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Cost-effectiveness analysis of health technologies when evidence is scarce

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To my family

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ABSTRACT

Given the increasing pressures on health care budgets, economic evaluation is used in many countries to assist decision-making regarding the optimal use of competing health technologies. Although the standard methods of estimating cost-effectiveness underpinning these decisions have gained widespread acceptance, concerns have been raised that many technologies would not be considered for funding, due to scarcity of evidence. However, as long as the amount and quality of evidence used for the analysis are properly characterized, scarce evidence per se should not be seen as a hindrance to perform cost-effectiveness analyses. Characterizing uncertainty appropriately, though, may pose a challenge even when there is a large body of evidence available, and even more so when evidence is scarce. The aims of this thesis are to apply a methodological framework of cost-effectiveness analysis and explore methods for characterising uncertainty when evidence is scarce. Three case studies associated with limited evidence provide economic evaluations on current decision problems, investigate the feasibility of using the framework, and explore methods for characterizing uncertainty when evidence is scarce.

The results of the case studies showed that, given current information, providing transfemoral amputees with C-Leg and Airsonett Airshower to patients with perennial allergic asthma could be considered cost-effective whereas screening for hypertrophic cardiomyopathy among young athletes is unlikely to be cost-effective. In the cases of C-Leg and Airsonett Airshower conducting further research is likely to be cost-effective. The case studies indicate that it is feasible to apply methods of cost-effectiveness in health care for technologies not commonly evaluated due to lack of evidence. The analysis showed that failing to account for individual experts' might have a substantial effect on the interpretation of the results of cost-effectiveness analysis. Formal expert elicitation is a promising method of characterizing uncertainty when evidence is scarce, and thus enable cost-effectiveness and value of further research to be appropriately estimated in such situations.

In conclusion, this thesis shows that scarcity of evidence should not preclude the use of cost-effectiveness analysis. On the contrary, in such cases it is probably more important than ever to use a framework that enable us to define key parameters for a decision problem and identify available evidence in order to determine cost-effectiveness given current information and provide guidance on further data collection.

SAMMANFATTNING

I takt med stigande kostnader för hälso- och sjukvård baseras beslut om att införa nya medicinska teknologier i ökande grad på resultat från hälsoekonomiska utvärderingar. De hälsoekonomiska utvärderingarna bygger oftast på information från tidigare publicerade studier som kombineras i så kallade beslutsmodeller för att undersöka hur de utvärderade teknologierna påverkar både kostnader och hälsoeffekter. Emellertid saknas det ej sällan relevant publicerad information som kan användas för sådana analyser. Det finns därför en oro för att dessa behandlingar inte ska kunna utvärderas med tanke på kostnadseffektivitet och således heller inte erbjudas till patienter. Det har på senare tid föreslagits att metoder för att inhämta expertutlåtanden bör användas när det saknas relevant information för en hälsoekonomisk utvärdering. Med hjälp av ett strukturerat tillvägagångssätt försöker man få experter att bidra med information om de parametrar där information saknas. En viktig del i denna process är att på ett adekvat sätt beskriva osäkerheten i de skattningar som experterna bidrar med, för att på så vis värdera risken för att fatta fel beslut och om det skulle vara värdefullt att investera i studier. Syftet med denna avhandling är att applicera metoder för hälsoekonomiska utvärderingar på tre aktuella kliniskt beslutsproblem där det finns begränsat underlag för effekterna av behandlingen. Där det saknas relevanta studier används expertutlåtande som underlag för analyserna. Syftet är att undersöka om behandlingarna kan utvärderas med tanke på kostnadseffektivitet trots knapp information från publicerade studier, och således eventuellt erbjudas till patienter, och om det finns skäl att initiera ytterligare studier för att minska osäkerheten kring ett sådant beslut.

Studierna visade att även när information från publicerade studier är begränsad är det möjligt att på ett adekvat sätt utvärdera kostnadseffektiviteten av behandlingarna. Studierna som ingår i denna avhandling visade att, det kan vara kostnadseffektivt att tillhandahålla en luftdusch till patienter med allergisk astma och en datorstyrd knäled till patienter som har amputerats över knäet. På grund av stor osäkerhet kring besluten kan det dock vara lönsamt att genomföra ytterligare studier samtidigt som behandlingarna införs. Att screena unga idrottare för att hitta de som har hjärtsjukdomen hypertrof kardiomyopati är troligtvis inte kostnadseffektivt. Många som inte har sjukdomen riskerar att felaktigt diagnostiseras och på så vis få försämrad livskvalitet. Att använda experter som underlag för hälsoekonomiska analyser när det saknas annan kunskap visade sig som en lovande metod så länge även osäkerheten fångas i de skattningar som experterna bidrar med.

