morbidity, because it also causes late deaths (0.5 to 1 year) in some patients (whereas the 86 deceased patients in our study had a median life span of only 3 days). Furthermore, pulmonary hypoplasia and iatrogenic ECMO morbidity may, more than in the past, lead to lower quality of life. To monitor the increasing prevalence of respiratory problems, standardized long-term follow-up is necessary. For example, the UK Collaborative ECMO Trial Group has examined morbidity in ECMO survivors at the age of 4 years. Their initial results suggest a favorable profile of morbidity when applying ECMO compared with conventional treatment in the United Kingdom.[30] However, the number of CDH patients was small. Thus, close follow-up of CDH patients still remains essential, because the severity of CDH necessitates distinguishing CDH patients from other diagnostic categories requiring ECMO.[31,32]

Concerning the indirect medical costs, no reliable data were available for calculating costs of medication use outside the hospital and use of medicinal oxygen at home. We consider, however, that this has not biased the outcomes. As *Table 3.3* shows, the share of the CDH patients younger than 20 years of age for whom medication is prescribed is even smaller than that in the general population. Admittedly, this is not true in older CDH patients, but it appears from the disease-specific questionnaire that 91% of the responders never use pulmonary symptom-relieving medicines. Thus, the medication use in this small group of responders probably is not caused by their CDH. Regarding the use of medicinal oxygen at home, it is fair to assume that only a minority of the patients is oxygen dependent at discharge from the hospital. Muratore et al.[25] found, for example, that 16% of 100 CDH survivors required oxygen at the time of discharge for a mean duration of 14.5 months. However, our CDH survivors were

not completely similar to the survivors in Muratore's study. Of all surviving patients in Muratore's study, 29% underwent ECMO treatment, which exceeds the proportion in our study (8%; 2 of 24). Because ECMO survivors are more likely to require supplementary oxygen at discharge than survivors that did not have ECMO (as Muratore observed), possibly an even smaller proportion than 16% of our survivors was oxygen dependent at hospital discharge. It must not be considered a great limitation that these 2 cost categories had to be ignored.

In the discussion section of our ARM study (Chapter 2) we reflected on several issues regarding the calculation of the effects of treatments. Our remarks on the response rate, the parents rating the quality of life of the young children, and the influence on the caregivers' quality of life are relevant to this study too and will not be repeated here. One issue, however, deserves attention. The differences in the prevalence of disease-specific symptoms between the CDH patients and the general population seem to be underestimated. The children in the control group suffer respiratory difficulties and stomach aches to such an extent that it is doubtful whether this group is representative of the general population. Probably, excluding CDH patients from the control group did not suffice. It is therefore recommended that, in the future, these data are collected, for example, in primary schools, instead of in children that visited the hospital's daycare department for minor day-case surgery.

It is evident that treatment for CDH has a favorable cost-effectiveness ratio. Considering the growing importance of cost-effective medicine, these are important and encouraging results. Health economics outlines the inevitability of making choices that directly affect patient care and places relative values on different health care programs. The results of this study provide convincing evidence that treatment for CDH is indeed cost effective.

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Chapter 4

Short-Term and Long-Term Health-Related Quality of Life After Congenital Anorectal Malformations and Congenital Diaphragmatic Hernia

ABSTRACT

Aims: To examine short-term and long-term health-related quality of life (HRQoL) of survivors of congenital anorectal malformations (ARM) and congenital diaphragmatic hernia (CDH), and to compare these patients' HRQoL with that of the general population.

Methods: HRQoL was measured in 286 ARM patients and 111 CDH patients. All patients were administered a symptom checklist and a generic HRQoL measure. For the youngest children (aged 1–4) the TAIQOL (a preliminary version of the TAPQOL) was used, for the other children (aged 5–15) the TACQOL questionnaire, and for adults (aged > 16) the SF-36.

Results: As appeared from the symptom checklists, many patients remained symptomatic into adulthood. In the youngest ARM patients (aged 1–4 years), generic HRQoL was severely affected, but the older ARM patients showed better HRQoL. In the CDH patients, the influence of symptoms on HRQoL seemed less profound. The instruments we used revealed little difference between adults treated for ARM or CDH and the general population.

Conclusions: These results show that for two neonatal surgical procedures, improved survival does not come at the expense of poor HRQoL in adults. Even though there is considerable suffering in terms of both morbidity and mortality in the youngest group, the ultimate prognosis of survivors of the two studied congenital malformations is favorable. This finding can be used to reassure parents of patients in need of neonatal surgery for one of these conditions about the prospects for their child.

4.1 INTRODUCTION

Improved survival among neonates with previously life-threatening congenital anomalies has created new dilemmas in neonatal surgery. Mere survival is no longer sufficient; the child's future health-related quality of life (HRQoL) is equally important. Moreover, the large amount of economic resources currently spent on neonatal care, coupled with increasing budget constraints, has evoked the question of whether the effects of a given treatment are worth the costs.[1-3] There is growing political interest in evidence-based, cost-effective medicine, including pediatric surgery.

Recently, we reviewed the literature dated 1989-98 on the prognosis in terms of HRQoL of newborns operated on for the congenital anomalies listed by Ravitch and colleagues.[1,4] It appeared that many studies fail to establish HRQoL and only present mortality rates and crude measures of childhood morbidity. With few exceptions,[5,6] follow-up data in adults are lacking. Furthermore, most studies appeared to stress physical rather than social or psychological functioning. To estimate the significance to an individual of an impairment or a functional limitation, generic HRQoL measures—containing physical, mental, and social domains—should be used. These allow for comparisons across patients suffering from various conditions, bringing out the relative severity of diseases.

To fill the knowledge gap, we analyzed long-term HRQoL effects for congenital anorectal malformations (ARM) and congenital diaphragmatic hernia (CDH). Studies in ARM patients, which predominantly focused on impairments and limitations in specific domains of functioning, suggested a relatively poor long-term HRQoL, even after successful surgical reconstruction.[7-9] CDH patients, though often faced with life-threatening morbidity during the neonatal period and a variety of symptoms in their first years of life,[10-12] generally seem to lead healthy lives eventually. This study attempts to clarify the HRQoL of survivors of ARM and CDH in a lifetime setting and looks to the question of how it compares with that of the general population.

4.2 MATERIALS AND METHODS

Patients

The patient population was comprised of patients treated for ARM or CDH after the year 1969 in the Sophia Children's Hospital, a level III children's hospital serving a referral area of 3.5 million inhabitants. Patients born after the year 1996 were excluded to ensure a minimal period of one year between the patient's birth and the date of investigation. Data were collected from 1997 to 1999. Study questionnaires were distributed by post. If patients did not respond, they were reminded once with a telephone call.

Outcome measures

The patients or their parents were asked to complete both a symptom checklist created by ourselves and an existing generic HRQoL questionnaire. The former served to measure symptoms. A symptom is defined as a patient's perception of an abnormal physical, emotional, or cognitive state.[13] Patients aged from 12 years filled in the symptom checklist themselves. Parents filled in proxy versions of the questionnaires on behalf of younger patients.

Because of the rapid developmental change in children, different HRQoL questionnaires had to be used for three age groups. These were the TNO-AZL Infant Quality of Life (TAIQOL) questionnaire (ages 1-4), the TNO-AZL Children's Quality of Life (TACQOL) questionnaire (ages 5-15), and the MOS Short-Form 36 (SF-36) questionnaire (ages 16+). The HRQoL questionnaires were self-administered from 16 years on.

Symptom checklists. The symptom checklist for ARM patients was comprised of seven items, among which were lack of urge sensation, inability to hold feces, the use of aids for defecation and diapers, and urinary incontinence (see *Table 4.1*). The total symptom score ranges from 0 to 12, representing maximum symptomatology. The CDH symptom checklist, covering 14 items, dealt with several respiratory difficulties and stomach problems (see *Table 4.2*). Again, higher scores correspond to more severe symptomatology, with a maximum score of 45.

Table 4.1 Symptom Checklist for ARM Patients

Item	**Reponse categories and scoring**		
	0	**1**	**2**
1. Soiling	Never	Sometimes	One or more times per day
2. Urge sensation	Yes	No	
3. Ability to hold feces	1 to 10 minutes	10 to 60 seconds	Less than 10 seconds
4. Ability to recognise the type of feces (solid feces, liquid feces, or gas)	Yes	No	
5. Using therapeutic aids for defecation	Never	2 to 3 times a week	Every day
6. Using diapers, pantyliners, and/or plugs	Never	On some occasions	Every day
7. Ability to hold urine	Always	Sometimes (at times an 'accident')	Never

Translated version. The questionnaire we used was in Dutch.
A symptom score was constructed using the sum of the numeric labels presented in the table. The total score ranges from 0 to 12, representing maximum symptomatology.

Table 4.2 Symptom Checklist for CDH Patients

Item		Reponse categories and scoring				
		0	**1**	**2**	**3**	**4**
1.	Respiratory difficulties*	Never	Sometimes	Regularly	Often	Almost always†
2.	Shortness of breath when performing heavy physical activities	Never	Sometimes	Regularly	Often	Always
3.	Shortness of breath when performing light physical activities	Never	Sometimes	Regularly	Often	Always
4.	Tightness of the chest during sleep	Never	Sometimes	Regularly	Often	Always
5.	Having a cold or a stuffed-up or runny nose	Never	Sometimes	Regularly	Often	Chronically†
6.	Inflammation of the respiratory tract during the last year	Never	Sometimes	Chronically†		
7.	Taking respiratory medications	Never	2 to 3 times per week	Every day		
8.	Experiencing constraints as a result of respiratory difficulties	Never	Sometimes	Regularly		
9.	Number of days per week with only few respiratory difficulties	Every day	Almost every day	3 or 4 days	1 or 2 days	No days
10.	Suffering from hiccupping (for example, due to its intensity or duration)	Never	Sometimes	Regularly	Often	Always
11.	Heartburn	Never	Sometimes	Regularly	Often	Always
12.	Stomach ache	Never	Sometimes	Regularly	Often	Always
13.	Other stomach complaints	Never	Sometimes	Chronically†		
14.	Suffering from chronic obstructive pulmonary disease or allergic reactions of the respiratory tract	No	Yes			

Translated version. The questionnaire we used was in Dutch.
The numeric labels shown in the table were summed to arrive at a symptom score. Higher scores correspond to more severe symptomatology, with a maximum score of 45.

* *Six different respiratory difficulties (i.e., 1) non-productive coughing, 2) sputum retention, 3) coughing up sputum when waking up, 4) coughing involving significant sputum production, 5) wheezing, and 6) wheezing and tachypnea), all using these response categories. In the symptom score we used the average score of these six symptoms.*

† *The respondents were instructed that 'almost always' or 'chronically' meant 5 or more days per week during the past three months.*

Clearly, the symptoms studied may also be prevalent in the general population. For example, lack of continence occurs in children born with ARM as well as in healthy children up to a certain age. Therefore, we set out to determine reference scores using a randomly selected sample of children who visited the day-care department of our hospital in 1998 for minor day-case surgery. These controls, who had no record of stool difficulties or respiratory problems, were administered both the ARM checklist and the CDH checklist.

TAIQOL questionnaire. The TAIQOL questionnaire was developed to be a reliable and valid instrument for measuring HRQoL in children between the ages of 1 and 4.[14] It includes 13 domains: lungs, stomach, skin, sleeping, appetite, eating problems, aggressive behavior, positive emotions, emotions of anxiety, vitality, social behavior, motor problems, and communication. The last three domains are applicable only to children aged 18 months and older. The number of items per domain varies from three to seven. Regarding eight of the domains, the TAIQOL investigates HRQoL by assessing functional problems weighted by the degree to which a child shows negative emotions in response to such problems. An example of such a TAIQOL item pair is presented in *Figure 4.1*. In the other five domains, the TAIQOL only measures the frequency of a specific limitation (see *Figure 4.2* for an example). Crude domain scores were linearly transformed to a 0-100 scale, with higher scores indicating better HRQoL.

Figure 4.1 An Item Example of the TAIQOL

Did your child cry at night?	❑ Never (4)	❑ Occasionally	❑ Often	
		At that time, my child felt:		
	❑ Fine (3)	❑ Not so good (2)	❑ Quite bad (1)	❑ Bad (0)

A single score is given for a combination of each functional item with the corresponding emotional item. The scoring grid of the example given above is given in brackets. As with all other items, a higher score corresponds to a better HRQoL.

Figure 4.2 An Item Example of the TAIQOL

Was your child able to play happily with other children?	❑ Never (0)	❑ Occasionally (1)	❑ Often (2)

The scoring grid of the example given above is given in brackets.

TACQOL questionnaire. The developers of the TAIQOL also created an instrument for use with children between the ages of 5 and 15 years, named the TACQOL questionnaire.[15] Its seven domains are: pain and symptoms, basic motor functioning, autonomy, cognitive functioning, social functioning, global positive emotional functioning, and global negative emotional functioning. Each domain consists of eight item pairs.[16] The first part of each item assesses the presence of health status problems. The second part assesses the emotional response to such problems. As with the TAIQOL questionnaire, each item pair is encoded into one single score, ranging from 0 to 4. However, no emotional responses are asked regarding 'global positive emotional functioning' and 'global negative emotional functioning', since this would lead to nonsensical results. In these two domains, the item scores range from 0 to 2. Consequently, the domain scores range from 0 to 32 for all domains, except those concerning emotional functioning, which range from 0 to 16. Higher scores correspond to better HRQoL. Both the TAIQOL and the TACQOL have been validated in several patient groups since they came into use, with promising results.[16,17]

SF-36 questionnaire. The SF-36 questionnaire consists of 36 items organized into eight domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The SF-36 domain scores range from 0 to 100, with higher scores indicating better HRQoL. Results can be aggregated into a physical and a mental health summary measure. These summary measures were linearly transformed to a mean of 50 and standard deviations of 10 in the general US population. Evidence on the psychometric performance of the widely used SF-36 is mounting.[18,19]

Statistics

Statistical analyses were carried out using the t test for two independent sample means and the t test for the significance of a correlation (two-tail probabilities). Results were considered statistically significant if they were at the $P < 0.05$ level.

4.3 RESULTS

Respondents

Of all 526 ARM patients and 285 CDH patients who underwent treatment for their conditions in the study period, we excluded patients who were deceased (ARM, n = 54; CDH, n = 86), were severely cognitively disabled (ARM, n = 8; CDH, n = 7), or could not be traced (ARM, n = 53; CDH, n = 24). The remaining 411 ARM patients and 168 CDH patients were sent questionnaires. The response rate amounted to 70% (n = 286) in ARM patients and 66% (n = 111) in CDH patients. Because extracorporeal membrane oxygenation (ECMO) was not applied in the hospital until January 1992, only four (all in the 1–4 years age group) of all 111 CDH patients participating in this study were treated with ECMO.

The respondents did not differ from the non-respondents in terms of sex or age. Males comprised a larger proportion of the respondents (59% in ARM patients *v* 53% in CDH patients). ARM patients were between 1 and 51 years of age (mean 15.1, SD 9.4). Age ranged from 1 to 42 years in CDH patients (mean 14.3, SD 8.6). There were no differences between ARM and CDH patients and the general population with respect to educational level, involvement in a relationship, or having children.

Symptom checklists were sent to (the caregivers of) 72 children in the control group and returned by 53 (74%).

Disease-specific symptoms

Across all age groups, ARM patients had higher symptom scores than the control group (*Table 4.3*). Over the years, the symptom score decreased in ARM patients, but remained statistically significantly higher than that of the reference group. To mention a few examples: 68% of all ARM patients sometimes or regularly soiled themselves versus 32% in the control group. Compared to the reference group, a relatively small part of the ARM patients was able to hold feces for at least one minute (67% *v* 92%) or was able to recognize the type of feces (64% *v* 85%).

The results presented in *Table 4.3* provide fairly strong evidence that, overall, the symptom score in CDH patients was higher than that of the control population. In the control group, the symptom score showed a clear decrease over the years, which does not match the pattern found in the CDH patients. Many respiratory difficulties and stomach problems were not unique to CDH patients, but almost all symptoms were reported more frequently in CDH patients than in the control group. For example, 76% of all CDH patients never coughed up sputum when waking up, in comparison with 90% in the control group. Of the CDH patients, 77% never experienced constraints as a result of respiratory difficulties, compared to 91% in the control group.

Health-related quality of life

In the youngest age group, differences in HRQoL between patients and the general population were found (*Table 4.4*). In as many as eight of the 13 TAIQOL domains, the difference between ARM patients and the general population is considered statistically significant. Of note is the low score of the ARM patients on the stomach domain, which consists of the items stomach ache or abdominal pain, colic, and nausea. In most domains, the scores of the CDH patients exceeded those found in the ARM patients. Nevertheless, statistically significant differences between the CDH sample and the reference group were found in five domains. By conventional statistical criteria, we found no clear evidence of a difference in the domain 'lungs', which is composed of the items bronchitis, difficulties with breathing or lung problems, and shortness of breath.

Table 4.3 Symptom Scores of ARM Patients and CDH Patients Compared with Reference Scores

	ARM patients			CDH patients			Reference group		Symptom score difference with reference group (95% CI[†])	
Age class	**n**	**Mean age**	**Mean score (SD)**	**n**	**Mean age**	**Mean score (SD)**	**n**	**Mean age**	**ARM**	**CDH**
1-4 y	40	2.7	5.9 (3.3)	20	2.9	7.3 (6.1)	18	3.0	3.5 (1.7 to 5.3)[**]	1.6 (-2.6 to 5.8)
5-10 y	67	7.2	4.2 (3.1)	23	8.0	7.5 (7.4)	22	7.3	2.9 (1.5 to 4.3)[**]	2.4 (-1.4 to 6.2)
11-15 y	52	12.9	3.8 (2.9)	16	13.5	5.9 (5.1)	11	12.9	3.2 (1.4 to 5.0)[**]	2.1 (-1.4 to 5.6)
≥ 16 y	127	23.8	2.7 (2.5)	52	21.8	7.1 (5.4)	2	17.0	2.7[‡]	4.3[‡]
Total	286	15.0	3.7 (3.0)	111	14.3	7.0 (5.9)	53	7.4	2.2 (1.4 to 3.1)[**]	2.1 (0.2 to 3.9)[*]

A missing value analysis (using an expectation-maximization algorithm) was performed for 79 (16%) of all 503 calculated symptom scores.

[*] *Significant at P < 0.05.*

[**] *Significant at P < 0.001.*

[†] *95% confidence interval for the difference between the group means.*

[‡] *Difference not tested (because of small sample size).*

Table 4.4 TAIQOL Scores of ARM Patients and CDH Patients Aged 1-4 Years Compared with Reference Scores

	Mean scores (SD)		Difference with reference group[†] (95% CI[‡])	
Domain	**ARM (n = 41[§])**	**CDH (n = 20)**	**ARM**	**CDH**
Lungs	91.3 (21.0)	86.8 (18.7)	-2.2 (-7.7 to 3.4)	-6.6 (-14.1 to 0.9)
Stomach	65.4 (23.8)	84.2 (22.6)	-26.5 (-31.6 to -21.5)***	-7.8 (-14.4 to -1.1)*
Skin	91.1 (11.2)	94.2 (9.8)	-0.9 (-4.4 to 2.6)	2.2 (-2.5 to 7.0)
Sleeping	73.0 (22.5)	81.6 (24.6)	-9.0 (-14.9 to -3.1)**	-0.5 (-8.6 to 7.6)
Appetite	76.9 (16.7)	87.7 (10.9)	-7.5 (-12.0 to -3.1)**	3.3 (-2.7 to 9.3)
Eating problems	83.1 (15.8)	91.7 (11.8)	-13.0 (-16.0 to -10.0)***	-4.5 (-8.2 to -0.7)*
Aggressive behavior	64.1 (18.2)	66.8 (19.1)	-3.6 (-8.7 to 1.6)	-0.9 (-8.0 to 6.2)
Positive emotions	93.5 (17.0)	94.7 (13.7)	-5.2 (-7.9 to -2.4)***	-3.9 (-7.2 to -0.6)*
Emotions of anxiety	66.7 (21.1)	76.7 (17.4)	-11.4 (-17.4 to -5.4)***	-1.4 (-9.5 to 6.8)
Vitality	88.2 (23.0)	92.5 (19.1)	-9.8 (-13.3 to -6.2)***	-5.5 (-9.6 to -1.3)**
For children from 18 months of age				
Social behavior	88.0 (19.8)	87.5 (19.4)	-3.0 (-9.5 to 3.5)	-3.5 (-12.3 to 5.3)
Motoric problems	92.9 (12.5)	88.4 (10.4)	-5.8 (-7.6 to -3.9)***	-10.3 (-12.3 to -8.2)***
Communication	88.6 (14.5)	89.8 (13.0)	-3.0 (-6.5 to 0.5)	-1.8 (-6.4 to 2.8)

* *Significant at P < 0.05.*
** *Significant at P < 0.01.*
*** *Significant at P < 0.001.*
† *Reference scores (n = 323) were obtained from the creators of the instrument at TNO Prevention and Health, the Netherlands (unpublished data). After our investigation, the TAIQOL was replaced by the almost identical TNO-AZL Preschool Children Quality of Life (TAPQOL) questionnaire. Normative data of the TAPQOL, of which an English version is available, have been published.*[17]
‡ *95% confidence interval for the difference between the group means.*
§ *n = 39 for the domains only applicable to children from 18 months of age.*

Tables 4.5 and 4.6 present the results of the TACQOL and the SF-36. In ARM patients, four TACQOL domains appeared to discriminate between patients and the general population. The outcomes indicate that the CDH patients scored relatively low in the domains 'basic motor functioning' and 'cognitive functioning'. Neither in ARM patients nor in CDH patients did the eight domains of the SF-36 or the physical summary measure discriminate between patients and the general population (*Table 4.6*). The mental summary measure suggests that ARM and CDH patients are even healthier than the general population. In summary, the long-term outlook of survivors of these congenital anomalies is favorable. However, there appeared to be some variability in the data, implying that small subgroups of the patients scored relatively low on the HRQoL questionnaires. The poor HRQoL outcomes in these subgroups were associated with the presence of disease-specific symptoms. This is illustrated by the negative relation between the SF-36 physical summary score and the symptom score (Pearson's correlation -0.41 in ARM patients (n = 124; $P < 0.001$) *v* -0.50 in CDH patients (n = 50; $P < 0.001$)). The correlation between the SF-36 mental summary score and the symptom score amounted to -0.20 in ARM patients (n = 124; $P = 0.02$) and -0.47 in CDH patients (n = 50; $P = 0.001$).

Table 4.5 TACQOL Scores of ARM Patients and CDH Patients Aged 5-15 Years Compared with Reference Scores

Domain	Mean scores (SD)		Difference with reference group[†] (95% CI[‡])	
	ARM (n = 118)	CDH (n = 39)	ARM	CDH
Pain and symptoms	27.5 (3.5)	28.1 (2.9)	-0.1 (-0.8 to 0.6)	0.5 (-0.6 to 1.7)
Basic motor functioning	30.0 (4.0)	30.3 (3.0)	-1.0 (-1.5 to -0.6)***	-0.7 (-1.5 to 0.0)*
Autonomy	30.6 (3.2)	30.9 (2.5)	-0.8 (-1.1 to -0.4)***	-0.4 (-1.0 to 0.2)
Cognitive functioning	29.0 (4.8)	28.3 (4.2)	-0.5 (-1.2 to 0.2)	-1.2 (-2.4 to -0.1)*
Social functioning	29.3 (3.7)	29.9 (2.3)	-0.7 (-1.2 to -0.3)**	-0.1 (-0.8 to 0.6)
Global positive emotional functioning	14.6 (2.3)	14.8 (1.8)	-0.4 (-0.7 to 0.0)*	-0.2 (-0.8 to 0.4)
Global negative emotional functioning	11.9 (2.5)	12.4 (2.3)	0.2 (-0.3 to 0.6)	0.7 (0.0 to 1.5)

The English version of the TACQOL is available on request.

* *Significant at P < 0.05*

** *Significant at P < 0.01*

*** *Significant at P < 0.001*

† *Reference scores (n = 1,311) were derived from a random sample of Dutch children (aged 6-11) in the general population after exclusion of all children with any (parent reported) chronic condition.[16] The means and standard deviations of six age and sex matched groups were combined.*

‡ *95% confidence interval for the difference between the group means.*

Table 4.6 SF-36 Scores of ARM Patients and CDH Patients Aged 16 Years and Older Compared with Reference Scores

Domain	Mean scores (SD)		Difference with reference group[†] (95% CI[‡])	
	ARM (n = 127)	CDH (n = 52)	ARM	CDH
Physical functioning	92.8 (14.3)	93.7 (14.0)	-0.3 (-2.7 to 2.1)	0.6 (-2.8 to 4.0)
Role-physical	87.6 (28.5)	90.2 (28.8)	1.2 (-4.2 to 6.6)	3.8 (-4.1 to 11.7)
Bodily pain	78.2 (17.0)	83.5 (11.4)	-2.7 (-6.3 to 1.0)	2.6 (-2.8 to 8.0)
General health	75.3 (22.1)	78.5 (17.7)	-2.9 (-6.4 to 0.7)	0.3 (-4.7 to 5.2)
Vitality	68.0 (17.2)	68.1 (21.7)	-2.7 (-5.9 to 0.5)	-2.6 (-7.4 to 2.2)
Social functioning	89.9 (15.6)	91.1 (20.3)	2.1 (-1.5 to 5.6)	3.3 (-2.2 to 8.8)
Role-emotional	90.1 (26.8)	90.9 (28.3)	4.7 (-1.0 to 10.4)	5.4 (-3.1 to 14.0)
Mental health	78.3 (15.1)	77.4 (19.4)	-0.4 (-3.4 to 2.5)	-1.3 (-5.8 to 3.1)
Physical component summary	52.2 (7.7)	53.7 (5.2)	-0.7 (-2.1 to 0.7)	0.9 (-1.2 to 3.0)
Mental component summary	52.5 (8.0)	51.9 (10.9)	3.6 (1.8 to 5.3)**	3.0 (0.3 to 5.7)*

Details on the SF-36 are available through http://www.sf-36.org/demos/SF-36.html.

* *Significant at P < 0.05.*

** *Significant at P < 0.001.*

† *Reference scores for the eight 'individual' domains were derived from a Dutch general population sample, aged 16-40. 'n' was estimated at 551 on the basis of the fact that the total sample, aged 16-94, contained 1,742 people.[34] To obtain reference scores for the summary scales, we had to rely on a US general population sample, aged 18-44 (n = 2,765).[35]*

‡ *95% confidence interval for the difference between the group means.*

4.4 Discussion

In this paper, we have been concerned with the HRQoL of survivors of ARM and CDH in a long-term setting. Many of them appeared to retain substantial residual symptomatology. Compared with reference data, the HRQoL of the patients (especially those with ARM) aged 1–4 was poor. In the patients aged 16 years and over, hardly any differences with the general population were found. It must be stressed that the relatively poor outcomes in the youngest patients are not offset by the encouraging outcomes in adult life. This stage of life has its own inherent importance for the developing individual. Therefore, future research should especially be targeted at finding ways to improve the HRQoL of the youngest children. It is clear from the current study that the relations between symptoms, impairments, limitations in functioning, and HRQoL should be interpreted with caution. An important lesson to be learned is that impairments are imperfect predictors of HRQoL. Not every impairment automatically triggers a decrease of the HRQoL.

The HRQoL of the ARM patients aged between 1 and 4 years was statistically significantly lower than population standards predicted, even though complaints of incontinence are not prominent until patients grow older. Their HRQoL improved considerably with growing age, notwithstanding the fact that stool difficulties are widely believed to disrupt HRQoL due to pain, feelings of shame, or inability to take part in social activities such as sports. A possible explanation is that diapers, therapeutic aids such as enemas, and dietary manipulations are effective tools in restoring satisfying functioning. Seemingly, the patients are able to cope successfully with their handicaps in one way or another.

A HRQoL questionnaire did not reveal a pronounced difference in the lung domain between CDH patients aged 1–4 years and a reference group. In a sense, these results are consistent with earlier research we performed in this specific patient group (median age 11.7 years) using lung function tests.[12] This study showed that in the long term no severe pulmonary impairment resulted from CDH. The reduced level of cognitive functioning in the CDH patients aged 5-15 years (none treated with ECMO) corroborates a small scale study previously carried out in our hospital.[20] In the current study, from a certain age the HRQoL of the CDH patients could hardly be distinguished from that of the general population. One explanation is that, particularly in the past, a major 'selection' took place in the first week of life due to the high mortality in patients with severe pulmonary hypoplasia and therapy resistant pulmonary hypertension. In other words, those patients in the worst shape are likely not to have survived. Finally, it should be noted that, while ECMO improves survival in selected, critically ill infants with CDH,[21] it is also true that the ECMO technique enables us to keep some patients alive with a relatively poor prognosis and that it may lead to iatrogenic morbidity.[22] Thus, close follow-up of CDH patients becomes even more essential in the future.

When evaluating the outcome of ARM and CDH, we did not include the patients who had died. Although it is of major importance to critically evaluate the deaths—as was done earlier in our pediatric surgical department[23,24]—this was beyond the scope of the current study. Here, we concentrated on assessing whether improved survival in neonatal surgery comes at the expense of poor HRQoL. Apart from that, 78% of the 54 deceased ARM patients died within their first year of life, with a median life span of 23 days. Of the 86 CDH patients who died, 87% died within their first year of life (median life span 3 days). The vast majority of the deceased were therefore too young to assess the quality of their lives. Similarly, we did not assess patients who were severely cognitively disabled. Cognitive disability, which is attributable to a wide variety of underlying causes ranging from birth asphyxia to severe chromosomal anomalies (including trisomy 21), is not common in these patient groups. Only 1.8% of all eligible patients had to be excluded for this reason (n = 15; mean age 24.6 years). A solid investigation into the HRQoL of this subgroup would have been difficult to accomplish within the current study. HRQoL can be assessed by proxy in these subjects, but one must seriously doubt whether the measures used would be sufficiently valid and reliable in these cases. The severely cognitively disabled patients may differ in their perception of HRQoL, and their ability to express their experiences is often very limited. This may reduce the parents' or caregivers' ability to make accurate judgments about aspects of the patient's HRQoL.

Assessment of HRQoL in children poses special problems. Because of difficulties that small children have with notions of abstract concepts and language, we had to rely on proxies. We are conscious of the variety of factors that can influence a parent's rating of his or her child's HRQoL and the equivocal findings reported in the literature.[25-27] Nevertheless, recent research findings in children[28-30] suggest that a parent is able to report appropriate information regarding his or her child's HRQoL, especially concerning observable behaviors. There is as yet no clear evidence of whether—when the parent and the child disagree—the parents over- or under-estimate HRQoL. A number of studies indicated that parents tend to rate the child as having a poorer HRQoL than the child does him or herself, a tendency which would result in a conservative estimate of the HRQoL.[31-33] These studies, often concentrating on acquired conditions, apply, however to children aged between about 7 and 13, who are able to give self reports, while our study also comprised younger children. Finally, as in most previous studies in this area, we limited ourselves to one source of information and did not obtain additional views of, for example, other relatives or teachers. Yet, the use of proxies other than parents may have value and merits further investigation.

In conclusion, our investigation into the HRQoL of survivors of ARM and CDH provides favorable results. The suggestion that improved survival can only be reached at the price of poor HRQoL is not substantiated. As expected a priori, ARM and CDH can cause considerable symptomatology. Nevertheless, the vast majority of the patients ultimately enjoy healthy lives.

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Chapter 5

Cost-Effectiveness of Neonatal Extracorporeal Membrane Oxygenation in the Netherlands

ABSTRACT

Objective: Extracorporeal membrane oxygenation (ECMO) involves a complex, labor-intensive technique, the benefits of which have been questioned. Our objective was to study the cost-effectiveness of neonatal ECMO in the Netherlands.

Design and setting: We conducted a prospective cohort study with a representative nation-wide historical control group. Patients born between 1991 and 2001 who were treated with ECMO in the two designated tertiary care centers were compared to patients born between 1986 and 1990 who were managed conventionally in the nine regional tertiary care centers before the introduction of ECMO and who would have been eligible for ECMO, were it available in those years.

Patients: A national population of 244 consecutive ECMO-treated newborns with a diagnosis of congenital diaphragmatic hernia (CDH) or meconium aspiration syndrome (MAS), as well as a total of 46 control patients with CDH or MAS.

Main outcome measures: Cost per life saved and cost per life-year gained from ECMO.

Results: Mean direct medical costs for treatment including ECMO amounted to € 38,553 per patient, that for a patient with CDH (€ 50,792) being considerably higher than that for a patient with MAS (€ 29,472). Costs of treatment of patients in the control group were comparatively low with an average of € 17,300. For CDH patients, the survival rate was 0.04 without ECMO and 0.52 with ECMO. For MAS patients, survival without ECMO was 0.50, as compared to 0.94 in the ECMO era. Costs per additional survivor were € 78,455, or € 3,153 per life-year gained, in the patients with CDH. For the patients with MAS, costs per additional survivor were calculated at € 17,287, or € 697 per life-year gained.

Conclusions: The study indicates that ECMO improves survival in selected severely ill newborns suffering from CDH or MAS, and that it does so at reasonable cost. Whether the encouraging outcomes are maintained when also long-term costs and health-related quality of life are considered, is a subject for future studies to address.

5.1 INTRODUCTION

For several decades now, extracorporeal membrane oxygenation (ECMO) has been available as a treatment option for acute respiratory failure in selected neonates in whom conventional methods of medical therapy fail. In essence, this complex technique oxygenates blood outside the body, obviating the need for gas exchange in the lungs, and, if necessary, provides cardiovascular support. Supplying oxygen via ECMO support gains time for the pulmonary pathology to resolve.[1,2]

Taking into account the increasing political interest in evidence-based and cost-effective medicine,[3] it is surprising that little is known about the costs and effects of ECMO. Based on studies using historical comparison groups, ECMO has been believed to improve survival rates in neonates with severe respiratory failure.[4-11] Two randomized studies using adaptive allocation schemes (a 'randomized play the winner' or a stopping rule) also suggested that ECMO improves survival compared to conventional ventilator therapy, but the number of infants recruited was small with very few patients assigned to the comparison group.[12,13] Another small-scale randomized trial that followed a standard design also indicated that ECMO saves lives—though this study is fairly hard to interpret since it has been presented only in abstract form.[14,15] Importantly, a properly designed randomized trial further strengthened the evidence that ECMO reduces mortality in neonates with severe but potentially reversible respiratory failure. In this study, mortality before 1 year of age differed significantly between the ECMO and the conventional management group (32% *v* 59%).[16]

Until recently, only four centers—all in the USA—have presented some data related to the cost or cost-effectiveness of ECMO.[17-20] All studies used hospital charges instead of real costs. Charges are, however, inaccurate measures of real economic costs.[21-23] Three studies had problems with their control groups,[17,19,20] for example because they consisted of patients who probably had a better prognosis than the ECMO patients. The fourth study did not perform a cost-effectiveness study of ECMO, but basically compared the costs and effects of early ECMO treatment to those of late ECMO treatment.[18] Then, Schwartz et al. estimated costs per case for ECMO and that of patients who received conventional care. These results however also apply to a US setting, whereas physicians' costs were largely excluded and the calculations were again based on hospital charges.[24] A recent study from Canada measured resource use and health outcomes of ECMO in both neonatal and pediatric age group patients,[25] but the cost-effectiveness ratios presented should be treated with great caution because the authors did not take account of the fundamental principle of cost-effectiveness analysis that one or more competing alternative treatment strategies should be included.[3,21] In addition, a couple of North American studies that were not directed at establishing cost-effectiveness of ECMO compared with conventional management offered some insight into the costs of ECMO

treatment.[26,27] Finally, following a preliminary literature-based cost-effectiveness analysis that speculatively suggested that an additional life would be gained at costs of £ 177,978 (at 1994 prices),[28] the UK Collaborative ECMO Trial revealed that ECMO increased survival but at additional cost of £ 51,222 for every additional survivor without severe disability at 1 year of age.[29] Recently, another cost-effectiveness analysis based on the UK Trial that used a 4 year time horizon arrived at an incremental cost of £ 24,775 per additional disability-free life year gained.[30]

In the Netherlands, the government initially approved the introduction of neonatal ECMO on a limited scale in two level III university hospitals, provided an extensive health technology assessment (HTA) study would be performed. This assessment mainly concerned the costs and effects of neonatal ECMO, whereas also ethical, legal and planning issues were assessed.[31] The economic evaluation presented here seeks to provide evidence on the cost-effectiveness of neonatal ECMO treatment in the Netherlands, partly building on this HTA study.

5.2 MATERIALS AND METHODS

In the design phase of this study, which took place around 1990, there was a vigorous debate on whether or not to randomize patients. Prospective randomization was however rejected on ethical grounds. After all, at the time, apparently favorable effects of ECMO on survival outcome were documented in the USA,[12,13] although these studies were criticized for their designs.[32-35] Consequently, it was decided to carry out a prospective cohort study with a representative historical control group.[36] The study protocol was approved by the Institutional Ethical Review Board at both participating hospitals.

Patients

Because ECMO is used to support the treatment of a variety of neonatal diseases with different prognoses, it is essential to distinguish between diagnostic categories. This study's population consisted of all neonates born with congenital diaphragmatic hernia (CDH) or meconium aspiration syndrome (MAS)—two clearly defined diagnostic groups and the largest subgroups in our neonatal ECMO population—that were treated with ECMO between January 1991 and December 2001 in either the Erasmus MC Sophia Children's Hospital or the Radboud University Nijmegen Medical Centre. These are both level III children's hospitals and, until the present day, the only two designated centers in the Netherlands offering neonatal ECMO. Building on earlier work in the United States,[12,37,38] specific exclusion and inclusion criteria for ECMO were developed to standardize the evaluation process (*Table 5.1*). Patients who meet these criteria were predicted to suffer high mortality (80-100%) despite optimal therapy and ECMO may thus be lifesaving for them. Throughout the study period, a standardized way to perform veno-arterial ECMO regarding ventilatory support, fluid management, and weaning from ECMO was used in both centers.

Table 5.1 Criteria for ECMO Eligibility

ECMO indications
- Birth weight ≥ 2,000 g
- Gestational age > 34 weeks
- Underlying pulmonary disease expected to be reversible within 10 days
- Supported by artificial respiration for less than 11 days
- Any one of the following:
- $AaDO_2$ > 600 mm Hg for more than 8 hours at a FiO_2 of 1
- Oxygenation index > 40 in 3 to 5 consecutive arterial blood gasses that were taken at 1 hour intervals
- Acute deterioration (PaO_2 < 40 mm Hg or pH < 7.15 during 2 hours) without reaction on maximal conventional treatment
- Development of a clear barotrauma
- Patients with CDH were only eligible if they had shown a PaO_2 > 80 mm Hg at a FiO_2 of 1 during some time
ECMO exclusion criteria
- Chromosomal or other serious disease associated with a lower survival probability
- Serious blood clotting disorders
- Serious congenital brain disorder or signs of cerebral bleeding on echoscopy
- Serious cardiac disorders

The costs and effects of ECMO treatment were compared to the costs and effects occurring to a comprehensive, nation-wide historical control group. To assess which patients should be included in this control group, all nine regional neonatal centers in the Netherlands were visited. In each center, medical records for all neonates with a birth weight of more than 2,000 grams, a more than 34 weeks' gestational age, without contra-indications, and treated in a level III NICU with artificial ventilation between 1988 and 1990, were examined to assess whether the patient would have met the criteria for ECMO treatment, were it available in those years. From three centers also data for 1986 and 1987 were available. Clinical and demographic characteristics of ECMO and control patients were compared using *t* tests for two independent sample means or Pearson's Chi-square tests, as appropriate (two-tail probabilities).

The comparability of ECMO patients and control patients was evaluated by applying a model developed by Toomasian et al.[39] This model, based on data of 715 newborn patients, predicts ECMO survival with the use of data gathered before ECMO treatment is started. The probability of survival is modeled with logistic regression:

$$P = \frac{1}{1 + \exp\left[-\left(-20.054 + 0.918\ (\text{birth weight}) + 2.465\ (\text{pH}) - 0.597\ (\text{rf}) + 0.386\ (\text{MAS}) - 0.304\ (\text{fem})\right)\right]}$$

where 'renal failure' (rf), 'MAS', and 'female' (fem) can be either 0 (no) or 1 (yes).

Costs

Only direct costs within the health care sector were taken into account. Costs were calculated for the total initial hospital admission, including days spent in referring hospitals before or after stay in our NICU departments. Thus, costs were considered from the moment patients were first admitted to an intensive care department until patients were discharged home or died. Data on resource use were collected, and subsequently multiplied by a unit cost price for each cost item.

Regarding the ECMO group, we distinguished between variable costs, costs of personnel, and fixed costs. Among the variable costs were costs of medical supplies, diagnostics, medications, interventions, and ECMO-related costs. Costs for medical supplies, ECMO facilities, and personnel were based on real costs, whereas costs for laboratory tests and diagnostic or therapeutic interventions were based on charges. Personnel costs covered costs of medical and nursing staff directly involved in the care of the patients. The category fixed costs comprised general costs unrelated to ECMO (administrative employees, housing, overhead, etc.), as well as costs of the ECMO facility (amortization and interest on the machine investment, and staff education). Costs were only calculated for the subgroup of the patients born before December 1994. This entailed a detailed assessment done within the framework of the base HTA study that has not yet been reported in the international literature.[40] To verify whether this subgroup was representative for the entire ECMO population, we compared the patients who were the subjects of the cost analysis and those who were not with regard to disease severity (as expressed by probability of survival), length of stay, and days on ECMO.

For the control group, data on the number of in-hospital days, interventions and the main 'expensive' diagnostic tests were available. Calculating cost prices for hospital days of all of these patients, who were treated in nine different hospitals, was practically not feasible. Therefore, costs of the day of admittance to the NICU were based on the ECMO patients' average costs of the first NICU day—thus, before ECMO treatment was started—separately for CDH patients and MAS patients. Costs for other NICU days were similarly based on the costs of an average NICU day for CDH patients and MAS patients from the ECMO group, after ECMO treatment was finished. Likewise, costs of a day spent in a medium care unit were estimated at the cost price of such hospital days in the ECMO group. Costs of diagnostics were estimated based on the pattern of diagnostic testing in the ECMO group, yet excluding ECMO specific diagnostic tests. Costs of therapeutic interventions (based on charges) were added separately.

All costs are presented in Euro's and valued at 2003 prices, using the inflation rates as measured by the Dutch 'consumer price index'.

Effects

With the help of the municipal registry offices, data on survival were collected until April 1, 2003. Survival analysis was conducted by using the Kaplan-Meier method. We collected exact event and censoring times by registering when patients died or were lost to follow-up. Regarding both patient groups, cumulative survival probabilities were plotted for both the control group and the ECMO group.[41] The nonparametric Mantel-Cox logrank test was used to assess the equality of the survival distributions.

ECMO is a complicated technique that requires some degree of familiarity. Like others,[39] we were interested to know therefore, whether a learning curve could be observed and whether survival rates improved with experience. Thus, two supplementary analyses were performed for the ECMO group. One-year survival rates were calculated for each birth year cohort. Also, one-year survival of the first 25 and 50 ECMO patients were compared to the results after excluding the first 25 and 50 cases (*t* tests for two independent sample means). This method of splitting groups is a straightforward technique to assess a learning curve in health technologies.[42]

Cost-effectiveness

Incremental cost per life saved and incremental cost per life-year gained were used as cost-effectiveness measures. For the latter measure, we assumed that the survivors in our study—among whom multiple, severe disabilities are not a common issue—would have a normal life expectancy (76.2 and 80.9 years at birth, for boys and girls respectively). Costs were not discounted, because all studied costs accrue in the first year of the child's life. Future effects (i.e., life years) were discounted at 4% per year.[43]

Sensitivity analyses

The robustness of the cost-effectiveness analyses to changes in certain assumptions underlying the calculations was determined in a multiway sensitivity analysis.[44] Both the life-expectancy of the survivors and the discount rate were varied over plausible ranges. We examined a best-case scenario (life expectancy, +10 years; discount rate, 0%) and a worst-case scenario (life expectancy, -10 years; discount rate, 5%).

5.3 RESULTS

Patients

Between January 1991 and December 2001, 100 neonates with CDH and 144 with MAS were treated with ECMO. Forty-six patients qualified as control patients (24 with CDH and 22 with MAS). Thus, the proportion of patients with CDH in the ECMO group was somewhat smaller than that in the control group (41% *v* 52%; $P = 0.16$). Demographic and clinical details of the study population are

summarized in *Table 5.2*. Compared with the historical group, patients in the ECMO group more often were male and more often were delivered by caesarian section, but pregnancy complications occurred less frequently (both diagnosis groups taken together). These differences however, did not reach statistical significance. Labor and delivery complications were also less common in the ECMO group ($P = 0.02$). The length of ECMO runs remained rather unchanged during the study period. When all ECMO patients are divided into three groups according to date of birth, the ECMO run time averages 7.4 days in the earliest group (n = 82), as opposed to 8.3 days in the middle group (n = 81) and 8.0 in the last group (n = 81) (ANOVA F-test, $P = 0.31$). The total length of the initial hospitalization was 53 days on average in the ECMO-treated CDH patients (median, 45 days; skewness, 1.9), as against 37 days in the patients with MAS (median, 32 days; skewness, 3.5)—the difference being significant ($P < 0.001$). According to Rosner's test for multiple outliers, the CDH group contained one statistical outlier (hospitalized for 273 days), while there were four outliers in the MAS group (191, 161, 153, and 97 days respectively).

Comparison of the survival probability for the separate diagnostic categories with the model developed by Toomasian et al. revealed that the ECMO patients and the control patients had a similar outlook. In the patients with CDH, the survival probability amounted to 0.62 both in the ECMO group and the control group ($P = 0.93$). In the MAS patients, the predicted survival rate was 0.79 in the ECMO group, as opposed to 0.80 in the control group ($P = 0.82$). Furthermore, we found no evidence of a statistically significant difference in predicted survival between the total ECMO group and the total control group (0.72 *v* 0.70; $P = 0.36$).

Costs

We first investigated whether the patients who were the subjects of the cost analysis were sufficiently similar to the other ECMO patients. The mean predicted survival (as expressed by the model of Toomasian et al.) in the subgroup was not significantly deviant from the other patients (0.75 *v* 0.72; $P = 0.10$). Neither did we find statistically significant differences between the patients being part of the cost study and the other patients in mean duration of ECMO (7.1 *v* 8.2 days; $P = 0.06$) and total length of stay (42 *v* 44 days; $P = 0.66$).