Sammanfattningsvis visar denna avhandling att avsaknaden av relevant publicerad information inte i sig behöver betyda att vi inte kan uttala oss om en behandlings kostnadseffektivitet.

LIST OF PAPERS

This thesis is based on the following four papers.

- I. Thor-Henrik Brodtkorb, Olle Zetterström and Gustav Tinghög
Cost-effectiveness of clean air administered to the breathing zone in allergic asthma. *The Clinical Respiratory Journal* 2010; 4: 104–110.
- II. Brodtkorb TH, Henriksson M, Johannesen-Munk K, Thidell F
Cost-effectiveness of C-Leg compared to non microprocessor controlled knees: a modelling approach. *Archives of Physical Medicine and Rehabilitation*. 2008 Jan;89(1):24-30.
- III. Brodtkorb TH, Bojke L, Henriksson M
Eliciting priors to characterize uncertainties in decision analytic models.
Manuscript
- IV. Brodtkorb TH, Henriksson M, Nylander E
Cost-effectiveness of screening for hypertrophic cardiomyopathy in young athletes. *Manuscript*

ABBREVIATIONS

| | |
|----------|---|
| AA | Airsonett Airshower |
| EVPI | Expected value of perfect information |
| HCM | Hypertrophic cardiomyopathy |
| ICER | Incremental cost-effectiveness ratio |
| miniAQLQ | Mini Asthma Quality of Life Questionnaire |
| NICE | National Institute for Health and Clinical Excellence |
| NMB | Net monetary benefit |
| NMK | Non-microprocessor-controlled knee |
| QALY | Quality-adjusted life-year |
| RCT | Randomized controlled trial |
| SBU | Swedish Council on Health Technology Assessment |
| SCD | Sudden cardiac death |

INTRODUCTION

Given the increasing pressures on health care budgets, economic evaluation is used in many countries to assist decision-making regarding the optimal use of competing health technologies [1]. Although the standard methods of estimating cost-effectiveness underpinning these decisions have gained widespread acceptance, there are concerns whether these methods are applicable to all health technologies. In particular, technologies associated with difficulties in gathering high-quality evidence pose a challenge to decision-makers, and indeed, analysts. Primarily, this concern has been raised regarding medical devices [2] and orphan drugs [3], where gathering evidence of high quality has been considered difficult compared to drugs intended for diseases with a higher prevalence. Several reasons for these difficulties have been declared, but the most prevailing reasons have been the low prevalence of disease for orphan drugs [3, 4], and the licensing process, device operator interaction and incremental development, for devices [2]. As these characteristics are inherent in technologies such as devices and orphan drugs, lack of high-quality evidence is likely to prevail. In these circumstances it is feared that these technologies are not suited for standard health technology assessment and are deemed not cost-effective merely due to the lack of evidence for a decision to support them [2, 3]; they may also be simply left without any guidance. The fact that 75 percent of the technologies appraised by the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom have been pharmaceuticals, and 22 percent devices, might also underpin this concern to some extent [5]. This concern could be even more warranted in Sweden, which has a national benefit board, deciding on public funding, exclusively for pharmaceuticals and dental care. Other technologies are thus to a large extent included, or excluded, without systematic assessment of cost-effectiveness.

However, as stated in the principles of evidence-based medicine, the decision on whether or not to make use of a new technology should be based on the synthesis of best evidence available, which encompass anything from randomized controlled trials to expert opinion [6]. Thus, as long as the uncertainties arising from the amount and quality of evidence are properly accounted for in the analysis, scarce evidence does not necessarily need to be an obstacle to perform cost-effectiveness analysis. In fact, it has been argued

that economic evaluation for health care should focus on two related but conceptually different questions [7]. Is a technology cost-effective, given current information? Is it worthwhile to collect more information to inform the decision in the future?