Overall costs of treatment including ECMO amounted to € 38,553 per patient (*Table 5.3*), approximately equivalent to 44,000 US dollars (2003). Half of the costs are due to costs for diagnostic tests and costs of personnel, with approximately half of the latter incurred in the period that the patient is on ECMO. Mean costs for treatment of a patient with CDH (€ 50,792) were considerably higher than for a patient with MAS (€ 29,472). This difference is mainly caused by the fact that the hospitalization period of neonates with CDH was 18 days longer, on average, than that of the MAS patients.

Table 5.2 Clinical and Demographic Characteristics of ECMO and Control Patients

Characteristic	ECMO			Controls			*P* value		
	CDH (n = 100)	MAS (n = 144)	Total (n = 244)	CDH (n = 24)	MAS (n = 22)	Total (n = 46)	CDH	MAS	Total
Sex (% male)	63	54	58	58	36	48	0.67	0.12	0.21
Gestational age (wk)	38.9 ± 2.0	40.3 ± 1.4	39.7 ± 1.8	39.4 ± 1.6	40.5 ± 1.5	39.9 ± 1.6	0.27	0.65	0.57
Birth weight (kg)	3.1 ± 0.5	3.5 ± 0.6	3.3 ± 0.6	3.1 ± 0.4	3.4 ± 0.5	3.2 ± 0.5	0.80	0.45	0.24
Caesarian delivery (%)	18	38	30	8	24	16	0.25	0.22	0.05
Pregnancy complications[*] (%)	18	14	15	30	19	25	0.17	0.51	0.12
Labor and delivery complications[†] (%)	28	27	27	30	62	45	0.78	0.001	0.02
1-minute Apgar score	4.5 ± 2.2	4.4 ± 2.4	4.4 ± 2.4	4.8 ± 2.8	4.6 ± 2.6	4.7 ± 2.7	0.65	0.66	0.51
5-minute Apgar score	5.8 ± 1.8	6.1 ± 2.1	6.0 ± 2.0	5.8 ± 2.2	6.2 ± 1.9	6.0 ± 2.0	0.99	0.79	0.93
Born in hospital (%)	88	90	89	92	81	87	0.59	0.25	0.67
Born in ECMO center (%)[‡]	37	5	18	NA	NA	NA	NA	NA	NA
Prenatal diagnosis (%)	36	NA	NA	29	NA	NA	0.51	NA	NA
Last pre-ECMO pH	7.26 ± .13	7.35 ± .15	7.31 ± .15	7.25 ± .15	7.39 ± .13	7.31 ± .16	0.87	0.20	0.89
Renal insufficiency[§] (%)	8	2	5	5	9	7	0.57	0.07	0.51

Continuous variables expressed by means ± SD. Abbreviations: NA, not applicable.

[*] *One or more of the following: use of drugs, ovulation induction/artificial insemination by donor/in vitro fertilization, preexisting diabetes, gestational diabetes, preexisting hypertension, hypertension in pregnancy, epilepsy, intrauterine growth retardation, other complications.*

[†] *One or more of the following: use of labor-inhibiting drugs (>1 day), post-term pregnancy, induced labor, prolonged membrane rupture (>24 hrs), maternal fever, other complications.*

[‡] *Proportion of all patients that were born in a hospital.*

[§] *Either creatinine > 1.5 mg/dl or patient on hemodialysis, hemofiltration, or continuous arterio-venous hemodiafiltration (CAVHD).*

Table 5.3 Direct Medical Costs for ECMO and Control Patients

		CDH	MAS	Total
ECMO patients		**n = 23**	**n = 31**	**n = 54**
Variable costs	Medical supplies	€ 2,642	€ 1,396	€ 1,927
	Diagnostics	€ 11,292	€ 7,585	€ 9,164
	Medications	€ 5,540	€ 2,324	€ 3,694
	Interventions	€ 1,595	€ 165	€ 774
	ECMO*	€ 7,454	€ 5,154	€ 6,134
	Various	€ 128	€ 62	€ 90
Costs of personnel		€ 14,139	€ 7,845	€ 10,525
Fixed costs		€ 8,002	€ 4,940	€ 6,244
Total costs		€ 50,792	€ 29,472	€ 38,553
Control patients		**n = 24**	**n = 21**	**n = 45**
Costs of stay on IC	First day	€ 855	€ 669	€ 768
	Subsequent days	€ 4,494	€ 9,542	€ 6,850
Costs of stay on MC		€ 2,002	€ 1,342	€ 1,694
Diagnostics		€ 5,179	€ 9,515	€ 7,203
Interventions		€ 736	€ 841	€ 785
Total costs		€ 13,267	€ 21,909	€ 17,300

All variables expressed by means. Abbreviations: IC, intensive care; MC, medium care.

* *This category involves resource use directly related to ECMO: costs of the cannulation/decannulation procedures, costs of priming the ECMO circuit, costs of the ECMO pack, costs of the ECMO run, device costs, and costs of Astrup and ACT (activated clotting time) tests.*

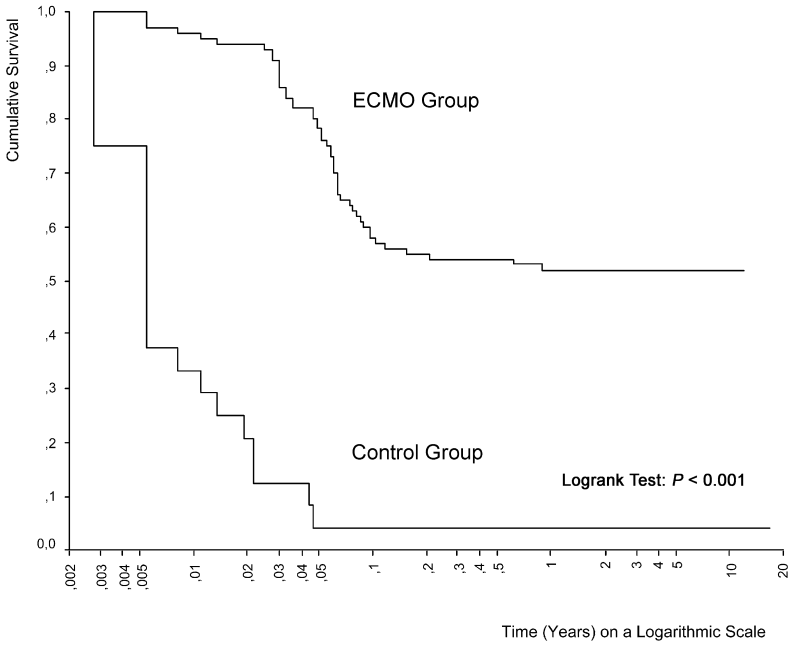
Direct medical costs for treatment of patients in the control group were comparatively low with an average of € 17,300 (*Table 5.3*).

Thus, the difference in costs was calculated at an average of € 21,253. For a part, this difference is due to the enhanced survival rates, which results in longer hospital stays.

Effects

During the study period, 57 of all 244 ECMO patients (23%) deceased, with a mean life span of 28 days (median, 18 days). Of all 46 control patients, 34 (74%) had died (mean life span, 4 days; median, 2 days). In this study's follow-up, no patients were found that died after their first year of life. For CDH patients, the survival rate was 0.04 without ECMO and 0.52 with ECMO, as seen in *Figure 5.1*. For MAS patients, survival without ECMO was 0.50, as compared to 0.94 in the ECMO era (*Figure 5.2*). Regarding the CDH patients, the relative risk of death of ECMO patients compared to the control group was 0.50 (95% confidence interval, 0.40 to 0.62). For the patients with MAS, the relative risk of death amounted to 0.13 (95% confidence interval, 0.06 to 0.27).

Figure 5.1 Kaplan-Meier Curves of the CDH Patients



As also in Figure 5.2, the stepped lines represent the cumulative survival probability. The cumulative survival drops each time a death occurs. After the last death, the curve remains flat until the longest censored survival time.

Figure 5.2 Kaplan-Meier Curves of the MAS Patients

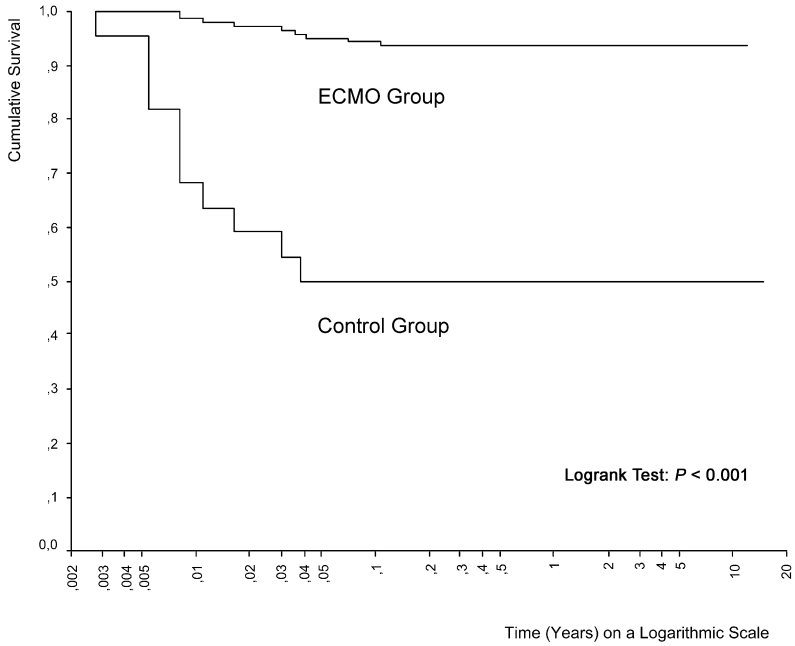


Figure 5.3 illustrates one-year survival rates with ECMO for each birth year cohort, combined with the annual number of patients treated with ECMO. With time elapsing, the number of ECMO patients increased considerably, whereas the survival rates improved only slightly (but with decreasing standard deviation of the data). As an additional analysis, we finally compared one-year survival rates of the first 25 and 50 ECMO patients to the results after excluding the first 25 and 50 cases. For the first 25 ECMO patients, the survival rate was lower than the rate after excluding these 25 patients (0.72 *v* 0.77; *P* = 0.57). Similarly, comparing the first 50 patients with the situation of leaving out these patients, no statistically significant difference in survival was found (0.74 *v* 0.77; *P* = 0.62).

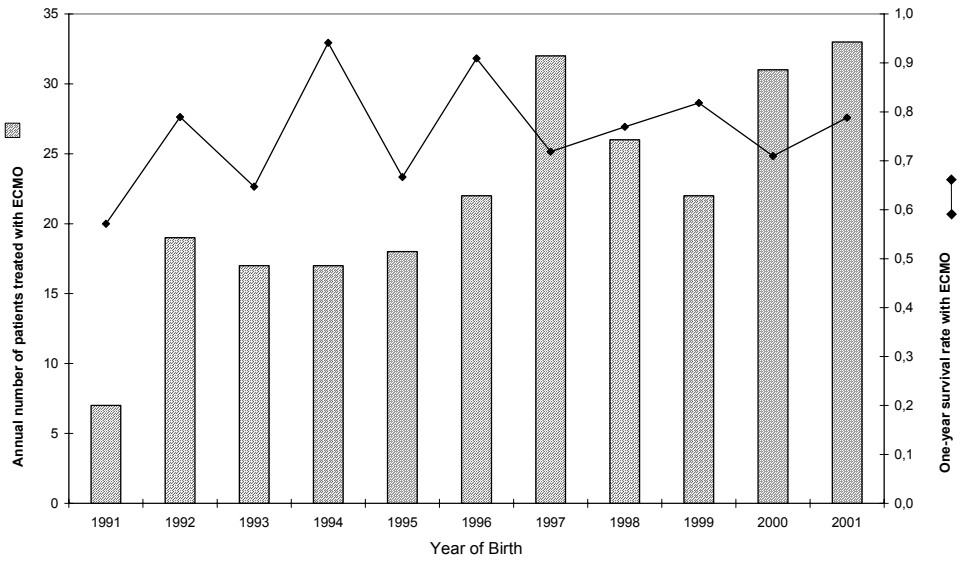
Cost-effectiveness

From the above, it follows that for the patients with CDH costs per additional survivor amounted to € 78,455, or € 3,153 per life-year gained. For the patients with MAS, costs per additional survivor were calculated at € 17,287, or € 697 per life-year gained.

Sensitivity analyses

The main conclusions are quite insensitive to the assumptions regarding the survivors' life-expectancy and the discount rate, as appears from the extreme scenarios. In the best-case scenario, cost-effectiveness ratios amounted to € 881 per life-year gained in CDH and € 195 per life-year gained in MAS. Even in the worst-case scenario, cost-effectiveness (€ 3,858 and € 854 per life-year gained in CDH and MAS respectively) was still good.

Figure 5.3 Annual Numbers of Patients Treated with ECMO and Annual One-Year Survival Rates (CDH and MAS Patients Combined)



5.4 Discussion

This paper has focused attention on the cost-effectiveness of neonatal ECMO in the Netherlands. One of this study's major strengths lies in its inclusion of a national population of 244 consecutive ECMO-treated neonates. Another strength was the inclusion of a comparison group that consisted of adequately similar non-ECMO-treated infants, as (even though the outcome predicted by this model differed from the actual outcome of our study in terms of survival or death) can be concluded from applying the predictive outcome model described by Toomasian et al.[39] The study shows that ECMO in severely ill newborns diagnosed with CDH or MAS is highly cost-effective. The cost-effectiveness ratios are within the range reported for other commonly used treatments in the field of neonatal intensive care,[27,45-50] and, generally, compare favorably to other evaluated health care interventions that 'society' considers to be acceptable expenditure of scarce resources.[21,51]

ECMO appeared to be a labor-intensive and costly technique. Still, costs of ECMO treatment are considerably lower in our study than in the American studies, which relied on charges and sometimes used cost-charge ratios to arrive at costs. Pearson and Short reported initial hospitalization costs of $ 91,804, Walsh-Sukys et al. $ 62,375, Metkus et al. $ 208,000 for CDH patients, and Schumacher et al. $ 53,700 in the late ECMO group.[17-20] Cost differences are even more impressive for conventional treatment, the cost of which ranges from $ 59,268 to $ 93,524 in the American studies.[17,19,20] These differences are probably for a large part due to the fact that treatment costs are lower for many medical interventions in the Netherlands than in the USA.[52] More specifically, one possible explanation is the use of inhaled nitric oxide (iNO), for which high prices have been charged in the USA and which was available in the USA many years earlier than in the Netherlands. It is difficult to say whether these differences can be explained by variations in the length of the average hospital stay, because the literature frequently does not give an account of these data, with a distinction made between the different diagnostic categories. What can be compared is the average length of an ECMO run. For the CDH patients in our study, the run time was practically equal to the figure reported by the Extracorporeal Life Support Organization (ELSO) (mean, 229 hours).[53] However, for the infants with MAS, the average ECMO duration in this study outweighed that of the patients who appear in the ELSO database (163 *v* 129 hours). Unlike studies that found an increase in the average length of an ECMO run since the 1990s,[26,54,55] which probably reflects a more complex patient case mix, the length of bypass appeared to be stable over time in this study.

We found survival probabilities of 52% (CDH) and 94% (MAS). These outcomes are nearly identical to those reported by ELSO.[53] Although not every study has shown positive effects, especially in CDH patients,[56-58] there is growing evidence that the introduction of ECMO accounts for enhanced survival rates in selected,

severely ill newborns—as mentioned in Section 5.1 above. Our study in patients with CDH or MAS corroborates these findings. We consider it unlikely that the improved survival as observed in our study is due to other factors than the application of ECMO. Of course, treatment protocols may have changed, since this study included a long observation period. We could not eliminate possible favorable effects due to other factors, in fact any technologic advance in neonatal medicine other than ECMO. Therefore, our study using historical controls may be biased toward improved survival rates in the most recent group studied. In the hypothetical situation that ECMO would have never existed, survival rates would now most likely have been better than the rates reported by studies done in the past, with a predicted mortality approaching 80%. Consider, for example, that there were 33 deaths in the 54 patients with CDH or MAS in the conventional management group of the UK Collaborative ECMO Trial (61%).[16] However, the survival improvement found in this study is too large to be explained by new treatment advancements other than ECMO. After all, new therapies such as exogenous surfactant therapy, high-frequency oscillatory ventilation, and iNO—and especially its combined use—have never been proven at this stage to have convincing effects on survival rates in critically ill infants in respiratory failure, as variable outcome data have been reported.[59-65] Certainly for patients with CDH, the optimal treatment modality remains a matter of discussion.

The use of the new adjuvant therapies mentioned in the preceding paragraph, though not on their own the panacea for the high mortality, may lead to a decline in the need for ECMO.[59,63-65] However, contrary to USA studies documenting a decreased use of ECMO in neonates with diverse causes of respiratory failure since the first half of the 1990s,[26,54,55,66-68] we did not observe in this study a decline in the need for ECMO in patients with CDH or MAS, although the increase seems to be diminishing. We expect that ECMO will retain its position amongst all treatment modalities for neonatal respiratory insufficiency for patients in whom other therapies fail, though probably more for one of the two diagnostic groups studied here (CDH) than for the other (MAS).[69-71]

We would like to emphasize here that survival is of course a key outcome measure, but that it is also crucial to consider health-related quality of life (HRQoL). This was however beyond the scope of the current study. It is reassuring that, although such studies have been difficult to control, long-term neurodevelopmental follow-up studies found that outcomes of children treated with ECMO do not compare unfavorably with those found in children treated with conventional therapy.[72-74] Moreover, the UK Collaborative ECMO Trial suggested a favorable profile of morbidity when applying ECMO compared to conventional treatment in the UK, at the ages of both 1 year and 4 years.[75,76] However, these research findings do not necessarily comfort us about the long-term HRQoL outcomes of the patients admitted to our ECMO centers. First, in many studies the number of CDH patients is small, whereas the severity of CDH necessitates distinguishing patients with CDH from other diagnostic categories requiring

ECMO.[77,78] Second, follow-up studies frequently concentrate on levels of symptomatology and functioning, thereby failing to establish HRQoL.[79] Third, although there may be no clear evidence that the introduction of ECMO has created an increase in the percent of children surviving with poor long-term outcomes, studies that compared to healthy children or did not include a control group arrived—not surprisingly—at less favorable conclusions.[5,78,80,81] So, following these children into childhood and beyond still remains essential. It is therefore that we contact all Dutch ECMO patients at the ages of 5, 8, and 12 years to undergo an assessment of neurologic and pulmonary sequelae, and multidimensional HRQoL. The data at 5 years of age which we are currently analyzing (recruitment rate of 88%) will provide us with representative data of ECMO patients in the Netherlands.

5.5 Conclusions

Especially during its early application, considerable doubts have been expressed about ECMO. The benefits of this therapy have always been considered controversial to some extent, particularly regarding the patients with CDH.[82] This study however adds to the evidence that ECMO should not be withheld from severely ill newborns suffering from CDH or MAS for reasons purely of cost-effectiveness. It remains for future studies to reveal whether the positive outcomes are maintained when long-term costs and HRQoL are included in the analysis.

Acknowledgments

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6 Chapter

Informal Care for Children Born with Major Congenital Anomalies: What Does It Ask and What Does It Do to Parents' Health-Related Quality of Life?

ABSTRACT

Objective: To investigate the caregiving tasks performed by parents of children with major congenital anomalies and to provide evidence of its impact on parents' health-related quality of life (HRQoL), encompassing physical, mental, and social domains.

Methods: A total of 306 parents (aged 22 to 59 years) of children born with either congenital anorectal malformations (ARM; n = 118) or congenital diaphragmatic hernia (CDH; n = 46) were surveyed.

Results: Approximately one third of the parents indicated that their child demanded above-average care. They mentioned activities such as giving enemas and changing diapers (ARM patients), or giving extra attention and administering medication (CDH patients). Relatively small shares of the parents had to forgo paid work or unpaid activities. Using the EQ-5D questionnaire, the parents' HRQoL was found to be relatively low compared with population statistics, especially in the parents of children with ARM and in female parents. Interestingly, on average the parents considered that their HRQoL would not be substantially better when someone would take over their caregiving activities.

Conclusions: Our study reveals that caregiving for children with major congenital anomalies requires above-average time and that significant HRQoL differences exist between the parents and the general population.

6.1 INTRODUCTION

Major congenital anomalies are diagnosed in approximately 2% of all births.[1] Children with these anomalies represent a special diagnostic and management challenge. They are treated in highly specialized centers, continuing long beyond childhood. So-called informal care—which has been defined as that care which is provided to disabled people by relatives and friends who are not paid for the help they provide[2]—supposedly constitutes a relatively large proportion of total care, as is also the case for a variety of other diseases.[3-5] Parents of children born with major anomalies play an invaluable role in the care, during the time that their child is hospitalized and far beyond.

Informal caregiving has obvious positive effects. Informal caregivers are often the major resource that prevents many chronically ill children from being admitted to an institution, saving the formal health care system billions of dollars annually. Parental caregiving represents a substantial economic value to society, as for example Heyman and colleagues recently documented regarding children with chronic conditions.[6] Moreover, for many families, caring for their child is rewarding. Yet, it can also place heavy demands upon parents. Caregiving may involve many diverse tasks, some of which are perceived burdensome, unpleasant or have to be performed at night-time, such as suctioning of tracheostomies and home parenteral nutrition. It may range from performing caregiving tasks a couple of hours a week to practically provision of 24 hour personal care, seven days a week. Very little has been written about the effects of caregiving on the parents of children born with major congenital anomalies.

It is all the more important not to disregard the position of informal caregivers given that demand for informal care is expected to rise in the future, while at the same time the possibilities for meeting this demand decrease. On the one hand, from acute diseases with a prompt outcome, many major congenital anomalies have increasingly become diseases with long-term morbidity and a continuing need for care.[7] Moreover, current trends toward early hospital discharge and outpatient treatment will contribute to greater dependence on informal caregivers, because the time spent caring for a child at home is likely to exceed the time spent caring for a child in residential care. On the other hand, the increase in female employment and the increasing numbers of single-parent families[8,9] will mean that there are less carers available and governments will not be able to rely on them so heavily in the future.

In view of these observations, it is essential to gain better insights into informal care provided by the parents (or: 'informal caregivers') of patients with major congenital anomalies. The current study includes parents of children born with either congenital anorectal malformations (ARM) or congenital diaphragmatic hernia (CDH). The former are complex anomalies with a high incidence of associated urological problems, but the malformations are not life-threatening as

a rule. The health-related quality of life (HRQoL) of patients with ARM however, is a subject of concern.[10-12] Despite the many advances in medical therapy and although recently better survival rates have been published,[13-15] the mortality rate in CDH still remains around 40%. In the survivors, a variety of symptoms has been reported especially in the first years of life,[16,17] but eventually most CDH survivors enjoy healthy lives.[18]

This study aims to explore the caregiving tasks done by these patients' parents. Note that the costs that fall to the caregivers (i.e., transportation costs incurred in visiting and costs associated with production losses) were already taken into account in the economic evaluations of treating ARM and CDH presented in Chapters 2 and 3.[19,20] A second objective is to assess the effects of providing informal care. To achieve this, there are various options, such as measuring general effects on the caregivers' wellbeing, marital and life satisfaction, or broadly-defined quality of life,[6,21] burden of informal care,[22-24] or HRQoL. We chose to measure generic HRQoL, as compared to the general population. HRQoL refers to the aspects of quality of life that relate specifically to a person's health. There is not yet any conclusive evidence on the effect of caregiving on the multidimensional HRQoL of caregivers for children suffering from congenital anomalies. A few earlier studies, which relate to other disease areas, suggested that performing caregiving tasks indeed has negative consequences for informal caregivers' HRQoL and that support for informal caregivers is needed.[25-27]

6.2 MATERIALS AND METHODS

Patients and their parents

The study population comprised all children who were born with either ARM or CDH and who had received neonatal surgery in the Sophia Children's Hospital. We included the parents of patients that were between 1 and 11 years of age. Parents whose child had died were excluded. Data were collected by means of a postal questionnaire that covered several aspects of informal caregiving. Two copies were enclosed for the parent(s) of each patient and, where relevant, both parents were asked to fill in the questionnaire.

As mentioned above, ARM is characterized by relatively high morbidity and relatively low mortality, whereas for CDH the opposite applies. We used this contrast in this study. Generally, caregiving for patients with ARM is expected to take more time and to be more discomforting than that for patients with CDH. Presumably, parents of patients with ARM have to perform heavier and more skilled care tasks (e.g., performing anal dilatations or dealing with a colostomy) for patients with more physical dysfunction such as long-lasting incontinence. This design of comparing two different congenital conditions with different types of caregiving demands is expected to provide valuable comparisons.

Caregiving and forgone activities

We investigated whether or not it was the parents' impression that their child demanded above-average care and, if so, using an open-ended question, what activities were involved. The parents were questioned about the amount of extra hours spent per week on caregiving compared with other children of the same age. Moreover, we studied whether the parents had to forgo paid work and unpaid activities, expressed as number of hours per week, in order to provide informal care. These questions were taken from a preliminary version of the Health and Labor Questionnaire.[28]

Measuring parents' health-related quality of life

Generic HRQoL measures—encompassing physical, mental, and social domains—are common and easy-to-use measures that apply to a wide range of conditions or populations.[29,30] We aimed at applying an easy-to-use, straightforward instrument to measure informal caregivers' HRQoL. The parents were administered the EQ-5D questionnaire. In the EQ-5D approach, HRQoL is conceptualized as having physical, mental, and social domains. The parents were first asked to classify their health on the EQ-5D descriptive system.[31] This involved responders classifying themselves on five dimensions of health, each with three levels of dysfunction: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. This 'descriptive system' generates 243 theoretically possible health states. Building on earlier work in the UK that elicited valuations for a subset of health states from a general population sample, Dolan published a value set for all the possible health states using modeling techniques.[32] This resulted in an index that assigned a value 1 to normal health and 0 to death. We calculated the parents' EQ-5D index scores using this model. These scores were compared to age- and sex-specific scores elicited in the general population.[33] Differences were considered significant if P is less than 0.05.

Second, the parents were asked to rate their current health state on the EQ-VAS, a 20 cms vertical rating scale calibrated from 0 (worst imaginable health state) to 100 (best imaginable health state).[31] This provided information on their self-assessed HRQoL and the scores were also compared to general population ratings.[33]

Third, the parents rated their health state on the EQ-VAS on the assumption that someone will take over their informal caregiving activities completely and free of charge, so that they will no longer have to spend time on their current caregiving tasks. This hypothetical scenario will hereafter be cited within the text as the CareQol scenario or the CareQol scale.

More details on the EQ-5D descriptive system and the EQ-VAS are available through http://www.euroqol.org.

Regression analysis of health-related quality of life differences between the parents and the general population

We hypothesized on whether it would be possible to explain HRQoL differences between the parents and the general population. Both the EQ-5D index scores and the EQ-VAS scores were taken as dependent variables. For further explanatory purposes, we selected only those independent variables that were considered most important. Moreover, predictors of HRQoL that correlated highly with other predictors were not selected. The nine independent variables were:

1. congenital anomaly (i.e., ARM or CDH);
2. the child's age;
3. symptom score of the ARM patients[a];
4. symptom score of the CDH patients;
5. taking care of the child alone or with a partner;
6. (not) having given up paid work as a particular consequence of the anomaly;
7. number of unpaid activities the parent can spend less time on (ranging from zero to six);
8. monthly gross income[b];
9. the child's HRQoL as assessed by the parent on the EQ-VAS.

Construct validity of the combination of EQ-VAS and CareQol

We set out to verify the construct validity of the combination of the EQ-VAS and the CareQol. We hypothesized that the parents who indicated that their health state would improve in the CareQol scenario (compared with those indicating that their health state would not differ or would even diminish) were more likely to:

1. be parents of ARM patients;
2. be female;
3. take care of a young child;
4. take care of the child alone;
5. have given up paid work;
6. report a shortage of time for more unpaid activities;
7. have a lower monthly gross income;
8. take care of a child with a relatively low HRQoL according to the symptom score and the EQ-VAS;
9. have a relatively low HRQoL (as expressed by the EQ-VAS scores and the EQ-5D descriptive system scores compared to the reference scores).

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[a] *For both patient groups a symptom score of the most relevant clinical symptoms was constructed. The ARM questionnaire measured stool difficulties such as lack of urge sensation, inability to hold defecation, and urinary incontinence, resulting in a symptom score ranging from 0 to 12 (maximum symptomatology). The symptom score of the CDH questionnaire, which aimed to measure respiratory difficulties, stomach aches, and other disease-specific symptoms, ranged from 0 to 45 (maximum symptomatology).*

[b] *Gross income from work was estimated on the basis of sex, age, and highest education.[34] Income from social security benefits or capital were not taken into account. For all children who have two caregivers with paid work, the incomes of both caregivers were considered.*

Table 6.1 Demographic Characteristics of the Patients and Their Parents

Patients characteristics		**ARM**	**CDH**
Number of patients		118	46
Mean age (SD)		6.1 (3.0)	6.0 (3.1)
Sex (% female)		42%	48%
Number of parents per patient (%):*	1†	12 (10%)	6 (13%)
	2‡	104 (88%)	40 (87%)
Parents characteristics		**Female**	**Male**
Number of parents		161	145
Mean age (range)		35 (22 - 48)	38 (24 - 59)
Total number of children in household		2.2	2.4
Caregiving together with a partner (thus, not alone) (%)		89%	99%

* *For 2 patients with ARM, we have no data on informal caregiving, as the section of the questionnaires concerning caregiving was skipped.*

† *When only one parent filled in the questionnaire, mostly (94% of all cases) this was a female.*

‡ *When two parents filled in the questionnaires, mostly (99% of all cases) these were a female and a male.*

6.3 RESULTS

Responders

Of the 198 patients with ARM, 18 patients died and 14 could not be traced. We also excluded 1 severely cognitively disabled patient, as in the other studies that are part of this research program,[18-20] because a solid investigation in this subgroup would be difficult to accomplish within the framework of the current research program. Thus, the parents of 165 patients were sent questionnaires. The response rate was 72% (n = 118). Of the 122 patients with CDH, we had to exclude 45 patients who died and 4 who could not be traced. The parents of the remaining 73 patients were sent questionnaires. Questionnaires were returned by 63% (n = 46). Demographic details of the patients and their parents (n = 306, both diagnostic groups taken together) are listed in *Table 6.1*.

Caregiving and forgone activities

Concerning the ARM patients, 48% of the female parents and 32% of the male parents had the impression that caregiving for their child required more time than that for other children of the same age. As hypothesized, these percentages are larger than those found in the parents of CDH patients (24% and 13% respectively). Parents who had to compare their efforts to parents of other children more frequently considered caregiving as taking above-average time than parents who had other children besides their child born with a congenital anomaly. These differences however, did not reach statistical significance. In patients with ARM, the parents' activities consisted of, for example, giving enemas and changing diapers or underwear (*Table 6.2*). The parents of CDH patients mentioned activities such as administering medication or the provision of oxygen. If we only take into consideration the parents that had the impression

that caregiving for their child required more time than that for other children, the amount of extra hours spent per week on caregiving was 7 in female parents of ARM patients, 5 hours in male parents of ARM patients, and 7 hours in both female and male parents of CDH patients.

Almost half of the female parents had given up paid work for taking care of their child (*Table 6.3*). However, it should be realized that these parents might have given up paid work anyway, regardless of the congenital anomaly of their child. Indeed, only a small proportion of the female parents indicated that they had given up paid work as a particular consequence of the anomaly. In male parents, these percentages were substantially lower. As a result, the net labor participation of all female parents that have a partner and whose youngest child is aged 0–4 years (n = 83), for example, was lower than that of their counterparts in the general population[9] (37% *v* 45%; *P* = .16). The parents also indicated whether they had spent less time on unpaid activities than they wished because of the child's malformation (*Table 6.3*). Parents of ARM patients and those of CDH patients appeared not to differ very much. Generally, male parents less often reported a shortage of time.

Health-related quality of life

EQ-5D and EQ-VAS compared with the general population. We compared the parents' EQ-5D index scores with those of the general population for two age classes of the parents of both patient groups (*Table 6.4*). The value of the health states of the female parents was relatively low. By conventional statistical criteria, this difference was significant only for the ARM patients' female parents between 25 and 34 years of age. With the exception of the male parents aged between 25 and 34, the EQ-VAS scores of the parents of the ARM patients were statistically significantly lower than those of the general population. The health state of the CDH patients' parents, by contrast, did not differ statistically significantly.

Table 6.2 Most Frequent Caregiving Tasks (Top Five)

	Parents mentioning this task*
Parents of patients with ARM	
Giving enemas/lavage	58%
Changing diapers or underwear/washing child	25%
Supervision/extra attention in general/cheering up	20%
Washing (textiles)	18%
Taking care of the child's stoma	15%
Parents of patients with CDH	
Supervision/extra attention in general/cheering up	44%
Administering medication	25%
Monitoring oxygen need/provision of oxygen	25%
Preparing special meals/helping with eating	25%
Visiting health care providers	19%

* *Proportion of all parents who reported that the time for taking care of their child was above average.*

Table 6.3 Forgone Paid Work and Unpaid Activities

	ARM patients' parents (%)		CDH patients' parents (%)	
	Females	Males	Females	Males
Parents who gave up paid work for taking care of their child	46	2	48	7
Parents who gave up paid work for taking care of their child as a consequence of the anomaly	12	1	7	0
Parents indicating that they can spend less time on unpaid activities:				
Household work	8	3	7	3
Shopping	7	2	7	3
Odd jobs	8	10	7	8
Club activities and volunteer work	7	4	5	3
Education	5	2	7	8
Sleep	12	8	14	11

Table 6.4 Parents' EQ-5D and EQ-VAS Scores Compared with the General Population

	Age class	ARM patients' parents (*n*)		CDH patients' parents (*n*)		General population	
		Females	Males	Females	Males	Females	Males
EQ-5D	25-34	0.83* (43)	0.94 (26)	0.86 (19)	0.93 (12)	0.93	0.93
	35-44	0.90 (57)	0.92 (55)	0.87 (22)	0.90 (28)	0.91	0.91
EQ-VAS	25-34	74.02* (44)	85.15 (26)	85.95 (19)	86.42 (12)	86.82	86.87
	35-44	76.35* (58)	82.79* (56)	82.18 (22)	82.89 (28)	86.35	86.81

* *Different from the general population at the 0.05 level (Student's t test).*

EQ-VAS versus CareQol. Contrary to our expectations, it emerged that for most parents, the hypothetical scenario implied by the CareQol did not produce different health states from the actual current health state as indicated on the EQ-VAS. Surprisingly, 9% of all parents indicated that their health state would in fact diminish in the CareQol scenario (*Table 6.5*). Mean scores for the CareQol and the EQ-VAS are also listed in *Table 6.5*.

Regression analysis of HRQoL differences with the general population. Even though the majority of the parents said that their health state would not be different in the CareQol scenario (*Table 6.5*), the analyses showed that differences existed between the HRQoL of the parents and the general population (*Table 6.4*). By doing a regression analysis, we have tried to explain this relatively low HRQoL of the parents (*Table 6.6*). Generally, the directions of the coefficients met our expectations, but the residual variance was rather large. Apparently, the most important predictors of HRQoL differences were type of anomaly (i.e., ARM or CDH), symptom score, income, and the child's HRQoL as assessed on the EQ-VAS.

Table 6.5 CareQol Compared with the EQ-VAS

CareQol versus EQ-VAS	Parents of patients with ARM (*n*)		Parents of patients with CDH (*n*)		All parents (*n*)
	Females	Males	Females	Males	
CareQol > EQ-VAS	24% (26)	11% (11)	13% (6)	10% (4)	16% (47)
CareQol = EQ-VAS	64% (70)	82% (80)	84% (38)	83% (34)	76% (222)
CareQol < EQ-VAS	13% (14)	7% (7)	2% (1)	7% (3)	9% (25)
Mean CareQol	74.15 (111)	81.64 (98)	83.60 (45)	84.32 (41)	79.49 (295)
Mean EQ-VAS	74.91 (114)	81.78 (101)	83.47 (45)	84.10 (41)	79.75 (301)

Table 6.6 Regression Analysis

Independent variables, standardized regression coefficients (Bêta)†	Dependent variable			
	Female parents		Male parents	
	Difference EQ-VAS and EQ-VAS$_{gp}$	Difference EQ-5D and EQ-5D$_{gp}$	Difference EQ-VAS and EQ-VAS$_{gp}$	Difference EQ-5D and EQ-5D$_{gp}$
1) Congenital anomaly	-0.21**	-0.01	-0.05	0.02
2) Child's age	-0.03	0.01	-0.06	0.00
3) ARM symptom score	-0.13	-0.09	-0.02	-0.13
4) CDH symptom score	0.03	-0.10	-0.05	-0.18*
5) Taking care alone or with a partner	0.02	-0.00	-0.10	-0.07
6) Having given up paid work	0.07	0.01	0.02	0.06
7) Unpaid activities to spend less time on	-0.04	-0.08	0.02	-0.02
8) Gross income	0.11	0.20*	0.15	0.17
9) Child's health-related quality of life	0.28**	0.08	0.24**	0.04
Adjusted R^2	0.12	0.04	0.03	0.03

GP = general population.
* *Significant at the 0.05 level.*
** *Significant at the 0.01 level.*
† *Besides a constant. Forced entry (tolerance: 0.0001).*

Construct validity of the combination of EQ-VAS and CareQol. While the CareQol score appeared not to differ significantly from the current health state as indicated on the EQ-VAS, this appeared however not to be the case for some subgroups (*Table 6.7*). This verified the construct validity of the combination of the EQ-VAS and the CareQol. All 294 parents were divided into three groups. Our hypotheses were largely confirmed. Generally, female parents, parents that had to forgo paid work or unpaid activities, parents of children suffering many symptoms and with a relatively low HRQoL (as reported by the parents) and parents with a relatively low HRQoL themselves (according to the EQ-VAS) were over-represented in the subgroup of people who claimed that their health state would increase in the CareQol scenario.

Table 6.7 CareQol Compared with the EQ-VAS (Both Female and Male Parents)

	CareQol > EQ-VAS (*n*)	**CareQol = EQ-VAS (*n*)**	**CareQol < EQ-VAS (*n*)**	***P* Value**[*]
Difference CareQol and EQ-VAS (mean)	11 (47)	0 (222)	-27 (25)	0.00
Anomaly (% parents for ARM patients)	79 (47)	68 (222)	84 (25)	0.10
Sex (% female)	68 (47)	49 (222)	60 (25)	0.04
Mean child's age	5.3 (47)	6.4 (222)	4.6 (25)	0.00
Percentage parents taking care alone	8.5 (47)	5.0 (222)	8.0 (25)	0.57
Percentage parents that gave up paid work	15 (46)	3 (215)	12 (24)	0.00
No. of unpaid activities to spend less time on	1.3 (43)	0.2 (212)	0.6 (22)	0.00
Mean monthly gross income	€ 2,857 (46)	€ 2,996 (198)	€ 2,057 (23)	0.01
Mean symptom score ARM[†]	9.0 (37)	5.9 (150)	6.7 (21)	0.00
Mean symptom score CDH[†]	12.7 (10)	6.3 (72)	7.6 (4)	0.02
Mean EQ-VAS (parent form)[†]	75 (47)	86 (219)	83 (24)	0.00
Mean difference EQ-VAS and EQ-VAS_{gp}	-16 (47)	-4 (222)	-10 (25)	0.00
Mean difference EQ-5D and EQ-$5D_{gp}$	-0.08 (46)	-0.01 (222)	-0.10 (22)	0.00

GP = general population.

[*] *One-way analysis of variance (ANOVA).*

[†] *While each parent (one or two) of a child had the opportunity to fill in a questionnaire on caregiving, the questions on symptoms and the EQ-VAS parent form were added only once and probably answered by one parent alone. Therefore, for some parents this information might reflect their partner's opinion on their child's health state.*

6.4 Discussion

This study focused attention on informal care for children born with major congenital anomalies. Several conclusions can be drawn: especially the parents of patients with ARM—who were sometimes involved in rather skilled care tasks—were of the opinion that caregiving for their child took them more time than that for other children of similar age. Relatively few parents had to forgo paid work or unpaid activities. We found differences between the parents' HRQoL and that of the general population, some of which can be explained by differences in anomaly (i.e., ARM or CDH), level of symptomatology and HRQoL of the child, and the family's income. On average, the parents considered that their HRQoL would not be substantially better when someone would take over their caregiving activities.

It is worth mentioning that our study may not have led to very strong results because we included, where relevant, both parents of each child, who are not all providing care to an equal extent. Besides, this study included parents of children of a wide age range and not only parents of children in the acute phase following birth. The parents may perceive informal caregiving tasks as normal tasks after a period of time. It may be difficult for them to distinguish between their role as caregiver and the 'normal' parenting role. Furthermore, coping resources and skills of the parents to deal with the strain resulting from their child's disorder are likely to have impeded the registering of larger declines in HRQoL.[35,36] Parents of

children with a disability are more likely to give positive or neutral answers than negative ones in response to questions about HRQoL.[37]

The EQ-5D was the instrument of choice. Among its advantages are that it is a short questionnaire easily understood by the responders and that it is suitable for mail administration. Another advantage is that it includes all basic domains of health, both psychological and physical. So far, many studies have mainly focused on psychological health. Studies of the physical health effects are less conclusive but suggest increased physical vulnerability, especially when the care recipient is physically disabled.[38-40] Thus, it is desirable to adhere to a broadly-defined HRQoL measure, without eliminating any domains in advance. The impact of caregiving may be underestimated when research restricts its scope to a unidimensional health outcome. Moreover, the EQ-5D, comprising the EQ-5D descriptive system and the EQ-VAS, has proven a reasonably valid instrument, also in patients suffering from health problems that mainly affect specific dimensions of health.[29,41-43] Thus, we consider it unlikely that the EQ-5D does not capture caregiving effects. Nevertheless, complement HRQoL studies are needed to confirm the implications of this exploratory analysis. Finally, we are conscious that even caring for a healthy child could disrupt HRQoL. Ideally, therefore, the EQ-5D reference values are derived from parents with healthy children, not the general population. Such data, however, were not available.

The most important predictors of HRQoL differences between the parents and the general population were type of anomaly (i.e., ARM or CDH), symptom score, income, and the child's HRQoL as assessed by the parent on the EQ-VAS. This corresponds with previous studies—albeit in other settings—that suggested that disease characteristics of the care recipient and income are important factors in explaining the health consequences of caregiving.[26,44-46] Several other studies found, however, that disease characteristics such as disease severity and level of impairment were not significantly associated with caregivers' health.[36,47-49] Remarkably, variables concerning the amount of caregiving tasks or abandoned activities did not belong to the most important predictors. This finding corroborates other studies that also found that the duration of caregiving did not negatively relate to caregiver's health.[45,48] A possible explanation is that the caregivers who were most intensely involved in caregiving had more opportunity to learn to cope and adjust. The fact that the child's age did not have a significant influence may have to do with the fact that opposite effects are related to age. On the one hand, the first years after birth are associated with many caregiving tasks while the parents are relatively inexperienced in their job. On the other hand however, the contrast to what is 'normal' becomes more apparent when the child is older. For example, functional problems such as incontinence may become more problematic when the child starts school. This cross-sectional study could not provide evidence of causal relationships between caregiving and time elapsed since the child's birth.

This study was primarily aimed at comparing the parents' scores on the EQ-5D with those of the general population. Alternatively, we assessed the exact magnitude of HRQoL changes related to caregiving with the newly developed CareQol scale, whose psychometric properties were not definitively established in this study. Its merit and novelty is that, in theory, the HRQoL change due to caregiving specifically, excluding so-called 'family effects', can be determined by looking at the difference between the scores on the EQ-VAS and the CareQol. The term 'family effects' was introduced to acknowledge that HRQoL changes will often stem not only from caregiving but also from the mere fact that the caregiver's child is ill or that help has to be arranged for the child—thus, even when no caregiving tasks have to be performed.[50] For example, informal caregivers may experience depressive feelings, because of the ever-present fear of recurrent medical problems. Parents of children diagnosed with congenital diseases often express persistent anger, feelings of inadequacy and guilt, anxiety and sense of shame.[51-53] Earlier studies—a recent study in pediatric cancer and diabetes being only one example[54]—made no explicit attempt to distinguish between these two types of effects. Nevertheless, it could be argued that the CareQol is not sufficiently valid given the answers provided by the responders and the fact that they scored lower on average in terms of HRQoL than the general population. Among explanations for the fact that most people do not indicate a HRQoL change in the CareQol scenario are:

1. It may be difficult for responders to self-assess HRQoL changes due to caregiving. They may not have the impression that health problems are related to caregiving and may have difficulty in estimating how their HRQoL would be affected if they did not have to provide care tasks. It may indicate that some people find it difficult to comprehend such a hypothetical question. Alternatively, there simply may be no significant effects on HRQoL (apart from 'family effects').
2. The fact that rather many people (9%) indicated that their HRQoL would decline in the CareQol scenario indicates that the responders may feel uncomfortable about the questions and give protest answers. Also, some parents may not want others (perhaps strangers) caring for their child's health. Furthermore, it may suggest positive experiences derived from caregiving, such as feelings of gratification, self-confidence, and finding meaning in the care.[2,55,56]
3. The instrument appears to detect HRQoL changes particularly in situations in which caregiving is substantially demanding (*Table 6.7*). Only in these very straining circumstances carers may actually experience health-related problems due to caregiving and be able and willing to report them.

Bearing in mind these reflections, the CareQol instrument seems more useful as a quick scan to detect caregivers 'at risk' rather than as an instrument capable of determining exact HRQoL losses.

This study was of importance because present understanding of the effects of caregiving on parents' multidimensional HRQoL is still rudimentary. Earlier studies in children with a chronic illness or disability mainly focused on the burden that informal caregiving may cause. Even though research findings are equivocal,[57-60] numerous studies have shown that the role as caregiver may interfere with personal life, interrupt daily activities, and involve stress, tiredness or financial burden.[61-65] Although burden and HRQoL are related, it is important to distinguish these concepts concerning the effect of caregiving. Burden, also referred to with terms such as 'stress', 'strain', and 'impact', seems to represent a unique domain of the caregiving situation, whereas HRQoL is considered an overall outcome.[66-68] We feel that measuring HRQoL has important value in the appraisal of the outcomes of caregiving. It would be of interest to continue investigating informal caregiving for children with congenital anomalies in future more definitive studies, refining the methodology applied in this exploratory study.