The first question relates to the inevitability inherent in decision-making. If there are two or more competing treatment options available for patients, one has to be chosen, regardless of the amount and quality of the available evidence. This implies that avoiding making a decision due to a scarcity of evidence is an unsatisfactory way to proceed. Rather, available evidence should be used to try to make an informed decision. This seems like a theoretically plausible position, but its applicability to cost-effectiveness analysis of technologies where evidence is scarce is still, to a large extent, untested.

The second question relates to whether it is worthwhile to collect more information to inform a decision in the future. Given that we have chosen treatment A or B based on current information, we have to consider whether uncertainty around the decision is so high that it is worth collecting more evidence and revising our decision once this evidence is available? Henriksson [8] has demonstrated that applying this framework for economic evaluations in some Swedish case studies, where evidence exists, lead to very different conclusions compared to using more conventional methods for economic evaluations in Sweden.

To address both the question of cost-effectiveness given current information and value of further research to inform the decision in the future, it is important that uncertainty is characterized appropriately. This may pose a challenge even when there is a large body of evidence available, and even more so when evidence is scarce. There are still challenges, such as correlation structure between model parameters when having data from randomized controlled trials [9] and heterogeneity from meta-analysis [10], when characterizing uncertainty from trial data. Overall these methods are, however, well founded in statistical theory, and methods to incorporate the associated uncertainty fairly established. Methods to incorporating uncertainty when evidence is scarce are on the other hand so far not established. Methods for characterizing uncertainty when evidence is scarce, based on formal expert elicitation, has been frequently used in Bayesian statistics [11] and to some extent in cost-effectiveness analysis [12, 13]. The feasibility of using formal

expert elicitation in cost-effectiveness analysis to handle uncertainty has, however, not been fully explored.

Aims

The main aims of this thesis are to apply a methodological framework of cost-effectiveness analysis and explore methods for characterizing uncertainty when evidence for cost-effectiveness of health technologies is scarce.

More specifically, this thesis will

- Provide economic evaluations on current decision problems, to provide guidance on the cost-effective use of three non-pharmaceutical health technologies;
- Investigate to what extent it is feasible to determine cost-effectiveness within the methodological framework of cost-effectiveness analysis for health technologies with scarce evidence; and
- Explore how formal methods of expert elicitation can be applied in cost-effectiveness analysis to handle uncertainty when empirical evidence is scarce.

These aims will be explored through three case studies and four papers:

Papers I and II are applications of the methodological framework of cost-effectiveness analysis for two technologies, an airshower for asthmatics and a prosthetic knee for amputees, where evidence is scarce, and represent areas where cost-effectiveness analyses seldom are performed. These analyses will provide measures of cost-effectiveness and uncertainty, sensitivity scenarios, and the value of further research, given current information.

Paper III will explore how methods of expert elicitation, applied to the same decision as in Paper II, can be used in cost-effectiveness analysis when evidence is scarce. This analysis will provide measures of cost-effectiveness and uncertainty and the value of further research, and explore how the use of expert elicitation changes these measures.

Paper IV is an applied analysis of screening for hypertrophic cardiomyopathy, where expert elicitation is applied due to scarce evidence on some of the key parameters for decision-making. This analysis will provide knowledge on the feasibility of expert elicitation in an actual evaluation, and provide measures of cost-effectiveness and uncertainty, sensitivity scenarios, and value of further research, given current information.

Overview of the thesis

First, a brief background to the basic methodological framework of cost-effectiveness analysis, value of information, and expert elicitation is presented. Next, the clinical decision problems investigated in the case studies and their results are presented and discussed. In the final part of the thesis, a general discussion is presented, and some conclusions offered.

Methodological framework

As pointed out in the introduction, there is an increased need to prioritize the health technologies that should be funded from available resources. A vehicle to estimate and compare costs and health consequences of alternative health technologies, and thus achieve an efficient allocation of scarce health care resources, is economic evaluations. The following chapter will provide an overview of the common analytical framework for evaluating cost-effectiveness of health technologies that is applied in the case studies.

Cost-effectiveness analysis

To assess whether to implement a new technology, its costs and health outcomes need to be compared with the costs and health outcomes of relevant comparator technologies for a defined patient population. The estimate of cost-effectiveness is often summarized as an incremental cost-effectiveness ratio (ICER). The ICER expresses the relationship between the difference in costs and the difference in health outcomes, or effects, between the treatment alternatives under investigation according to the formula

$$ICER = \frac{(C_T - C_C)}{(E_T - E_C)} = \frac{\Delta C}{\Delta E} \quad (1)$$

where C_T (E_T) is the mean costs (effects) associated with the new treatment and C_C (E_C) is the mean costs (effects) associated with the comparator. If ΔC is negative and ΔE is positive (treatment dominates the comparator), the new treatment is clearly cost-effective. Equally, if ΔC is positive and ΔE is negative, the new treatment is clearly not cost-effective, as it is both more costly and less effective. It is thus not necessary to calculate an ICER. In cases where a technology yields positive (negative) health outcomes at a higher (lower) cost, the ICER has to be calculated and compared with a threshold value, or a willingness to pay for a unit of effect. For example, a threshold of €35 000 means that 1 unit of effect is expected to be lost for every €35 000 the decision-maker has to find by curtailing other activities to accommodate the new and more costly technology [14]. Should the ICER for the new technology be below the threshold, implementing the new treatment would thus be considered.

As ratios have rather unhelpful statistical properties, an alternative is to express the results as net monetary benefit (NMB) [15]. For the NMB, the results are rearranged to value the effects of the treatment in monetary terms according to

$$NMB = \lambda(E_T - E_C) - (C_T - C_C) \quad (2)$$

where λ is the threshold value. If the NMB is positive it implies that the value of the effect of the new treatment is larger than the cost incurred, and the treatment should, in principal, be adopted.

Choice of effect measure in economic evaluations

The most commonly used outcome measure in economic evaluations, and the one used in the four case studies, is quality-adjusted life-years (QALY). The QALY combines the time lived in a health state and the quality of life. With this measure, the time spent in a health state is weighted by a quality-adjustment weight, or utility, between 0 (dead) and 1 (full health) [16]. One QALY is thus equivalent to one year with full health. As QALY is a generic health outcome, treatments prolonging life or enhancing health-related quality of life can be compared with the same measure. Furthermore, comparison between different disease areas is possible, making QALYs a useful outcome in economic evaluations performed to inform policy decisions regarding the allocation of scarce health care resources.

As noted earlier the ICER have to be compared with a threshold value, or a willingness to pay for a unit of effect to establish whether the treatment under investigation is cost-effective. There is currently no fixed value or official range of willingness to pay for a QALY in Sweden. In the case studies several different thresholds are therefore referred to. However, for ease of discussion and as a common point of reference, a willingness to pay per QALY of €35 000 is applied in this thesis.

Methods to estimate cost-effectiveness

Traditionally clinical trials have been a vehicle for economic evaluation [17] and hierarchy of evidence determined whether more research should be conducted or not. However, in the context of economic evaluation, recent requirements have pointed out the shortcoming of clinical trials as the sole basis for cost-effectiveness analysis [18]. In brief these requirements for economic evaluation are: comparing all relevant treatments, utilizing an appropriate time horizon, incorporating all relevant evidence, apply the relevant decision context and characterizing the uncertainty appropriately. To fulfil these requirements using decision modelling, as a method to estimate cost-effectiveness, has been put forward as more likely to meet these requirements than clinical trials [18].

Decision modelling

With the need to incorporate all relevant evidence into the cost-effectiveness analysis, comparing the new technology with the full range of relevant alternatives and reflecting uncertainty in the evidence in the conclusion of the analysis [19], decision analytic modelling has increasingly been used to establish cost-effectiveness for policy decisions. Decision-analytic modelling offers a systematic and analytic approach to decision-making under uncertainty [20]. By identifying the set of consequences of concern to the decision-maker that might result from each available option, decision analysis identifies the option that maximizes net benefits, as optimal [17].

Decision modelling as a method fulfils several of the requirements of economic evaluations seeking to inform decision-making. As all relevant evidence seldom comes from a single source, we need to synthesize data from several sources to estimate the cost-effectiveness. Decision modelling offers a framework in which evidence from different sources can be brought to bear on the decision problem, and the relationship between intermediate outcomes and the ultimate measure of health gain required for cost-effectiveness analyses can be accounted for [18, 19].

As all relevant treatment alternatives are rarely compared in one single trial, , data from several trials need to be brought together using appropriate methods [21]. Also, as many health care interventions will affect the cost and health outcomes for a longer period than normally monitored in a clinical trial, it is necessary to extrapolate the results to an appropriate time horizon. Decision modelling is a vehicle to achieve both these tasks, being a framework that allows synthesized data to be incorporated, and allows for structuring the extrapolation of costs and effects over time [19].