Finally, this study stimulated us to establish in our hospital a support team for the parents of children born with (multiple) congenital anomalies that addresses the health consequences of caregiving. Apparently, female parents, parents of patients with ARM, parents of patients suffering from many symptoms, and parents with a relatively low socioeconomic status were identified in this study as the most vulnerable group of caregivers. Considering earlier experiences reported in the literature,[69-72] we expect such a support program to be important in reducing the perceived pressure from informal care and in maintaining carers' HRQoL. At the same time, providing support for the parents will facilitate the development of the child and benefit his or her HRQoL. An important avenue for future research would be to clarify the value of support teams. What is already clear is that it is of major importance not to disregard the position of informal caregivers when preparing our health care systems for the future.

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Chapter 7

Cost-Effectiveness of Neonatal Surgery: First Skepticized, Now Increasingly Accepted

ABSTRACT

Mortality rates in neonatal surgery have dropped markedly, illustrating the enormous progress made in the field. Yet, new and pressing questions have arisen. For one, improved survival might come at the price of poor patients' health-related quality of life (HRQoL). Then, health care budgets have tightened. It follows that the effects of medical interventions should be weighted against their costs. As evidence of the cost-effectiveness of neonatal surgery was still lacking, our research group performed economic evaluations for treatments of congenital anorectal malformations and congenital diaphragmatic hernia. The results are consistent, indicating that both treatments produce good cost-effectiveness. Other groups, mainly in the Northern Americas, have also published cost-effectiveness studies in the field of neonatal surgery, as demonstrated by a literature review over the period 1999 through 2005. The total number is still small, however.

In general, a society is better off by using resources efficiently. This is also true for health care resources, which explains the need for the economic analysis of health care. Yet, decisions on how much priority to give to a particular health care procedure must never be based on economic grounds only. In the case of neonatal surgery, crucial ethical questions may arise, for example, when deciding whether therapy should indeed be offered, or perhaps withheld. Occasionally, the child's 'best interest' may justify withholding or withdrawing of life-prolonging surgical intervention. Apart from the perspective of individual medical decision making, there are yet other factors that play a role in determining how much priority neonatal surgery should be accorded in comparison and competition with other areas of health care. Most crucial among these factors other than cost-effectiveness seem arguments of equity, which reflect the feeling that health care policy should incorporate societal concerns for 'the worst off'. Many equity approaches appear to require that high priority be given to treating the young or those with the most severe diseases. Quality-adjusted life years (QALYs) gained in newborns suffering from life-threatening anomalies therefore have a high value.

We conclude that from the evidence available at present it is safe to say that neonatal surgery yields good value for money and contributes to an equitable distribution of health and health care. The situation of favorable cost-effectiveness ratios may change, however. On the one hand, new technical advances in neonatal surgery are bound to drive up health care costs. On the other hand, life-saving technologies with their inherent iatrogenic morbidity may result in more residual morbidity and poorer HRQoL. The way forward lies in performing more economic evaluations in the field of neonatal surgery. This will involve tackling methodological issues in health economics, for example relating to 'the proxy problem', the position of the parents, and discounting.

7.1 INTRODUCTION

Neonatal surgery has reached a high level of sophistication by now. Its progress over the past decades is perhaps best brought out by the markedly improved survival rates. Yet, the increase in survival rates came together with new and pressing issues. First, survival is of course an important measure of success, but improved survival might come at the price of poor health-related quality of life (HRQoL) in later life. Second, while medicine has provided better opportunities, budgets have become tighter over the years. This leads to worrying dilemmas. We simply cannot afford all diagnostic and treatment procedures that are perceived effective or even have been shown to be so. Instead, we inevitably have to make choices. In this respect, there is a growing consensus on the necessity of assessing the cost-effectiveness of medical interventions.

As evidence of the cost-effectiveness of neonatal surgery was largely lacking until then, we initiated cost-effectiveness studies in the first half of the 1990s to investigate whether the effects of neonatal surgery justify the cost. Section 7.3 of this chapter summarizes the outcomes of these studies, and in addition presents an overview of the state of the art by reviewing recent empirical studies. Section 7.2 introduces cost-effectiveness analysis—coupled with an attempt to clear up some misapprehensions—and explains its relevance. In Section 7.4, attention is paid to the consequences of this type of research for health policy. It is discussed how cost-effectiveness interacts with other relevant determinants of priority setting for health care interventions. Other determinants in neonatal surgery may be, for example, the mere fact that young children are involved or the ethical question whether everything that technically can be done should be done in all cases. Section 7.5 goes into some important research areas concerning cost-effectiveness analyses in neonatal surgery. The chapter will end with some concluding remarks.

There is one important caveat to all this: the achievements in neonatal surgery have been outstanding, but are largely restricted to the industrialized Western world. Developing countries, where still 98% of all 4 million annual neonatal deaths worldwide happen,[1,2] are faced with far more severe budget constraints. In these countries, per capita annual public expenditure on health is often below US$ 10.[1] Budget allocation decisions generally concern choices between public health measures and basic outreach and family/community interventions, rather than prioritization between costly, high-technology interventions. Although cost-effectiveness analysis can aid also in resource-poor health care settings—priorities must be set even in these settings, or even more given the significant budget constraints—this chapter focuses on the choices in higher-income countries, in which neonatal surgery is more widespread.

7.2 THE RELEVANCE OF COST-EFFECTIVENESS ANALYSES

Economic evaluations aim at establishing whether the effects of a given treatment are worth its cost, compared to an alternative treatment.[3,4] Such evaluations are useful, as patients are not treated 'in isolation'. Behind every patient there are other patients and even healthy people (i.e., future patients) claiming a reasonable amount of health care resources. As Williams put it: anyone who says that no account should be paid to costs is really saying that no account should be paid to the sacrifices imposed on others.[5]

People still tend to distrust economic analyses of health care interventions and even perceive them as unethical, especially those who still—mistakenly—feel that money should not be a factor in health care decision making. The word economics can evoke emotional and stereotypical responses from health care professionals and the general public alike, culminating in a negative attitude towards cost-effectiveness analyses. In reply to these concerns, we would like to emphasize the following critical points, vital for assessing cost-effectiveness analysis on its real merits.

First, economics is not about money, but rather about scarcity and choice. This means that cheap is not always best: a procedure can be more expensive and still be more cost-effective than an alternative treatment. Second, (potential) patients are exposed to conflicting interests. Naturally, patients and their families wish for the best interventions available, regardless of how expensive these interventions are or how uncertain their benefits. However, fulfilling all these demands would certainly lead to mounting health care expenditures. Both patients and the general public would probably be unwilling to pay the resultant much higher insurance premiums, taxes or out-of-pocket expenses. To quote Eddy: costs are real and people care about paying them.[6] Third, having to make choices is not a new phenomenon in health care. For example, doctors have always had to choose how to allocate their time, and, in the hospital setting, to whom to allocate the available beds and operating facilities—all of which suggest that priorities are being set. The main difference with the past is that, currently, this process of priority setting is becoming more explicit and operates on a more aggregate level.

What is expected from doctors?

Modern medicine has become a scene of conflicts between the individual and society. Doctors are expected to conform to recognized ethical principles, such as the one dictating to do everything possible that might benefit their patients. At the same time they should not neglect society's needs and budgetary constraints when deciding on what type and amount of medical care to deliver. So, there is increasing pressure for doctors to serve two masters.[7] Better identification of the roles of the different stakeholders involved in the process of priority setting might relieve this pressure. In that respect, society as a whole (the people who will actually receive the benefits and pay the costs) should decide which health

services are worth their costs and which not. To this end, building on the results of cost-effectiveness analyses, decision makers have to carry out the task of determining which health care programs are to be given priority, a task that should be open to public debate. It is the authorized policy makers, and not the doctors, that should bear the responsibility for making these difficult decisions about the allocation of scarce resources. While complying with the limits that society imposes, physicians ought to do everything possible. As such, doctors in their daily practice are not responsible for what they can not accomplish.[8,9] Of course, this does not alter the fact that ethical physicians of their own accord should feel responsible for efficient spending of scarce means. The medical profession is well aware of this: witness the fact that more and more clinical guidelines or practice policies now incorporate cost-effectiveness information.[10,11] However, this practice is not yet widespread in neonatal surgery. Although clinical guidelines are increasingly produced, guidelines that make at least some reference to cost or cost-effectiveness are still sporadic—guidelines on hypertrophic pyloric stenosis and on neonatal circumcision being two examples.[12,13]

What is of utmost importance is that doctors are encouraged to grasp the basics of cost-effectiveness analysis—a relatively new field which may be perceived as highly abstract compared with taking care of patients. Moreover, the medical profession should be actively involved in cost-effectiveness research and, on a policy level, participate in decision processes. As one author noted: priority setting and rationing will not work without the support of clinicians.[14]

7.3 EMPIRICAL RESULTS

Quite a few medical technologies have already been assessed on their cost-effectiveness.[15-17] Neonatal surgery is still understudied however. A review dating from 2000 identified just two complete economic evaluations in this field.[18] One, Hackam and co-workers documented that, in terms of cost-effectiveness, a single-staged approach to Hirschsprung's disease is to be preferred over multiple-staged therapy.[19] Two, Roberts provided evidence of the cost-effectiveness of extracorporeal membrane oxygenation (ECMO), as compared to conventional management of severe respiratory failure.[20] It seems highly relevant to collect further evidence on the cost-effectiveness of neonatal surgery, the more so since treatment of neonatal surgical conditions may be expensive. For example, initial hospitalization costs (per patient) for congenital diaphragmatic hernia, extensive short bowel syndrome, and gastroschisis were reported to amount to US$ 137,000, US$ 315,000, and US$ 123,200, respectively.[21-23] The question is whether the high costs related to neonatal surgery are justified in terms of outcome.

In the early 2000s, our research group performed economic evaluations of treatment of congenital anorectal malformations (ARM) and congenital diaphragmatic hernia (CDH).[24-26] The results may briefly be summarized as follows. The direct medical costs were found to be considerable, with long-term costs after the initial treatment being only a fraction of these costs. HRQoL in patients once treated for ARM and now between 1 and 4 years of age was lower than that of the general population. The older children showed better HRQoL. Although surgery for ARM was associated with substantial residual symptomatology, patients aged 16 years and over showed hardly any HRQoL differences with population standards. We found CDH to be still associated with high mortality rates, despite the many advances in treatment over recent decades. Although respiratory difficulties and stomach aches were reported, HRQoL in CDH survivors did not differ significantly from that of the general population. Costs per quality-adjusted life year (QALY) amounted to € 2,482 for ARM and € 2,434 for CDH treatment.

How to interpret cost-effectiveness ratios?

Seeing that cost-effectiveness ratios like these are not very informative in themselves, we need to bring in figures from other health care programs for comparison to draw meaningful conclusions. Put in the perspective of the many times higher cost-effectiveness thresholds that seem to guide public authorities in decisions to accept or reject a technology, the costs per QALY we calculated for ARM (€ 2,482) and CDH (€ 2,434) are clearly very modest. Examples of such thresholds are those of the UK National Institute for Clinical Excellence (about £ 35,000 or £ 40,000 per QALY, which equals € 52,000 or € 60,000 at current exchange rates)[27] or the Australian Pharmaceutical Benefit Advisory Committee (between AU$ 42,000 and AU$ 76,000 per life-year, which is approximately € 27,000 and € 48,000).[28] In the Netherlands, a threshold of approximately € 18,000 per life-year is sometimes seen as an acceptable cost-effectiveness ratio.[29]

In the context of this chapter, we shall assume that our encouraging results also apply to surgical treatment of other congenital anomalies. This assumption seems fairly plausible, since ARM and CDH were not selected randomly but purposefully chosen as being opposite extremes in terms of mortality and morbidity. ARM is characterized by relatively low mortality and relatively high morbidity into adulthood, whereas for CDH the opposite applies. Notwithstanding the diversity of the conditions, treatments are remarkably close in terms of cost-effectiveness. So, treatments for other 'isolated' anomalies such as Hirschsprung's disease and esophageal atresia are likely to be cost-effective as well. Because most neonates having to undergo surgery present with just one major anomaly, the overall conclusions drawn from our research are favorable for neonatal surgery in general.

The 2000 review updated

We updated the earlier review cited above[18] to see whether recent years have brought more empirical results. We searched the literature from the year 1999 onwards for complete economic evaluations of both diagnostic and therapeutic interventions in neonatal surgery. In spite of the fact that we applied liberal criteria for inclusion—several studies, for example, only evaluated postoperative complication rates rather than more advanced patient outcome measures—we identified no more than 11 relevant studies, including our economic evaluations in ARM and CDH referred to earlier. Even though our review covered just a few years and only included studies published in English, the conclusion can only be that the number of published economic evaluations in the field of neonatal surgery is still small. *Table 7.1* details the interventions investigated in all these studies, differentiating between the six groups of congenital anomalies listed by Ravitch and colleagues[30] and other conditions. The authors predominantly draw favorable conclusions on cost-effectiveness. What attracts attention is that, leaving our studies on ARM and CDH out of consideration, all studies except one (dealing with circumcision) concentrated on particular novel aspects of treatment or diagnosis. So, drawing more conclusions on the entire treatment process of neonatal surgery, next to our studies on ARM and CDH, is not possible.

7.4 Is there a role for arguments other than cost-effectiveness?

Above, we argued that it is not necessarily unethical to consider cost-effectiveness arguments. However, we feel it would be unethical indeed to base decisions on how much priority to give to a particular health care procedure on economic grounds exclusively. In the case of neonatal surgery, crucial ethical questions arise for example when considering whether therapy should be offered or perhaps withheld, which often involve life-and-death decisions. In the case of children with serious birth defects, the 'best interest' of the child may justify withholding or withdrawing life-prolonging surgical intervention. There may be fundamental uncertainties as to the child's future development, or in some situations, a life strongly burdened by disability and dependency on life-support systems may be the ultimate outcome.[31-33] Treatment modalities that may involve such ethical dilemmas include ECMO, the care for extremely premature infants, and prenatal diagnosis and fetal surgery.[34-38] Apart from ethical arguments, religious, cultural, aesthetic, or legal aspects need to be considered in neonatal surgery, such as a child's right to be free of intrusive unnecessary medical and surgical procedures before having reached the age of full and legal discretion (e.g., neonatal circumcision[39]).

Table 7.1 Economic Evaluations for Interventions in the Field of Neonatal Surgery (Published From 1999 Onwards)

	Study no.	Country of origin	Alternatives studied		Time horizon	Primary analysis results, expressed as difference from the comparator		
			Intervention	Comparator		Costs	Effects	Cost-effectiveness ratio
Ravitch's index diagnoses								
Congenital diaphragmatic hernia	88	Canada	Inhaled nitric oxide	Oxygen	Until discharge to home or death	+ CA$ 11,478	Higher mortality rate (50% *v* 40%)	Needed not be calculated, because the intervention was both more costly and less effective
	25	Netherlands	Neonatal surgery and subsequent treatment	No treatment	Basically life-time	+ € 42,658	+ 17.5 QALY	€ 2,434 per QALY gained
	89*	USA	Inhaled nitric oxide	Conventional management	First year of life	- US$ 1,880	+0.030 QALY	Needed not be calculated, because the intervention was both less costly and more effective
	40*	UK	Extracorporeal membrane oxygenation	Conventional management	First 4 years of life	+ £ 17,367	Lower death or severe disability rate (37% *v* 59%)	£ 16,707 per life-year gained/ £ 24,775 per disability-free life-year gained
Intestinal atresia	–							
Esophageal atresia and tracheo-esophageal fistula	–							
Imperforate anus	24	Netherlands	Neonatal surgery and subsequent treatment	No treatment	Basically life-time	+ € 31,593	+ 12.7 QALY	€ 2,482 per QALY gained
Hirschsprung's disease	90	USA	One-stage laparoscopic pull through	Two-stage Duhamel procedure	About 7 to 12 months	- US$ 15,014	Fewer complications	Needed not be calculated, because the intervention was both less costly and more effective
Omphalocele and gastroschisis	–							

	Study no.	Country of origin	Alternatives studied		Time horizon	Primary analysis results, expressed as difference from the comparator		
			Intervention	Comparator		Costs	Effects	Cost-effectiveness ratio
Other diagnoses								
Suspected craniosynostosis	91	USA	3 diagnostic strategies compared with each other: 1) no imaging, 2) radiography (if abnormal, followed by 3D CT), 3) 3D CT		20 years	In low-risk infants, the imaging strategies (strategies 2 and 3) resulted in cost per QALY of more than US$ 560,000. In intermediate-risk infants, strategy 2 had a cost per QALY of US$ 54,600. In high-risk infants, strategy 3 was most effective with a cost per QALY of US$ 33,800[†]		
(Suspected) hypertrophic pyloric stenosis	92	USA	Volumetric measurement of nasogastric aspirate for selection of imaging study	Ultrasonography as the first study	Initial hospital care	- US$ 50[‡]	No difference[§]	Needed not be calculated, because the intervention was both less costly and equally effective
	93	USA	Standardized feeding protocol	Variable feeding protocols	A few weeks after initial hospital care	- 11.9%	No significant difference in complication rate	Needed not be calculated, because the intervention was both less costly and equally effective
	94	USA	Ad libitum feeding protocol	Conventional regimented protocol	Not exactly clear	- US$ 1,270	Higher rate of significant emesis (32% *v* 26%)	Not calculated
Neonatal circumcision	95	USA	Neonatal circumcision	Not circumcising	Life-time	+US$ 828	+ 0.0153 well-years lost	Needed not be calculated, because the intervention was both more costly and less effective

Study no. refers to references. Abbreviation: 3D CT, three-dimensional computed tomography.
Original research (excluding reviews) published in English from 1999 through January 2005. We conformed to the following definition of a complete economic evaluation: 'the comparative analysis of alternative courses of action in terms of both their costs and consequences'.[3] Any outcome measure was accepted, and no quality requirements for the studies were set.
Database searched: PubMed (http://www.ncbi.nlm.nih.gov/entrez). We searched no other literature databases for economic evaluations, because this was expected to be of little additional value—as Sassi and colleagues demonstrated.[96]

* *These studies also included other diagnostic categories than congenital diaphragmatic hernia and did not present separate cost-effectiveness ratios.*
† *The authors present incremental cost-effectiveness ratios for the three different strategies, separately for three risk groups (completely healthy children, healthy children with head deformity, and children with syndromic craniofacial disorders). Not all cost-effectiveness ratios calculated by the authors can be duplicated here.*
‡ *Or, as reported by the authors: at least US$ 4,464 and 30 hours of physician time in the total group of 89 infants.*
§ *Both alternative strategies would correctly detect all cases.*

More from a policy perspective rather than the perspective of individual medical decision making, there are still other factors in determining how much priority neonatal surgery should be accorded in comparison and competition with other areas of health care. However important economic evaluations are, they are only one source of information among several used to assist in decision making processes. It essentially comes down to the question of how cost-effectiveness interacts with other factors relevant at the social choice level. Arguments of equity, justice, or fairness (hereinafter all loosely referred to as equity) are probably the most influential of these other factors. Equity arguments have occasionally emerged in neonatal and pediatric cost-effectiveness studies. For example, Petrou and Edwards in their study into the cost-effectiveness of neonatal ECMO reflected that "it is conceivable that decision makers place a greater value on health gains experienced by the young than those experienced by other groups of the population".[40] Others also refer to equity arguments, but in a somewhat more general sense. Lantos, for example, states that neonatal intensive care units (NICUs) implicitly make a compelling moral claim upon society. This claim insists that we not turn our back on these tiny, vulnerable babies. NICUs stand for our society's moral commitment to children.[41] Indeed, children, as 'sympathy-arousing victims of disease', greatly appeal to a wide public, and many people would therefore tend to give them high priority in assigning limited resources. 'Blind instincts of nature' may contribute to our preference for youth over age in distributing access to social goods and services, as Loewy observed with a critical eye.[42]

Equity approaches

The previous section leaves unanswered the question of how to integrate cost-effectiveness and equity arguments in a theoretically sound manner. In recent times, researchers have increasingly struggled with this problem of the so-called 'equity-efficiency trade-off',[43-47] trying to find ways to capture both efficiency considerations (maximization of the community's health) and equity considerations (e.g., reducing inequalities in health). We will now describe various equity approaches put forward, and give insight into their relevance to neonatal surgery.

The so-called fair innings principle reflects the feeling that everyone is entitled to some 'normal' span of health. Anyone failing to achieve this has in some sense been cheated, while anyone getting more than this is 'living on borrowed time'. Various survey reports suggest that there is indeed support amongst the population for the idea of discriminating in favor of the young when confronted with unavoidable choices.[48,49] The fair innings principle is thus concerned with the likelihood that people over their lifetime will achieve a certain target number of QALYs. This approach must be distinguished from—though it may be combined with—evidence suggesting that society attaches different weights to a year of perfect life lived by people of different ages (an effect of age per se).[50-56] Generally, priority is given to the young over the elderly, even by the elderly

themselves. Interestingly, studies consulting the public have found that—despite the preference for the young in general, requiring that a newborn should be given priority over a 70-year old for example—a newborn should not be treated in preference to a slightly older child. The logic of this may be that, compared to a child, a newborn is less aware of its situation, is less of a 'person', and has had a smaller investment of parental effort and emotion. Apart from these reasons, responders in these studies bring up reasons that reflect efficiency arguments rather than equity arguments, namely (although it was not intended that responders made this assumption) the idea that treatment has a larger chance of success in children than in newborns.

Another category of equity concepts attaches primary importance to disease severity. One such approach refers to the idea that explicit priority should be given to the most life-threatening diseases. Jonsen called this the 'rule of rescue': the moral response to the imminence of death demands that we rescue the doomed.[57] The principle argues that life is priceless. We should strive for saving as many lives as possible rather than life-years. Other theories within this category place primary importance on the 'initial starting point'. In surveys from different countries, responders expressed a strong preference for allocating resources to those with the worst initial health state.[58-61]

Finally, the recent concept of 'proportional shortfall' contends that interventions for patients who, if not treated, would miss out on a large proportion of their remaining quality-adjusted life expectancy should be given higher priority.[46,62]

This brief overview suggests several conclusions. Many equity approaches appear to focus, either deliberately or indirectly, on age or disease severity, which is highly relevant to the case of neonates suffering from major anomalies. Many theories require that high priority be given to treating the young—though with a distinction made between newborns and older children—or the most life-threatening diseases. It follows from this reflection on equity issues that QALYs gained in newborns suffering from major life-threatening anomalies are relatively valuable. Then, it must be acknowledged that the 'fair innings' approach and similar theories like that of 'saved young life equivalents'[63] do not seem to put any limit to the resources to be poured into the objective of achieving marginal extensions of life in newborns at or near the point of death.[43] As an absurd consequence, any allocation of medical resources to anyone other than the terminally ill newborn would seem to impede equity. This shows that no single equity perspective should be the basis of priority setting.