Handling uncertainty

As uncertainty is pervasive in all cost-effectiveness analyses, costs and effects of treatments can never be predicted with 100 percent precision. Hence, it is important to establish how uncertainty in predicted costs and effects could be reflected in the cost-effectiveness analysis. Decision modelling offers a suitable framework for this task, as the uncertainty in all relevant parameters in the model can be characterized with an appropriate probability distribution, and propagated through the model with Monte Carlo simulation. With this approach uncertainty in input parameters is reflected in the output parameter of interest, namely cost-effectiveness [22]. This way of propagating uncertainty in inputs through the model is referred to as probabilistic sensitivity analysis [23]. From the probabilistic sensitivity analysis the probability of the intervention being cost-effective can be determined and presented as cost-effectiveness acceptability curves [24]. In addition to estimating the uncertainty surrounding the adoption decision, quantifying the uncertainty in model inputs is necessary to calculate the correct cost and effect of the treatment alternatives when there is a non-linear relationship between model inputs and outputs [14].

In addition to the parameter uncertainty accounted for by probabilistic sensitivity analysis, there are also other sources of uncertainty relevant to estimating the cost-effectiveness of a technology. Two other sources of uncertainty commonly described are methodological and structural, or model, uncertainty [23]. Methodological uncertainty pertains to, for example, the choice of effect measure or discount rate. While such methodological uncertainty can be important it is not suitable for probabilistic sensitivity analysis but should rather be explored in sensitivity scenarios. Even the structural uncertainty, related to the structure of the chosen model, has

traditionally been handled with sensitivity scenarios. However, recent research in this area suggests that structural uncertainty could be handled in analogy with parameter uncertainty, and thus handled through probabilistic sensitivity analysis [25].

Estimating the value of further research

Basing the decision only on expected cost-effectiveness would not take into account the value of collecting further information [7]. Even if a treatment has a preferable expected cost-effectiveness given current information, it is, in principal, always associated with uncertainty. Therefore, establishing the cost of making a wrong decision, and hence, the value of information, can be just as important as having access to a cost-effective treatment [14].

By quantifying the probability and consequences of making a wrong decision, the value of further research can be quantified. Since eliminating all uncertainty surrounding the decision, would eliminate the possibility of making the wrong decision, the expected cost of uncertainty could be interpreted as the expected value of perfect information (EVPI) [7]. Given that we have a fixed number of treatments to choose from $j= 1, 2, \dots, J$, and a decision model with unknown parameters θ . The optimal decision given current information is to choose the treatment alternative that yields the highest net monetary benefit, $\max_j E_\theta \text{NMB}(j, \theta)$ [26]. We do not know the true values of θ but if they were known we could maximize over the treatments, $\max_j \text{NMB}(j, \theta)$. As θ is unknown, the expected NMB of making the decision with perfect information can be found by averaging this expression over the joint distribution of θ , $E_\theta \max_j \text{NMB}(j, \theta)$ [26]. The EVPI can then be calculated by the difference between the value of the decision with perfect information and value of the preferred treatment under consideration [27], as shown by Equation 3.

$$EVPI = E_\theta \max_j \text{NMB}(j, \theta) - \max_j E_\theta \text{NMB}(j, \theta) \quad (3)$$

This equation calculates the expected value of perfect information for the individual patient. However, information gained can be used to inform treatment decisions for all patients to whom the same decision problem applies. The value per patient could therefore be multiplied by the expected

patient population to reflect the effective EVPI that is relevant to a decision about future research [26]:

$$EVPI_{pop} = EVPI * \sum_{t=1}^T \frac{N_t}{(1+r)^t} \quad (4)$$

Where T is the effective lifetime of the technology, r the discount rate, and N is the number of eligible patients at time t.

Utilization of decision modelling and quantifying uncertainty in monetary terms to determine the value of further research can be seen as having distinct advantages over the methods currently used by for example Swedish Council on Health Technology Assessment (SBU). Reviewing the ten latest reports from SBU [28-37], all of these have “insufficient evidence for guidance” among the key recommendations. As SBU’s recommendations only include evidence from cohort studies or controlled trials, one could argue that the determination is made without taking all relevant evidence fully into account. Therefore, SBU does not explore the most relevant treatment option, given current evidence, or the value of further research. This leads to arbitrary decision-making, as patients will get some treatment, anyway, or in some cases, no treatment, which also has its costs and effects. One clear example of this is SBU’s guidance concerning screening for abdominal aortic aneurysm. When reviewing the published evidence [38], SBU concluded that, due to the absence of trials investigating cost and effects in Sweden,

Any kind of screening program for abdominal aortic aneurysms that is contemplated in Sweden should fall within the scope of a scientific study that evaluates all potential consequences.