7.5 Where do we go from here?

Like for example ECMO and neonatal intensive care already did, new technical advances in neonatal surgery will continue to drive up health care costs. We may

also expect that life-saving neonatal technologies with their inherent iatrogenic morbidity will more and more result in survival with residual morbidity and poor HRQoL. It is not obvious, therefore, that current favorable cost-effectiveness ratios will remain unchanged. On the contrary, those involved in neonatal surgery should fully strive at retaining good cost-effectiveness. The discipline will otherwise not be able to maintain a strong position in allocation decisions, bearing in mind that health economics in our view will remain important.

The way forward not only involves the practical application of health economics to neonatal surgery, but also tackling methodological issues in health economics. In this context we will touch upon three vital issues in economic evaluations of neonatal surgery: a) the proxy problem, b) the position of the parents, and c) discounting.

a) The proxy problem

In HRQoL studies, children often are not consulted directly, but through proxies such as their parents. Reporting by proxy, though, carries an inherent risk of measuring the impact of the child's disease too much from the perspective of the parents, which is disturbed by the impact on their own situation. Further methodological research on the validity of age-specific questionnaires is needed, so that the views and preferences of children from the age of about 5 years can be included. For younger children, it will remain inevitable to appeal to proxies. Encouragingly, recent research findings suggest that parents are able to provide appropriate information on their child's HRQoL, especially concerning observable, concrete behaviors.[64-66] Moreover, the evidence for the validity of proxy versions of HRQoL questionnaires is strengthening.[67-69]

b) The position of the parents

Recent years have been marked by a variety of changes in the care offered to young children to minimize their anxiety and stress from hospitalization and to manage the pain they experience, simultaneously reducing duration of hospital admissions, use of medical resources, and readmission rates. Interdisciplinary teams, ambulatory treatment programs, or home support teams, which have been established for children with intestinal failure, children with diabetes, or infants on home parenteral nutrition for example,[70-73] can be expected to be very helpful in this respect. From a societal perspective, however, we must question whether the beneficial effects on the patients would perhaps coincide with a shift to negative effects on parental 'burden of care', HRQoL, or the costs of informal caregiving. Caring for a child, although usually rewarding, can place heavy demands upon parents. It is good to see that support teams have been instituted for the caregivers of children suffering from a variety of conditions, such as Down's syndrome and craniofacial anomalies, and of technology-dependent children.[74-77] Initiatives in our department include an interdisciplinary team for the in-patient and post-discharge management of short bowel syndrome and an interdisciplinary support team for caregivers of children born with major

(multiple) anomalies. Until today, the cost-effectiveness of all such programs still remains largely unexplored.

c) Discounting

In cost-effectiveness analyses, both future costs and future effects are typically discounted: costs and effects have less value if they occur in the future. This principle reflects the 'positive rate of time preference' that individuals and society tend to hold. In other words, people prefer desirable consequences, such as effects, to occur earlier in life and undesirable consequences, such as costs, to occur later.[3] There are several sources for this time preference, such as the fact that money earns interest, the risk of death, or pure myopia. Clearly, this methodological rule is highly relevant to life-saving neonatal surgery. Discounting—at a rate of 3-5% per year, as usually recommended—can have a profound effect on the cost-effectiveness ratio of neonatal surgery, the effects of which cover the patient's entire life span.[24,25] There is currently a vigorous debate going on regarding discounting, particularly as to whether future effects should indeed be discounted at the same rate as future costs,[78-82] as is still common practice.[83] It could be argued that discounting the health effects at a lower rate would be more appropriate. If this should become standard practice, neonatal surgery would generally show relatively more favorable cost-effectiveness compared to interventions in other fields.

7.6 Conclusions

It is the central argument of this chapter that, according to the evidence available at present, treating surgical newborns yields good cost-effectiveness. In addition, this chapter has gone some way towards explaining that pediatric surgeons are in a position to ethically accept rationing policies. Embracing the idea of fidelity to the patient does not clash with that of stewardship for society's resources.[14] Faced with the reality of economic scarcity, it has to be accepted that cost-effectiveness considerations matter, in neonatal surgery as much as in other branches of medicine.

This chapter has highlighted that the difference between newborns, children, and adults—most particularly the age difference—can have major implications for economic evaluations of health interventions, an issue which until today has received only moderate attention.[84] One point typical of cost-effectiveness analyses of neonatal surgery is that, compared to older patients that enjoy the same HRQoL or even a worse HRQoL, the productivity of health care in terms of QALYs is higher in the case of severely ill neonates, simply because they are younger. In other words: the favorable cost-effectiveness is partly due to newborns' potential to gain many QALYs. On such grounds, cost-effectiveness analyses (i.e., QALY maximization) have been sharply criticized for being ageist, most notably by Harris.[85] It can be disputed however whether such critique is

entirely justified, for, as was shown above, many equity theories precisely require that priority be given to the young and to the most life-threatening diseases.

This is not the answer to all questions, however. One significant problem remains that each of these theories loses its force at some point. For example, it would be senseless to assign all health care interventions a priority ranking according to patients' age, and direct more and more money to those assigned the highest priority (e.g., severely ill young children), no matter its effectiveness or costs. This shows that equity principles should be given effect while taking into account cost-effectiveness arguments. Just as decision makers are expected to weigh efficiency and equity objectives, the different possible equity approaches should be wisely balanced against each other (in a so-called equity-equity tradeoff). How exactly to consider equity in prioritizing health care programs for resource allocation is an issue around which there is at present times not yet any methodological consensus. One point of this discussion however, is fairly clear: we must be willing to sacrifice some overall efficiency for a more equitable distribution of health. Incorporating equity arguments would probably better explain policy decisions in areas where cost-effectiveness analyses have been published.[86] Apparently, decision makers and the public place greater emphasis on equity than is reflected by cost-effectiveness analysis. Importantly, survey findings indicate that politicians are indeed prepared to accept a lower growth in per capita health in exchange for increased equity.[45,87]

Finally, continued efforts are called for to retain the good cost-effectiveness of neonatal surgery and to properly assess cost-effectiveness in the future, with attention to new and advancing research themes such as the position of the parents and discounting. For the moment, it is safe to conclude that neonatal surgery—although met with skepticism by people questioning the high costs of treatment and the possibility of poor HRQoL in the survivors—yields good value for money. It also contributes to an equitable distribution of health and health care.

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Chapter 8

General Discussion: A Guided Tour Providing Four Different Views of the Results

8.1 Introduction

This thesis has focused on the cost-effectiveness of neonatal surgery. Its main conclusion is that neonatal surgery is costly, but worth the expense. This conclusion holds both for the entire treatment processes for two prevalent diagnostic groups (i.e., congenital anorectal malformations (ARM) and congenital diaphragmatic hernia (CDH); Chapters 2 to 4) and for a particular treatment modality (i.e., extracorporeal membrane oxygenation (ECMO); Chapter 5). The encouraging outcomes do not change when the position of the parents is considered (Chapter 6). Neither do they change when it is recognized that arguments other than cost-effectiveness have a role at the social choice level (Chapter 7).

Summarized so briefly, these conclusions seem clear and not open to ambiguous interpretation. Yet, there are many ways to see things. Things may look quite different if alternative perspectives are taken. Therefore, in this final chapter, we would like to invite the reader on an imaginary tour along different perspectives of the results presented in the preceding chapters, with each perspective being useful for different audiences with different needs. Additionally, it can stimulate the different audience groups to remain aware of their own frame of reference and to keep their minds open to other points of view. During the tour, we will stop at four locations, taking the perspectives of, respectively, the child and his or her parents, the pediatric specialist, society and its agents (the decision makers), and the health economics researcher. After having taken the four different perspectives, we will reconsider the main conclusions stated above.

8.2 Perspective 1: The child and his or her parents

The first part of our tour explores the results from the perspective of the patient and his or her parents. The results that will most likely catch the eye of the patient and his or her family include our findings on the mortality attributable to neonatal surgical diseases. Analogous to the observation presented in Chapter 1 that mortality rates for almost all anomalies belonging to the field of neonatal surgery have dropped markedly, mortality rates for ARM were found to be low by now. Of all 179 patients born in the most recent decade (from 1987 to 1996) of the study period of the research described in Chapter 2, 18 (10%) had died. However, we found CDH to be associated with still high mortality rates, despite the many advances in treatment over recent decades (Chapter 3). The mortality rate was 39% (44 out of 114), for example, in the patients born from 1987 to 1996.

When confronted with the birth of a child with a major congenital anomaly, the parents are anxious to know not only whether their child will live, but also what quality of life to expect. For this reason, this thesis set out to study the health-

related quality of life (HRQoL) of survivors of ARM and CDH from childhood to adulthood (Chapter 4). A discussion of the findings of this study is preceded here by the following point, which is that it appeared essential to include various types of outcome measures to gain a full understanding of the long-term outcomes of neonatal surgical diseases—a point equally relevant to the researcher (see further Section 8.5). Each type can capture patient outcomes that the others cannot reveal. A first measure of health includes biological and physiological factors, which focus on the function of cells, organs, and organ systems. Then, an individual may or may not have the perception of an abnormal physical, emotional, or cognitive state (which can be termed 'symptoms'). On another level, there may occur problems in body function or structure, such as loss of vision or loss of a leg. Then, one may want to study physical, social, or emotional functional status, that is, the ability of the individual to perform particular defined tasks. Finally, to estimate the significance to an individual of impairments or limitations in functioning, HRQoL measures should be used—containing physical, mental, and social domains. To convey the full effect of the disease from the perspective of the patient, or the parent on his or her behalf, measuring HRQoL should be an important component of long-term follow-up. The research by Van Deurloo from the Netherlands on esophageal atresia is a noteworthy example of another recent study in neonatal surgery that differentiated between a broad variety of outcome measures.[1] The outcomes studied included esophageal function, gastrointestinal symptoms such as dysphagia or gastroesophageal reflux, limitations in daily life functioning, and generic HRQoL.

Our examination in patients with surgically corrected ARM using different outcome measures produced a mixed picture. The patients appeared to retain substantial residual symptomatology. Their HRQoL was somewhat lower than that of the general population, especially for the youngest patients. Nonetheless, their HRQoL improved considerably with age, beyond the level that we expected a priori. This finding was essentially confirmed in a recent Dutch nationwide study in adult patients with ARM that used the same generic HRQoL questionnaire (SF-36) and arrived at largely the same HRQoL scores.[2] A couple of other recent HRQoL studies in patients with ARM did not include a comparison with a reference group, but studied the effect of new treatment modalities on HRQoL. The results suggest that individualized biofeedback training[3] and artificial bowel sphincter implantation or the gracilis neosphincter procedure[4] can improve patients' HRQoL. These are relevant findings, and more such studies should be carried out with the aim of optimizing the management of this patient group. After all, as this thesis showed, there is room for seeking to improve the HRQoL of especially the youngest patients with ARM.

From a comparison with the general population we found that the patients with CDH experienced disease-specific symptoms such as respiratory difficulties and stomach aches. However, the HRQoL of adolescent and adult CDH survivors could hardly be distinguished from that of the general population. It is interesting to

compare our results with those from a recent HRQoL study in 45 adults born with CDH from Finland, also using the SF-36 questionnaire.[5] The HRQoL of 27% of the patients was considered poor, as their score on one or both SF-36 summary measures was 1 standard deviation lower than the average score found in healthy controls (which exceeded the figure of 16% expected beforehand). We arrived at a somewhat better but quite similar result: 16% of our adult patients with CDH had a score on one or both of the SF-36 summary measures of more than 1 standard deviation below the average reference score. Our study in CDH has not yet been followed by still other similar long-term HRQoL studies. Yet, it remains relevant to follow patients with CDH and to study long-term HRQoL, with the purpose of improving clinical management and informing the patients and their parents. After all, the present adult patients were born decades ago in a time characterized by a survival of the fittest, with the most critically ill patients dying. In the present, it is possible to keep more patients with relatively severe conditions alive, so long-term HRQoL may be poorer than observed in our cohort.

Two additional observations on the follow-up of patients born with surgical diseases may be made. First, in recent years it has been recognized that this group of patients—especially those with major anomalies—requires long-term periodic follow-up, using a multidisciplinary, coordinated approach from surgeons, neonatologists, pediatricians, psychologists, dieticians, and social workers for example.[6] As scientific knowledge advances, follow-up will become even more encompassing. When, for example, information on the (genetic) etiology of the anomalies improves, it will be possible to provide accurate genetic counseling to women who consider pregnancy, which is an increasingly common event in women treated for neonatal surgical diseases. Given that the etiology of the majority of the anomalies treated by pediatric surgeons is considered to be sporadic or multifactorial, genetic counseling is important in enabling risk assessment and focused and timely consultation for prenatal ultrasound, amniotic fluid sampling, etc. Furthermore, a recent advancement is the increasing awareness of the value of preconceptional counseling as an integral part of the care for these former patients and their families. Preconceptional interventions such as folic acid supplement use (to reduce the risk of neural tube defects) or smoking cessation programs have the potential to improve the pregnancy outcome in these women—just as, of course, in all other women of reproductive age.[7,8]

Second, attempts should be made to avoid a circumstance that may particularly hinder follow-up, namely the fact that pediatric surgeons generally lose contact with their patients as they become adults. The patients may continue having their check-ups with the pediatric specialist, but often the care is transferred to 'adult' doctors (e.g., surgeons, urologists, or gynecologists) or the patients 'drop out' of medical follow-up. A recent study in patients with ARM from the Netherlands reported that the follow-up of 34% of the adult patients was transferred from pediatric to adult surgeons. Of these patients, 31% encountered transfer

problems, such as that the expertise of the adult surgeon was insufficient or that is was not possible to find a suitable surgeon.[9] Clearly, ensuring the effective transition from pediatric to adult care needs to be given further thought.[10] Promising examples of such structured collaboration between pediatric and adult doctors are the Erasmus MC Pelvic Floor Center in Rotterdam (the Netherlands), and the LATER (Long-Term Effect Registration) outpatient clinics in pediatric oncology, which is a Netherlands nationwide initiative.

Seeing the results through the eyes of the parents, the findings presented in Chapter 6 will surely catch attention. This chapter considered the issue of parental caregiving for patients born with either ARM or CDH. It studied the caregiving tasks performed and provided evidence of the impact of caregiving on the parents' HRQoL. This thesis did not take the position of the parents for granted, but recognized explicitly that the parents play a critical role in the care for these children, which in our opinion should be given greater weight in cost-effectiveness analyses. In summary, our study found that approximately one third of the parents indicated that their child demanded above-average care. Only a relatively small share of the parents had to forgo paid work or unpaid activities. Nevertheless, the results suggest significant differences between the parents' HRQoL and that of the general population. The study of determining exact HRQoL changes related to caregiving was however not without several measurement and methodological challenges, for example due to the diverse effects associated with caregiving (including positive effects), the difficulty of separating effects of caregiving from 'family effects', the specific characteristics of caregiving in a parent-child relationship, and the parents' uncomfortableness with the survey questions. So, the results only provide a beginning foundation for understanding the HRQoL effect of caregiving for children with neonatal surgical diseases. It would be worth tackling these challenges in future more definitive studies in this area, which are still few in number.

8.3 PERSPECTIVE 2: THE PEDIATRIC SPECIALIST

Continuing our tour, we will now stop at the viewpoint of the pediatric specialist. Reflecting upon the results of this thesis, pediatric surgeons and all others caregivers involved in the management of neonatal surgical diseases (representing the pediatric surgical specialties, general pediatrics, and the pediatric subspecialties) will become aware that the pressure to treat patients cost-effectively increases. There is a growing need to justify health care services on the basis of value for money, as the competition for scarce resources intensifies.[11] If the discipline fails to deliver evidence on the cost-effectiveness of neonatal surgery, it will face a weaker position in allocation decisions. In this era of rising health care costs, especially high-cost technologies such as neonatal surgery are coming under closer scrutiny. Limitations may be placed on some of the most expensive procedures as a way to cut costs. This means it is vital that

physicians should understand and approve of the relevance of economic evaluations. This thesis, most notably Chapters 1 and 7, clarified the relevance of economic analysis by stressing that health care resources are inevitably scarce. By revealing the relationships between costs and effects of medical interventions, cost-effectiveness analyses enable achieving the optimum benefit for the money spent. Hopefully, this thesis has been a step towards allowing pediatric specialists to better understand the basic principles of economic evaluations. It may have helped to avoid the notion that cost-effectiveness analysis is a cost-containment tool rather than a technique to obtain better value for money. Doctors sometimes still see cost-effectiveness analysis as a smokescreen for cost-cutting efforts.[12]

Moreover, this thesis has pleaded that pediatric specialists invite health economic researchers to join them in their research efforts at an early stage. And, the other way around, health economic researchers should welcome pediatric specialists to actively participate in cost-effectiveness studies. This would prevent the undesirable situation of health economics researchers having to collect health economic data such as costs retrospectively, with all the uncertainties that this will bring. It is recommended that pediatric specialists and their departments of pediatric surgery—which all spend fortunes on costly interventions, such as neonatal intensive care, ECMO, and Mother and Child Centers—involve health economics researchers in their activities on a structural basis.

Taking a closer look at the results, the pediatric specialist will see that the cost-effectiveness outcomes in neonatal surgery are generally favorable. One reason for this is that treatment appeared to result in a gain of many life-years or quality-adjusted life years (QALYs). Treating ARM yielded an average gain of 42.2 QALYs (Chapter 2), treating CDH resulted in 46.5 QALYs (Chapter 3), and treatment with ECMO yielded on average 37.8 life-years in CDH patients and 34.4 life-years in meconium aspiration syndrome (MAS) patients (Chapter 5) (all undiscounted). Moreover, we concluded in this thesis that the overall conclusions drawn from our specific investigations most likely apply to neonatal surgery in general.

Nevertheless, this favorable interpretation of the outcomes may not completely reassure the doctor, attending his or her individual patients. This thesis (e.g., Chapter 7) showed that, seen from a societal point of view, both cost-effectiveness and equity arguments generally dictate that relatively high priority be given to neonatal surgery. The good cost-effectiveness, though, will not apply to cases of serious, multiple congenital anomalies. In these cases, costs will be higher, and the number of QALYs to gain smaller than in most of the cases we examined. For example, many of the patients born with multiple congenital anomalies who were part of our cost-effectiveness study in ARM (Chapter 2) had died. The ARM patients with multiple anomalies who survived seemingly brought about above-average costs and had a relatively poor HRQoL. Notice for example that among the patients with the highest direct medical costs were 3 patients

with multiple congenital anomalies described by the acronym VACTERL (vertebral, anal, cardiac, tracheoesophageal, renal, and limb). The direct medical costs were € 51,775, € 50,786, and € 37,385, respectively, which was clearly above the group mean of € 22,082 (Chapter 2). Yet, this thesis did not seek to address this issue in further detail. It is clear however that there was high variability in the data series. In the most serious cases of newborns with birth defects, arguments at the level of individual decision making will prevail arguments relevant at the societal level, like cost-effectiveness and equity considerations—as a matter of fact, both kinds of arguments point largely in the same direction. This could result in the decision to abstain from treatment in selected severely ill newborns, based on principles such as 'primum non nocere'. Thus, decision making on the basis of large numbers and means must not take precedence over the interests of individual cases at the extreme end of the spectrum. Just as an aside: the societal decision maker (see further below) will not agitate against this. Because decision makers mainly focus on high-volume or high-priced treatments, these individual cases, with their relatively low budget impact, are in a sense less relevant to them than the majority picture of neonatal surgery (i.e., the many patients with a surgically correctable anomaly and a reasonably good prognosis).

8.4 Perspective 3: The decision maker

The third place to stop at during this tour is the position of the decision maker, which enables us to view the results from the public policy perspective. Appraising this thesis' results, the decision maker might experience a sense of discomfort. He or she might realize that setting priorities on the basis of explicit criteria, such as cost-effectiveness, can be a politically dangerous course of action. This may tempt him or her towards an implicit approach to priority setting in health care. After all, what is not known cannot be questioned, challenged, probed. An explicit approach has the effect that the resulting decisions will be explicit also for those who suffer from them and this clear identification of the 'victims' may trigger considerable societal protest.[13,14] Yet, this thesis supported the idea that priority setting based on transparent, explicit criteria is preferable. Resource allocation decisions do have to be made, and an explicit approach can be discussed and, if necessary, corrected more easily. It is more likely to bring us closer to achieving a maximum level of efficiency and equity and an optimum balance between these two objectives.

If the decision maker sets aside any such possible objections towards an explicit approach, his or her conclusion has to be that the cost-effectiveness ratios presented in this thesis put neonatal surgery in a good position compared to other interventions that 'society' considers acceptable expenditure of scarce resources. Of course, summarizing the results of an economic evaluation in a single measure and ranking cost-effectiveness ratios in a 'league table' is a perilous undertaking,[15,16] but the relatively favorable cost-effectiveness of

treating ARM (cost per QALY of € 2,482), treating CDH (cost per QALY of € 2,434), and ECMO (cost per life-year of € 3,153 and € 697 in CDH and MAS respectively) is beyond a doubt (see Chapters 2, 3, and 5).

Then however, the decision maker may argue that health policy making entails more than simply ranking cost-effectiveness ratios. Indeed, this thesis recognized that the cost-effectiveness criterion deserves to be given weight, but in almost all policy processes other priority criteria should play important roles (Chapter 7). There are bound to be some cases in which there are compelling reasons for adopting a technology even when the cost-effectiveness criterion is not satisfied, or for rejecting a technology even when it is. Chapter 7 noted that especially equity, which is concerned with the fair distribution of health and health care, needs to be taken into account in health care policy making. In that chapter it was also observed that decision makers and the public seem to place greater emphasis on equity than is currently reflected by cost-effectiveness analysis (i.e., the traditional QALY maximization approach).

Here arises the issue of why decision makers may still be reluctant to use cost-effectiveness analyses. Of course, there are many factors explaining why such analyses currently seem to have a modest impact on health care decision making.[17-20] Among these may be fundamental misunderstandings about resource constraints, a perceived lack of relevance, or a mistrust of the methods among decision makers as well as physicians, coupled with the public's deep-seated distaste of limits.[12] Yet, the concern that cost-effectiveness analysis may lead to an allocation of limited resources that is inequitable seems an important factor hindering the acceptance of cost-effectiveness analysis. If decision makers, together with researchers, would succeed in finding ways to capture these equity concerns, this would considerably enlarge the potential impact of cost-effectiveness analyses. As clarified in Chapter 7, many of the equity approaches presently put forward appeared to focus on age or disease severity, and give high priority to treating the youngest or the sickest patients. Chapter 7 demonstrated at the same time that diverse authors brought up diverse equity approaches, resulting in partly different outcomes of the priority setting process. Which equity approach is morally most defensible and most consistent with societal values and preferences, is far from being a settled issue. There are more questions than answers at this stage. It is an important responsibility for decision makers to make choices regarding the best way to encapsulate equity concerns in economic evaluation, a responsibility that they will have to take on with the help of researchers, and building on the results of further public opinion surveys on the trade-off between equity and cost-effectiveness criteria.

8.5 PERSPECTIVE 4: THE HEALTH ECONOMICS RESEARCHER

We have covered most of our tour. The final view offered is the perspective of the health economics researcher. Looking at the results of this thesis from a research perspective, it attracts attention that evidence on the cost-effectiveness of neonatal surgery was largely lacking in the past, and, to a lesser extent, still is. In Chapter 1, a review by Stolk and colleagues was cited to show that evidence was still rudimentary in the year 2000.[21] The studies presented in this thesis and some other studies brought expansion, but on the whole current evidence remains limited (Chapter 7). Extending the evidence base on the conditions studied in this thesis (ARM, CDH, and, much less, MAS) would be welcome, because, as one reason, the studies in this thesis involved only one country and only one, sometimes two, pediatric centers. Further evidence is all the more needed for the other neonatal surgical diseases, about which this thesis could only hypothesize. Apart from this, economic evaluation is not a one-time exercise, but should be an ongoing effort. Changing patterns of disease and innovations in treatments may render a once cost-effective technology less cost-effective. As Chapter 7 discussed, it is not obvious that current favorable cost-effectiveness ratios in neonatal surgery will remain unchanged. To give an example: when new alternative treatment modalities, such as exogenous surfactant therapy, high-frequency oscillatory ventilation, and inhaled nitric oxide, evolve further, this will have an effect on the cost-effectiveness of ECMO (cf. Chapter 5). To conclude, we should try to get more, and better, data in the future. However, this confronts us with the problem that rigorously designed clinical research is difficult to realize in neonatal surgery, as explained in Chapter 1. It will require the (inter-)national collaboration of pediatric surgical centers, because even the large centers alone do not have the number of patients needed to reach an optimal conclusion. Encouragingly, international collaboration has already started in some areas, such as in CDH (the International CDH Study Group)[22] and in pediatric oncology (under the umbrella of the International Society of Pediatric Oncology (SIOP)).

Then, several methodological issues will attract the attention of the researcher. Among the methodological challenges identified in this thesis on the specific area of neonatal surgery were: the in- or exclusion of future health care costs in added life years (Chapters 2 and 3); measuring productivity losses regarding both paid and unpaid activities, in patients or in caregivers (ibidem); measuring utilities for health states in children (ibidem); more broadly measuring symptom status and HRQoL in infants and children, partly relying on proxies (in particular Chapter 4); costs and effects accruing to the parents (Chapters 2, 3, and 6); discounting (Chapters 2, 3, and 5); tracking patients who underwent treatment many years ago, which bears the possibility of large and/or selective nonresponse (passim); and the consideration of equity when prioritizing health care programs for resource allocation (Chapter 7).

The in- or exclusion of health care costs of unrelated diseases (or: comorbidities) is in our view among the most interesting methodological issues that arose in this study. We restricted the direct medical costs calculated in Chapters 2 and 3 to costs of treating ARM and CDH as much as possible. Similarly, the indirect medical costs were in principle restricted to health care costs related to ARM and CDH. Generally the distinction could be made, but to some degree costs of comorbidities seem to have entered the calculations. One patient for example not only suffered from ARM, but was also treated for an inguinal hernia and for an accessory ear. Treatment of these latter two conditions (among which was a hospital admission) could be discerned well from the treatment of ARM. Another patient—to give another example—was born with both ARM and esophageal atresia. Many cost elements could still be distinguished (e.g., regarding the surgeries and a hospital admission for 24-hour pH measurement), but this was not always possible (e.g., the initial hospital admission will have been longer than normal due to the esophageal atresia). Future empirical studies should offer more insight into this issue, for example highlighting whether comorbidities were relevant and whether is was possible to differentiate their costs. This is particularly relevant in the case of neonatal surgery, because the costs of unrelated diseases could make up a relatively large fraction of the total costs. Moreover, there is a need for more theoretical clarity on this issue, on which opinions differ strongly as already described in Chapter 1. One might argue, for example, that costs of unrelated diseases should be included (only, of course, if this has an effect on the cost difference between the alternatives studied), because these costs are real economic consequences (which requires us to assume that future treatments indeed will be offered). A second argument could be that the remaining life-expectancy and HRQoL are partly a consequence of treating unrelated diseases. Another advantage, for that matter, would be that it avoids the practical difficulty of separating treatment for related and unrelated diseases. The option of including costs of unrelated diseases has been advocated recently.[23-25] For example, a taskforce on good research practices for cost-effectiveness analysis established by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) recommended to collect data on resource use not related to the intervention.[25]

Not only this study, but also others uncovered methodological issues that remain to be addressed. Several reviews, all of recent date, demonstrated that standard health economic methods have their limitations in the special population of pediatric patients. These reviews made clear that pediatric (thus, not only neonatal) health economic evaluation has its unique aspects, as compared to evaluation in adult populations. First, Ungar and Santos developed the Pediatric Quality Appraisal Questionnaire, and assessed the quality of 149 pediatric economic evaluations published from 1980 to 1999.[26,27] Thirty-eight percent of the evaluations were rated as very good to excellent, while 19% were rated as good, and 43% were rated as fair or worse. Whereas some of the deficiencies found were attributable to a lack of rigor in applying general health economic

methods, they also related to the unique challenges of conducting economic evaluations in children. An example of the latter kind was that parental time costs were usually excluded. A second review, by De Civita and colleagues, critically appraised HRQoL studies in pediatric populations from the period 1999 to 2003.[28] The authors conclude that there is no consensus on the conceptual definition of HRQoL as it relates to children. Furthermore, the authors state that insufficient attempts have been made to account for a possible 'response shift' in HRQoL evaluations. Then, the authors show that there are unresolved questions about, inter alia, the proxy issue and about selecting the reference group. Finally, they comment on the techniques used in children to derive 'utilities', which exhibit society's preferences for varying health states and which are used for calculating QALYs. This is close to the topic of a review by Griebsch et al. on 54 cost-utility studies in child health published until 2004[29] and that of two papers by Petrou et al.[30,31] Together these papers seem to justify the following conclusions. For the health state description—the first step necessary to calculate utilities—the children or the parents are increasingly being used, by applying instruments such as the Health Utilities Index (HUI)[32] and the EuroQol EQ-5D.[33] Yet, it may be a problem that such instruments generally are developed for adult populations, so that they may not fully reflect the health dimensions applicable to (very young) children, and that unfortunately no such instrument is available for children younger than 5 years. To add preferences for childhood health states—the other step for calculating utilities—instruments do not include preferences of children but rely on preferences of the adult general public, if societal preferences are used at all.

Another aspect that has received little attention so far is the incorporation of the beneficial impact of interventions in neonatal and pediatric medicine on parental utility in economic evaluations. Assuming that people altruistically care about others' health, it might be appropriate to incorporate the (health and non-health) effects of improvements in patients' health on the welfare of individuals other than the patient such as the parents, which effects can be termed 'spillover effects' or 'externalities'.[34-36] Today's methods of health economic evaluation do not take these effects into account. For neonatal surgery, this might be even more relevant than it may be in general, considering newborns' dependence on parents, requiring comprehensive support to meet all their basic needs, and the severity of the patients' diseases. Note that this would be different from, and complimentary to, incorporating costs that fall to the parents (such as productivity costs) and parental health effects of caregiving, and from addressing equity in the distribution of health care as discussed in Chapter 7.

As emerges from the foregoing discussion, the following general conclusion can be drawn from the perspective of the health economics researcher. Not until very recently has it been acknowledged that the uniqueness of the pediatric population can have important implications for economic evaluations in children, adding complexities to the standard methodological toolbox.[37] There is broad variation in

the methods used, for example, to assess the costs related to work absence by parents and other caregivers, to measure future productivity costs of children, to evaluate children's HRQoL, and to measure utilities and calculate QALYs in children. Methods of these and other components of pediatric economic evaluations merit further research.

8.6 Concluding remarks

We have reached the end of our guided tour, which was aimed at seeing the results from a variety of perspectives. This short tour could by no means cover all this thesis' results. We selected some topics, while setting aside others. Important issues were treated rather summarily. Still, we should now be able to reconsider the main message of this thesis stated at the beginning of this chapter. This comes down to answering the question of whether the results depend on the perspective chosen. What is being argued here is that the results are firmly in favor of neonatal surgery, and not merely a matter of perspective. The analysis presented in this chapter confirmed that the child and his or her parents, the pediatric specialist, the decision maker, and the health economics researcher have different perspectives. Somewhat different aspects of the results may attract attention from each of these perspectives. Yet, if we try to arrive at a common conclusion, the general tenor of it is favorable for neonatal surgery. Generally speaking, the common conclusion would read as follows.

This thesis approached the question of the balance between the costs and effects of neonatal surgery and that of the balance between the cost-effectiveness argument and other arguments in health care allocation debates—a matter of balance indeed. The results revealed that neonatal surgery yields good cost-effectiveness. However, this conclusion should be tempered with a fourfold caveat, as can be derived from the guided tour described in this chapter. First, the favorable cost-effectiveness may not be true in each and every case: the good results may not be valid in the exceptional cases of patients born with severe multiple anomalies. Second, further advancements in the care of patients with ARM or CDH remain wanted: the mortality and HRQoL outcomes of these patients appeared imperfect, leaving room for improvement. Third, expanding the knowledge of the cost-effectiveness of neonatal surgery would still be welcome, the road to which has to involve upgrading the methodology of economic evaluations in pediatric populations. This especially applies to neonatal surgical diseases other than ARM and CDH, on which this thesis offered only rather speculative conclusions. Fourth, cost-effectiveness is not all that counts: conflicts between the moral claims of efficiency and equity may arise, and when allocating resources, trade-offs between them must be made. This should be recognized especially for neonatal surgery, as equity arguments (considering the patients' age and disease severity) and ethical arguments at the level of individual decision making may be powerful. Despite these reservations, this thesis represents a

novel contribution to the literature on the cost-effectiveness of neonatal surgery. Given today's importance of taking account of cost-effectiveness issues, the integral involvement of health economics researchers in the activities of pediatric surgical departments needs to be assured. As follows from the work detailed in this thesis: neonatal surgery simply cannot afford, in the current world, not to keep a careful check on the cost-effectiveness of its operations.

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Gloss.

GLOSSARY

Charge (or: tariff)

A price imposed on health care goods or services. Economic evaluations often use charges (set by the market place or by regulation) as a proxy for costs. Yet, charges may bear little resemblance to real economic costs.

Comparator

The intervention against which the intervention under appraisal is compared. The comparator can be existing clinical practice or 'no treatment', for example.

Cost-effectiveness analysis

A term often applied to a specific type of economic evaluation in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (e.g., reduction of blood pressure, heart attacks avoided, life-years gained, deaths avoided). In this thesis however, it is used as a synonym for economic evaluation. See 'Economic evaluation'.

Cost-effectiveness ratio

The main outcome measure of economic evaluations—expressed as monetary cost per unit of outcome, such as cost per life saved, cost per QALY, or cost per life-year—used to assist in comparisons among programs. The cost-effectiveness ratio is calculated as the difference in the costs of the intervention under appraisal and the costs of the comparator, divided by the difference in the effects.

Cost-effectiveness threshold

A certain cost-effectiveness ratio (such as cost per QALY of $ 30,000) against which evidence from economic evaluations is compared. Decision makers will use the 'threshold' cost-effectiveness ratio to make judgments about the cost-effectiveness of health technologies. If a technology's cost-effectiveness is below the cost-effectiveness threshold, its probability of acceptance increases.

Cost per life saved (or: cost per additional survivor)

An example of a cost-effectiveness ratio. See 'Cost-effectiveness ratio'.

Cost per life-year (gained)

An example of a cost-effectiveness ratio. See 'Cost-effectiveness ratio'.

Cost per QALY (gained)

An example of a cost-effectiveness ratio. See 'Cost-effectiveness ratio'.

Cost-utility analysis

A specific type of economic evaluation that measures consequences of different interventions in units of utility or preference, often as QALYs.

Direct medical costs (or: direct health care costs)

Fixed and variable health care costs associated directly with a health care intervention (e.g., costs of drugs and physician salaries).

Direct nonmedical costs (or: direct non-healthcare costs)

Costs incurred outside the health care sector that accrue to patients and their families while receiving health care. For example: transportation costs for visiting health care providers.

Discounting

Conversion of future costs and effects into equivalent present values, done because costs and effects occurring in the future have a lower value than costs and effects incurred today (independent of inflation). Discounting reflects people's preference for benefits to be experienced in the present rather than in the future and the preference for costs to be experienced in the future rather than in the present.

Economic evaluation

The comparative analysis of alternative courses of action in terms of both their costs and consequences. The three main forms of economic evaluation are cost-benefit analysis, cost-effectiveness analysis, and cost-utility analysis.

Equity

Fairness in the distribution of resources or benefits among different individuals or groups.

Equity-efficiency trade-off

Decision makers, as well as the general public, are not only concerned with maximizing society's overall health (efficiency), but also with how health gains are distributed (equity; mainly due to aversion of inequality). An efficient distribution of health may discriminate against the poor, the elderly, or those in poorest health. A fair distribution, however, is not necessarily the most

efficient one. We are therefore faced with a trade-off between equity and efficiency.

Functioning

An outcome measure that reflects any loss or abnormality of physical, social, or emotional functioning. In other words, this term qualifies functional status, that is, the ability of the individual to perform particular defined tasks. To be distinguished from outcomes such as biological and physiological factors, symptoms, body function or structure (such as loss of vision or loss of a leg), and health-related quality of life.

Health-related quality of life (HRQoL)

A combination of physical, mental, and social aspects of a patient's well-being that are relevant and important to the patient. Restricted to aspects of quality of life that are likely to be influenced by health interventions. Measuring HRQoL is different from, and thus should be distinguished from, measuring outcomes such as biological and physiological factors, symptoms, body function or structure, and functioning.

Indirect medical costs (or: indirect health care costs)

Health care costs made after the period that refers to the direct medical costs. Two categories of indirect (or: future) medical costs may be distinguished: costs of clinically related diseases and costs of other, unrelated diseases (co-morbidities).

Indirect nonmedical costs (or: indirect non-healthcare costs)

Costs associated with production loss and replacement caused by illness, disability, and death of productive persons, both paid and unpaid. Indirect nonmedical costs are also referred to as productivity costs.

Informal care

Care provided to disabled people by relatives and friends who are not paid for the help they provide.

Perspective in economic evaluation

The viewpoint from which an economic evaluation is performed. It may be that of the patient, hospital, health care system, government, or society. The societal perspective is the preferred perspective in economic evaluation. This implies that all costs and effects of a studied intervention should be taken into account, irrespective of to whom they accrue.

Quality-adjusted life-year (QALY)

An index of survival adjusted for the patient's health-related quality of life (valued on a utility scale). QALYs have the advantage of combining, in a single measure, gains or losses in both quantity and quality of life. The QALY measure applies to all individuals and all diseases, thereby enabling comparisons across diseases and across programs.

Rationing

Any policy that causes some patients to forgo medically beneficial treatment, regardless of their ability or willingness to buy it. Rationing is inevitable because providing unrestricted access to all medically useful services from shared resources would be unaffordable.

Scarcity

The study of the allocation of scarce goods among competing ends. Scarcity means not having sufficient resources to produce enough to fulfill unlimited subjective wants, which implies that different goods must be traded off against each other. Note that this economic definition of scarcity differs from the notion of scarcity in ordinary language, according to which resources are called scarce when their availability falls below some threshold.

Sensitivity analysis

A process through which the robustness of the cost-effectiveness analysis is assessed. Sensitivity analysis involves varying key variables over plausible ranges to determine to what extent certain assumptions underlying the calculations influenced the results. Thus, it examines the impact of uncertainty in the analysis.

Symptom

A patient's perception of an abnormal physical, emotional, or cognitive state. To be distinguished from outcomes such as biological and physiological factors, body function or structure, functioning, and health-related quality of life.

Utility

A measure of the strength of an individual's preference for a given health state in relation to alternative health states. A utility scale assigns numerical values on a scale calibrated from 0 (worst imaginable health state) to 1 (best imaginable health state).

Sum.

Summary

This thesis addresses the cost-effectiveness of neonatal surgery. Beginning after the Second World War, neonatal surgery has been making enormous progress. Mortality rates for the majority of anomalies belonging to the field fell from almost 100% to less than 10%. Contemporaneously with these medical advancements came new and pressing dilemmas. First, survival is of course an important measure of success, but improved survival might come at the price of poor health-related quality of life (HRQoL) in later life. Second, the economic consequences of health care have become larger, in an era where budgetary restrictions are becoming tighter. As in other branches of medicine, medical advancements contributed to increasing costs in neonatal surgery as well. It is against this background of concerns about the HRQoL of the surviving infant and the increasing costs associated with neonatal surgery that the need for information about the cost and effects of neonatal surgery was recognized. This thesis directly emerges from these concerns, as explained in Chapter 1. This chapter, which introduces and motivates this thesis, also explains why costs should be considered in health care, and clarifies that we will not be able to offer certain medical practices that are known to have favorable effects, but whose effects are too small to justify the cost. It highlights the relevance of cost-effectiveness analyses of health care, which aim at establishing whether the effects of a given treatment are worth the budget needed, compared to an alternative treatment. For the case of neonatal surgery, results from cost-effectiveness analyses would make it possible to counteract critiques leveled against the discipline. Neonatal surgery has been criticized with arguments of cost-effectiveness: the high costs of an operation have been feared to come with low HRQoL after survival. Clearly, the current lack of evidence on the cost-effectiveness of neonatal surgery is a main problem worth tackling. It threatens to give the discipline a weaker position in health care allocation decisions.

This study's main objective is to collect evidence on the cost-effectiveness of neonatal surgery and to place this evidence in its proper context. The explicit intention is to include a large group of newborns, to adopt a long-term time horizon since treatment may have impacts on cost and outcomes basically over a patient's life time, and to study a wide range of relevant costs and effects. So, the study does not focus exclusively on the health care costs during the initial hospitalization, as earlier studies often did. Yet, a wide range of other cost categories is assessed, including direct non-healthcare costs (such as out-of-pocket expenses), indirect health care costs (future costs in added life-years), and indirect non-healthcare costs (productivity costs). Furthermore, the time horizon will be sufficiently long to capture all significant effects. After all, many of the most important outcomes of neonatal surgery, such as language or cognitive abilities, educational attainment, and adult employment status, are developmentally programmed to occur years if not decades after the intervention. Also, to gain a full understanding of the long-term outcomes of neonatal surgical diseases, we will include various outcome measures, such as measures of symptomatology and HRQoL, and not only traditional ones such as avoided

mortality. Finally, it is intended to consider not only the costs and effects occurring to the patients themselves but also those to the parents, whose position must not be ignored in cost-effectiveness studies of neonatal surgery. Caring for a child with a major congenital anomaly may have a negative influence on the parents' HRQoL. Also, caregiving may take the parents significant amounts of time, and may be associated with high out-of-pocket expenses and costs associated with production losses. Quantitative data to support these perceptions are however largely lacking in neonatal surgery. Besides its aim to present evidence on the cost-effectiveness of neonatal surgery, this thesis can serve as an introduction into cost-effectiveness analyses to pediatric surgeons. It will give them the opportunity to become acquainted with the principles of cost-effectiveness analysis.

Chapter 2 presents a full economic evaluation of neonatal surgery and subsequent treatment for congenital anorectal malformations (ARM). Using the technique of cost-utility analysis, the costs and effects of treatment of patients with ARM are compared to 'no treatment'. Total costs of treatment are calculated at € 31,593, mainly consisting of direct and indirect medical costs. ARM patients after surgical correction suffer considerable stool difficulties and their medical consumption is relatively high. The EQ-5D questionnaire, however, shows that the HRQoL of ARM patients is only slightly lower than that of the general population (0.88 *v* 0.93). Treatment results in a gain of 12.7 quality-adjusted life years (QALYs). Cost-effectiveness (cost per QALY of € 2,482) is good.

Chapter 3 contains a cost-utility analysis of treatment for congenital diaphragmatic hernia (CDH), closely resembling the methods used in Chapter 2. Total costs—for the most part initial hospitalization costs and indirect medical costs—average € 42,658. Productivity losses in both the patients and their caregivers appear to be minor. Former CDH patients suffer from respiratory difficulties and stomach aches, even at adult age. According to the EQ-5D, however, their HRQoL does not differ from the general population, suggesting that these symptoms barely affect overall HRQoL. Treatment yields a gain of 17.5 QALYs. Costs per QALY amount to € 2,434, which indicates good cost-effectiveness.

Chapter 4 covers an in-depth analysis of the short-term and long-term HRQoL of survivors of ARM or CDH. The patients or their parents are administered symptom checklists and generic HRQoL instruments to find out how the patients are doing compared to the general population. Many patients appear to retain substantial residual symptomatology into adulthood. In the youngest ARM patients (aged 1–4 years), generic HRQoL is severely affected, but the older ARM patients show better HRQoL. In the CDH patients, the influence of symptoms on HRQoL seems less profound. The instruments used reveal little difference between adults treated for ARM or CDH and the general population. These results show that for these two neonatal surgical procedures, improved survival does not come at the

expense of poor HRQoL in adulthood. Even though there is considerable suffering in terms of both morbidity and mortality in the youngest group, the vast majority of the patients ultimately enjoy healthy lives.

We then examine the cost-effectiveness of neonatal extracorporeal membrane oxygenation (ECMO), an intervention the cost-effectiveness of which probably has been questioned more than that of any other intervention in neonatal surgery (Chapter 5). A nation-wide population of 244 consecutive ECMO-treated newborns born between 1991 and 2001 with a diagnosis of CDH or meconium aspiration syndrome (MAS) is compared to a historical control group of patients with CDH or MAS who would have been eligible for ECMO, were it available at the time. Mean direct medical costs for treatment including ECMO amount to € 38,553 per patient, those for a patient with CDH (€ 50,792) being considerably higher than that for a patient with MAS (€ 29,472). Costs of treatment of patients in the control group are comparatively low with an average of € 17,300. For CDH patients, the survival rate is 0.04 without ECMO and 0.52 with ECMO. For MAS patients, survival without ECMO is 0.50, as compared to 0.94 in the ECMO era. Costs per additional survivor are € 78,455, or € 3,153 per life-year gained, in the patients with CDH. For the patients with MAS, costs per additional survivor are calculated at € 17,287, or € 697 per life-year gained. These findings indicate that ECMO improves survival in selected severely ill newborns suffering from CDH or MAS, and that it does so at reasonable cost.

Chapter 6 goes on to consider the position of the parents of children who as newborns underwent treatment for ARM or CDH. It is investigated what it takes to care for these children (aged 1–11 years) and whether caregiving has an effect on the parents' HRQoL, encompassing physical, mental, and social domains. Approximately one third of the parents indicates that their child demands above-average care. They mention activities such as giving enemas and changing diapers (ARM patients), or giving extra attention and administering medication (CDH patients). Relatively small shares of the parents have to forgo paid work or unpaid activities. Using the EQ-5D, the parents' HRQoL is found to be relatively low compared with population statistics, especially in the parents of children with ARM and in mothers. Interestingly, on average the parents consider that their HRQoL would not be substantially better when someone else would take over their caregiving activities.

Chapter 7 returns to the issue of the relevance of cost-effectiveness analyses in neonatal surgery, already touched upon in Chapter 1. It is argued that pediatric surgeons are in a position to ethically accept rationing policies. Moreover, examining the state of the art in this area, it is found that the number of published cost-effectiveness studies in the field of neonatal surgery is still small. A literature review over the period 1999 through 2005 identifies no more than 11 relevant studies. Then, we generate insights into how cost-effectiveness interacts with other relevant determinants of how much priority should be given to

neonatal surgery. It is shown that crucial ethical questions may arise, for example, when deciding whether therapy should indeed be offered or perhaps withheld, which often involves life-and-death decisions. More from a policy perspective rather than the perspective of individual medical decision making, there are yet other factors that play a role in determining how much priority neonatal surgery should be accorded in comparison and competition with other areas of health care. Most crucial among these factors other than cost-effectiveness seem arguments of equity, which reflect the feeling that the use of cost-effectiveness analysis (in the sense of QALY maximization) may lead to unfair distribution of health care. Issues like these have received hardly any attention so far in the literature on neonatal surgery. Nevertheless, given their high impact, it would be of interest to analyze how equity considerations would work out for the case of neonatal surgery, or, in other words, whether or not they add weight to the outcomes of cost-effectiveness analyses of neonatal surgery. Chapter 7 demonstrates that—although it is far from a settled issue how exactly to consider equity when prioritizing health care programs for resource allocation—one of the equity dimensions that seem not to be sufficiently accounted for in cost-effectiveness analyses, is the age of the patient. Most studies consulting the public presented evidence that a life saved, QALYs gained, or a year of perfect life are valued more when they occur to the young than to the old. Yet, while the young are generally preferred over the older, newborns are sometimes not given priority over slightly older children. It is concluded that, because many equity approaches require that high priority be given to treating the young or those with the most severe diseases, QALYs gained in newborns suffering from life-threatening anomalies have a relatively high value.

Finally, Chapter 8 draws together the results presented in the various chapters. It starts with this thesis' main conclusion that neonatal surgery is costly, but worth the expense. Yet, the results can be viewed from different perspectives, with each perspective being useful for different audiences with different needs. Consequently, the reader is invited on an imaginary tour, which aims at looking at this thesis' results from the perspectives of, respectively, the child and his or her parents, the pediatric specialist, society and its agents (the decision makers), and the health economics researcher. It appears that, from each of these perspectives, somewhat different aspects of the results may attract attention. Still, the results are firmly in favor of neonatal surgery, and not merely a matter of perspective. To sum up: this thesis approaches the question of the balance between the costs and effects of neonatal surgery and that of the balance between the cost-effectiveness argument and other arguments in health care allocation debates—a matter of balance indeed. The results reveal that neonatal surgery yields good cost-effectiveness. However, this conclusion should be tempered with a fourfold caveat. First, the favorable cost-effectiveness may not be true in each and every case: the good results may not be valid in the exceptional cases of patients born with severe multiple anomalies. Second, further advancements in the care of patients with ARM or CDH remain wanted:

the mortality rates and HRQoL outcomes in these patients appeared imperfect, leaving room for improvement. Third, expanding the knowledge of the cost-effectiveness of neonatal surgery would still be welcome, the road to which has to involve upgrading the methodology of economic evaluations in pediatric populations. This especially applies to neonatal surgical diseases other than ARM and CDH, on which this thesis offered only rather speculative conclusions. Fourth, cost-effectiveness is not all that counts: conflicts between the moral claims of efficiency and equity may arise, and when allocating resources, trade-offs between them must be made. This should be recognized especially for neonatal surgery, as equity arguments (considering the patients' age and disease severity) and ethical arguments at the level of individual medical decision making may be powerful. Despite these reservations, this thesis represents a novel contribution to the literature on the cost-effectiveness of neonatal surgery. Given today's importance of taking account of cost-effectiveness issues, the integral involvement of health economics researchers in the activities of pediatric surgical departments needs to be assured. As follows from the work detailed in this thesis: neonatal surgery simply cannot afford, in the current world, not to keep a careful check on the cost-effectiveness of its operations.

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SAMENVATTING

Dit proefschrift gaat over de kosteneffectiviteit van neonatale chirurgie, oftewel over de kosteneffectiviteit van operaties bij pasgeborenen. Na de Tweede Wereldoorlog heeft de neonatale chirurgie enorme vooruitgang geboekt. Dit blijkt vooral uit het feit dat het sterftepercentage voor de meeste aandoeningen in dit vakgebied is gedaald van vrijwel 100 procent tot minder dan 10 procent. Tegelijkertijd met de medische vooruitgang ontstonden er geleidelijk nieuwe dilemma's. In de eerste plaats is de mate van overleving uiteraard een belangrijke maatstaf voor succes, maar de hogere overlevingskans zou gepaard kunnen gaan met een slechte gezondheidsgerelateerde kwaliteit van leven. In de tweede plaats brengt de gezondheidszorg steeds grotere economische consequenties met zich mee, in een tijd waarin de druk op het budget groter wordt. Net als bij andere takken van de geneeskunde, heeft de medische vooruitgang ook in de neonatale chirurgie tot hogere kosten geleid. Tegen deze achtergrond van enerzijds bezorgdheid over de kwaliteit van leven van kinderen die hun aandoening overleven en anderzijds de toenemende kosten van de behandelingen, is er behoefte ontstaan aan inzicht in de kosten en effecten van neonatale chirurgie. Zoals in Hoofdstuk 1 wordt uitgelegd, vloeit dit proefschrift rechtstreeks voort uit bovengenoemde overwegingen. Behalve dat dit hoofdstuk dit proefschrift inleidt en de motivatie ervoor verstrekt, wordt uitgelegd waarom kosten een overweging zouden moeten vormen bij besluitvorming in de gezondheidszorg. Het maakt ook duidelijk dat we bepaalde medische interventies, waarvan bekend is dat ze gunstige effecten hebben maar waarvan de effecten te klein zijn om de kosten te rechtvaardigen, niet kunnen aanbieden. Voorts benadrukt dit hoofdstuk de relevantie van kosten-effectiviteitsanalyses in de gezondheidszorg, die beogen vast te stellen of de effecten van een bepaalde behandeling het benodigde budget waard zijn, vergeleken met een alternatieve behandeling. In het geval van de neonatale chirurgie zou de beschikbaarheid van resultaten van kosten-effectiviteitsanalyses de kritiek die geuit is tegen het vakgebied wellicht kunnen weerleggen. Er zijn immers argumenten op het gebied van kosteneffectiviteit aangevoerd: men vreest wel dat de hoge kosten van een operatie gepaard gaan met een lage kwaliteit van leven bij de kinderen die overleven. Het moge duidelijk zijn dat het nu nog ontbreken van bewijs voor de kosteneffectiviteit van neonatale chirurgie een groot probleem is dat aandacht verdient. Het dreigt het vakgebied een zwakkere positie te bezorgen bij de allocatie van middelen in de gezondheidszorg.

Het hoofddoel van dit onderzoek is gegevens over de kosteneffectiviteit van neonatale chirurgie te verzamelen en in het juiste perspectief te plaatsen. Het is de bedoeling om grote groepen pasgeborenen te bestuderen en een lange tijdshorizon te hanteren, aangezien de behandelingen kosten en effecten tot gevolg kunnen hebben gedurende praktisch het hele verdere leven van de patiënten. Voorts wordt een groot scala aan relevante kosten en effecten onderzocht. Dit onderzoek beperkt zich niet tot de medische kosten rondom de eerste opname van het kind, wat wel vaak het geval was in eerder onderzoek door anderen. Integendeel, diverse andere kostencategorieën worden bekeken,

zoals directe niet-medische kosten (bijkomende uitgaven, bijvoorbeeld voor vervoer naar het ziekenhuis), indirecte medische kosten (toekomstige medische kosten in gewonnen levensjaren) en indirecte niet-medische kosten (productiviteitskosten). Voorts wordt er een tijdshorizon gekozen die lang genoeg is om alle relevante effecten van neonatale chirurgie te includeren. Belangrijke uitkomstmaten, zoals taalvaardigheid, cognitieve ontwikkeling, vorderingen op school en arbeidsparticipatie, zijn immers pas jaren, zo niet decennia na de behandeling meetbaar. Teneinde een volledig beeld te krijgen van de uitkomsten op lange termijn wordt overigens gebruikgemaakt van verschillende uitkomstmaten, zoals symptomen en kwaliteit van leven, en niet alleen van traditionele maten, zoals vermeden sterfte. Bovendien worden niet alleen de kosten en effecten die aan de patiënt toevallen beoordeeld, maar ook die welke betrekking hebben op de ouders. De positie van de ouders kan immers niet buiten beschouwing blijven bij kosten-effectiviteitsonderzoek van neonatale chirurgie. De zorg voor een kind met een ernstige aangeboren afwijking zou een negatieve invloed kunnen hebben op de kwaliteit van leven van de ouders. Deze zorg kan de ouders ook veel tijd kosten, en er kunnen hoge uitgaven voor eigen rekening mee zijn gemoeid, evenals kosten door productiviteitsverlies. Dit zijn evenwel veronderstellingen waar nauwelijks kwantitatieve gegevens ter onderbouwing voor beschikbaar zijn. Hoofdstuk 1 bevat ten slotte de opmerking dat dit proefschrift, afgezien van het doel bewijs te leveren voor de kosteneffectiviteit van neonatale chirurgie, kinderchirurgen bij wijze van inleiding de gelegenheid biedt zich vertrouwd te maken met de beginselen van kosten-effectiviteitsanalyses.

Hoofdstuk 2 presenteert een volledige economische evaluatie van chirurgische ingrepen en de verdere behandeling van pasgeborenen met congenitale anorectale misvormingen (CAM). Door middel van een kosten-utiliteitsanalyse worden de kosten en effecten hiervan vergeleken met 'niets doen'. De totale kosten per patiënt bedragen gemiddeld € 31.593, waarvan directe en indirecte medische kosten het grootste deel uitmaken. Na de chirurgische correctie hebben deze patiënten vaak nog grote problemen met de stoelgang, en hun medische consumptie is naar verhouding hoog. Aan de hand van de EQ-5D-vragenlijst blijkt echter dat hun kwaliteit van leven maar iets lager is dan die onder de algemene bevolking (0,88 versus 0,93). Het wel behandelen geeft een winst van 12,7 'voor kwaliteit van leven gecorrigeerde levensjaren' (QALY's). Gezien de kosten per QALY van € 2.482, is de kosteneffectiviteit goed te noemen.

Hoofdstuk 3 betreft een kosten-utiliteitsanalyse van de behandeling van congenitale hernia diafragmatica (CHD), vrijwel overeenkomstig de methoden die in Hoofdstuk 2 worden gebruikt. De totale kosten per patiënt—in dit geval hoofdzakelijk voor de eerste ziekenhuisopname en indirecte medische kosten—zijn gemiddeld € 42.658. Er blijkt slechts gering productiviteitsverlies te zijn, voor zowel de voormalige patiënten als hun ouders. Voormalige CHD-patiënten vertonen ademhalingsproblemen en maagklachten, zelfs nog op volwassen

leeftijd. Uit de EQ-5D-vragenlijst blijkt echter dat hun kwaliteit van leven niet verschilt van die onder de algemene bevolking, wat doet vermoeden dat deze symptomen daar nauwelijks invloed op hebben. Behandeling levert een winst op van 17,5 QALY's. De kosten per QALY bedragen € 2.434, hetgeen wijst op een goede kosteneffectiviteit.

Hoofdstuk 4 geeft een diepgaande analyse van de kwaliteit van leven op de korte en lange termijn van voormalige patiënten met CAM of CHD. Aan de hand van symptomenchecklists en generieke kwaliteit-van-leveninstrumenten (sommige voor de patiënten, sommige voor de ouders) ontstaat een indruk van hun situatie in vergelijking tot die onder de algemene bevolking. Veel voormalige patiënten blijken aanzienlijke symptomen te houden tot op de volwassen leeftijd. De jongste CAM-patiënten (1–4 jaar) vertonen een relatief slechte generieke kwaliteit van leven, maar voor de oudere CAM-patiënten is deze beter. Bij de CHD-patiënten lijkt de invloed van symptomen op de kwaliteit van leven minder ver te strekken. Aan de hand van de gebruikte instrumenten blijkt er weinig verschil te zijn tussen volwassenen die als pasgeborenen voor CAM of CHD zijn geopereerd en de algemene bevolking. De resultaten van deze studie laten zien dat voor deze twee ingrepen op het gebied van de neonatale chirurgie de verbeterde overleving niet gepaard gaat met een slechte kwaliteit van leven op volwassen leeftijd. Ofschoon er bij de jongste patiënten sprake is van aanzienlijk lijden, zowel qua morbiditeit als qua mortaliteit, leidt het overgrote deel van de patiënten uiteindelijk een gezond leven.

Vervolgens komt in Hoofdstuk 5 de kosteneffectiviteit van extracorporale membraanoxygenatie (ECMO) bij neonaten aan de orde. Dit is een techniek waarvan de kosteneffectiviteit waarschijnlijk meer dan die van enige andere interventie op het gebied van de neonatale chirurgie in twijfel is getrokken. Een groep van 244 opeenvolgende neonaten geboren tussen 1991 en 2001 die met ECMO werden behandeld voor CHD of meconiumaspiratiesyndroom (MAS) wordt vergeleken met een controlegroep van kinderen met CHD of MAS uit een vroegere periode die in aanmerking zouden zijn gekomen voor ECMO als het destijds beschikbaar was geweest. De gemiddelde directe medische kosten voor behandeling inclusief ECMO bedragen € 38.553 per patiënt, waarbij de kosten voor een CHD-patiënt (€ 50.792) aanzienlijk hoger zijn dan die voor een MAS-patiënt (€ 29.472). De behandelingskosten van de patiënten uit de controlegroep zijn naar verhouding laag, met een gemiddelde van € 17.300. Voor CHD-patiënten is de overlevingskans 0,04 zonder ECMO (controlegroep) en 0,52 met ECMO. Voor MAS-patiënten is de overlevingskans zonder ECMO 0,50, tegen 0,94 in het ECMO-tijdperk. De kosten per additionele overlevende bedragen € 78.455, of € 3.153 per gewonnen levensjaar, in het geval van CHD. Voor de MAS-patiënten bedragen de kosten per additionele overlevende € 17.287, of € 697 per gewonnen levensjaar. Deze bevindingen wijzen erop dat ECMO-behandeling de overlevingskans verhoogt van bepaalde, ernstig zieke pasgeborenen met CHD of MAS, en dat tegen redelijke kosten.

Hoofdstuk 6 gaat vervolgens in op de situatie van de ouders van kinderen die als pasgeborenen werden behandeld voor CAM of CHD. Er wordt onderzocht wat de verzorging van deze kinderen (1–11 jaar) met zich meebrengt en of dit van invloed is op de kwaliteit van leven van de ouders, bestaande uit lichamelijke, mentale en sociale domeinen. Ongeveer een derde van de ouders geeft aan dat hun kind bovengemiddelde verzorging nodig heeft. Zij vermelden hierbij activiteiten zoals het aanleggen van klysma's en het verschonen van luiers (in het geval van CAM), of het geven van extra aandacht en het toedienen van medicatie (in het geval van CHD). Betrekkelijk weinig ouders hebben betaald werk of onbetaalde activiteiten moeten opgeven. Uit de EQ-5D blijkt de kwaliteit van leven van de ouders betrekkelijk laag te zijn in vergelijking met cijfers voor de algemene bevolking, met name voor de ouders van kinderen met CAM en voor de moeders. Interessant is dat de ouders in het algemeen van mening zijn dat hun kwaliteit van leven niet aanzienlijk beter zou zijn als iemand anders hun verzorgende taken zou overnemen.

Hoofdstuk 7 keert terug naar het onderwerp van de relevantie van kosten-effectiviteitsanalyses van neonatale chirurgie, dat reeds werd aangeroerd in Hoofdstuk 1. Er wordt beargumenteerd dat kinderchirurgen in een positie verkeren waarin ze ethisch gezien rationeringsbeleid kunnen accepteren. Verder blijkt uit een verkenning van de 'state of the art' op het gebied van de neonatale chirurgie dat het aantal gepubliceerde kosten-effectiviteitstudies nog maar klein is. Een literatuurstudie over de periode 1999 tot en met 2005 levert niet meer dan 11 relevante studies op. Voorts verstrekken we inzicht in de wijze waarop kosteneffectiviteit in wisselwerking staat met andere relevante determinanten van de prioriteit die aan neonatale chirurgie zou moeten worden gegeven. We laten zien dat er sprake kan zijn van cruciale ethische vraagstukken, bijvoorbeeld als er dient te worden besloten of een therapie inderdaad moet worden aangeboden of misschien wel achterwege moet blijven. In zulke gevallen gaat het vaak om vragen van leven en dood. Er zijn bovendien nog andere factoren die een rol spelen bij het nemen van beslissingen over hoeveel prioriteit zou moeten worden verleend aan neonatale chirurgie in vergelijking en competitie met andere gebieden in de gezondheidszorg. Deze factoren liggen meer op het vlak van de maatschappelijke beleidsvorming dan op het vlak van de medische besluitvorming voor individuele gevallen. Afgezien van de kosteneffectiviteit lijken rechtvaardigheidsargumenten van doorslaggevend belang te zijn. Deze argumenten vormen een weerslag van de idee dat de toepassing van kosten-effectiviteitsanalyses (in de zin van QALY-maximalisatie) een oneerlijke verdeling van gezondheidszorg tot gevolg kan hebben. Aan dit soort zaken is tot nu toe nauwelijks aandacht besteed in de literatuur over neonatale chirurgie. Gezien hun grote impact is het niettemin van belang om te analyseren hoe rechtvaardigheidsoverwegingen zouden uitwerken op het geval van de neonatale chirurgie (met andere woorden: of ze al dan niet extra gewicht geven aan de uitkomsten van kosten-effectiviteitsanalyses). Hoofdstuk 7 laat zien dat—alhoewel het nog lang niet is uitgemaakt hoe rechtvaardigheid precies moet

worden meegewogen bij het prioriteren van gezondheidszorgprogramma's—een van de dimensies van rechtvaardigheid die nog niet voldoende lijken te zijn verdisconteerd in kosten-effectiviteitsanalyses, de leeftijd van de patiënt is. De meeste studies waarin naar de mening van het publiek werd gevraagd wekken de indruk dat aan een gered leven, gewonnen QALY's of een jaar in perfecte gezondheid een hogere waarde wordt toegekend als zij ten goede komen aan jonge mensen in plaats van aan ouderen. Echter, ondanks dat in het algemeen jongeren de voorkeur genieten boven ouderen, krijgen pasgeborenen soms toch geen prioriteit boven iets oudere kinderen. Omdat bij de toepassing van rechtvaardigheidsargumenten inderdaad vaak hoge prioriteit wordt toegekend aan het behandelen van jongeren of van hen met de ernstigste ziektes, luidt de conclusie dat gewonnen QALY's bij pasgeborenen met levensbedreigende afwijkingen een naar verhouding hoge waarde hebben.

Ter afsluiting brengt Hoofdstuk 8 de in de voorafgaande hoofdstukken gepresenteerde resultaten met elkaar in verband. Als uitgangspunt geldt de belangrijkste conclusie van dit proefschrift, namelijk dat neonatale chirurgie duur is, maar de kosten waard. De resultaten kunnen nochtans van verschillende kanten worden bekeken, waarbij elk gezichtspunt geschikt is voor een ander publiek met andere behoeften. De lezer wordt daarom uitgenodigd voor een denkbeeldige tocht waarbij naar de resultaten van dit proefschrift wordt gekeken vanuit het perspectief van achtereenvolgens het kind zelf en zijn of haar ouders, de kinderspecialist, de samenleving in de persoon van de beleidsmaker, en de onderzoeker in de gezondheidseconomie. Het blijkt dat vanuit elk van deze gezichtspunten andere aspecten van de resultaten in het oog vallen. Desalniettemin vallen de resultaten in het algemeen goed uit voor de neonatale chirurgie, onwillekeurig welk gezichtspunt wordt ingenomen. Concluderend mogen we stellen dat dit proefschrift ingaat op het probleem van de balans tussen de kosten en effecten van neonatale chirurgie, en op dat van de balans tussen het kosten-effectiviteitsargument en andere argumenten in het debat rond de allocatie van middelen in gezondheidszorg—inderdaad een kwestie van balans. Uit de bevindingen blijkt dat de neonatale chirurgie een goede kosteneffectiviteit kent. Deze conclusie dient echter te worden genuanceerd door een viertal overwegingen. Ten eerste gaat de gunstige kosteneffectiviteit niet onverminderd op voor elk geval: de goede uitkomsten gelden waarschijnlijk niet voor de uitzonderlijke gevallen van patiënten die bij de geboorte ernstige meervoudige afwijkingen vertonen. Ten tweede zou er verdere vooruitgang moeten worden geboekt in de zorg voor patiënten met congenitale anorectale misvormingen of met congenitale hernia diafragmatica: de sterftecijfers en de kwaliteit-van-levenuitkomsten bij deze patiënten blijken ruimte te bieden voor verbetering. Ten derde is meer kennis op het gebied van de kosteneffectiviteit van neonatale chirurgie wenselijk en de weg daartoe dient mede te bestaan uit het verfijnen van de methodologie van economische evaluaties bij kinderen. De wenselijkheid van kennisuitbreiding geldt vooral voor de andere dan de in dit proefschrift bestudeerde aandoeningen bij pasgeborenen die een chirurgische ingreep

vereisen, waarvoor dit proefschrift slechts enigszins speculatieve conclusies kan aanreiken. Ten vierde is kosteneffectiviteit niet allesbepalend: de morele claims doelmatigheid en rechtvaardigheid kunnen met elkaar in conflict komen, en bij de allocatie van middelen moeten deze tegen elkaar worden afgewogen. Dat zouden we ons zeker bij de neonatale chirurgie voor ogen moeten houden, omdat rechtvaardigheidsargumenten (vanwege de leeftijd van de patiënten en ernst van de ziektes) en ethische argumenten op het niveau van de individuele medische besluitvorming van groot gewicht kunnen zijn. Niettegenstaande deze nuanceringen vormt dit proefschrift een nieuwe bijdrage tot de literatuur over de kosteneffectiviteit van neonatale chirurgie. Gelet op het belang dat tegenwoordig wordt gehecht aan kosten-effectiviteitsoverwegingen kunnen we er niet onderuit onderzoekers in de gezondheidseconomie structureel te betrekken bij het werk van kinderchirurgische afdelingen. De neonatale chirurgie kan het zich vandaag de dag eenvoudigweg niet veroorloven geen zicht te houden op de kosteneffectiviteit van haar wijze van opereren.

Ackn.

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About the Author

Born in De Meern (NL) in 1976, Marten Poley attended Gymnasium education at Dr. F.H. de Bruijne Lyceum in Utrecht from 1988 to 1994. He went on to study Health Policy and Management at Erasmus University Rotterdam from which he graduated MSc in 1999. From 1996 to 1999, he was a student research assistant at the institute for Medical Technology Assessment (iMTA)/ institute of Health Policy and Management (iBMG) of Erasmus MC Rotterdam. After his graduation, he joined iMTA/iBMG as a researcher.

His field of interest is the cost-effectiveness evaluation of health care interventions. He has undertaken a wide range of evaluations, for example regarding medication distribution systems, general practitioners' laboratory test ordering, and the combining of economic and ethical arguments in prioritizing health care interventions. From 1996 onwards, his main research area is the cost-effectiveness of neonatal surgery, the subject of this thesis. To this end, a collaboration between iMTA and the Department of Pediatric Surgery at Erasmus MC-Sophia Children's Hospital in Rotterdam was established. Part-time employed by this department since October 2002, his current research activities range from cost-effectiveness studies of interdisciplinary care teams, parental support programs, and patient safety programs, to the follow-up of adults who as newborns underwent surgery for major birth defects.

Next to his professional activities, Marten is reading law at Erasmus University School of Law. He expects to graduate by mid 2006, with a thesis in the field of health care law.

Colophon

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