However, when analysed [39] within the decision-analytic framework described above, the value-of-information analysis revealed that

...performing another trial to study costs and health outcomes is unlikely to contribute much to inform the decision on whether or not to implement a screening programme. Instead, research could focus on certain parameters, notably the probability of rupture, as the uncertainty regarding the overall cost-effectiveness of the programme appears to be low.

As clearly shown by this example, making decisions based on rules of number and hierarchy of trials, rather than taking all evidence into account, may lead to less than optimal decisions, and potentially, health forgone. The direct consequence in the case of screening for abdominal aortic aneurysms would be that 800 expected QALYs could potentially be foregone in Sweden every year. In this case, the decision-analytic approach lead to a structuring of the decision problem, helping to identify non-randomized evidence of relevance that had been discarded in the previous recommendations. In this sense, decision analysis does not prejudice evidence as acceptable or unacceptable based on specific criteria, but help to identify the type of evidence that may be important to support the cost-effectiveness analysis [17].

Capturing experts beliefs

As pointed out in the sections above, the use of decision analysis provides an explicit framework to estimate cost-effectiveness based on current information. It also provides means of quantifying uncertainty in monetary terms in order to determine the value of further research. One of the most important benefits of utilizing this framework is the possibility to inform decisions in a relevant manner taking all available evidence into account. This is the case regardless of whether trial data is available or not [40].

It is important to remember that, even a lack of evidence from trials, or other published material, does not mean that we are left without any knowledge about the decision of interest. Clinicians or others treating patients observe the consequences of different treatments every day, and although not formally collected, this may constitute the best available evidence. Thus, they could, and perhaps should, be used to inform parameters in decision models in the absence of other evidence. In these situations, typically, single values such as the mean have been elicited when lacking data on parameters [12], thus ignoring any uncertainty in the experts' beliefs. For the reasons outlined above, accounting for the uncertainty of these estimates is, however, just as important as for data from trials. Methods capturing both the mean value and the associated uncertainty should therefore be applied. A method providing such estimates is formal expert elicitation.

An expert elicitation is intended to link an expert's underlying beliefs to an expression of these beliefs in a statistical form [41]. The use of formal expert elicitation has gained a lot of interest as a method for specifying the prior distribution for one or more unknown parameters in Bayesian statistical analysis [41]. Even if Bayesian statistics has been the main area of application, expert elicitation has also been used in a variety of other contexts [11]. However, its use in the context of economic evaluation of health technologies is, so far, limited [12, 13].

As one of the central aims of using formal expert elicitation in cost-effectiveness analysis is to account for the uncertainty, the methods applied have to capture the experts' uncertainty about an estimated quantity. Behavioural methods such, as the Delphi technique, are therefore regarded as inappropriate as they rule out much of the uncertainty by enforcing consensus [42]. Rather, elicitation based on a mathematical approach, has been proposed. These methods do not attempt to reach consensus but to characterize the true uncertainty of an unknown quantity. There is no agreement on which specific elicitation method that should be used to elicit parameters within the mathematical approach [11]. However, it seems that people are poor at directly estimating the variance, as used to parameterise parameters in a decision-analytic model, and perform better when asked to quantify opinions about credible intervals [41]. The approach used in the case studies in this thesis is the histogram approach. This approach has proven to be feasible in earlier studies within the field of economic evaluation of health technologies [13] and has been widely applied elsewhere [43].

The histogram approach is a discretised version of the continuous density function and presents experts with multiple fixed intervals. In the histogram approach, the expert is presented with a frequency chart on which he/she is asked to place a given number of crosses in intervals or bins (Figure 1). In the case studies 20 crosses were used and each cross therefore represents 5% of the distribution. The crosses reflect the expert's belief about the expected value of the quantity. Experts should assign more crosses to a specific value, if they are more confident that this would be the accurate expected value. Use of the histogram approach avoids the need to specify the quartiles of interest or fit parametric distributions to subjective probabilities [44]. In practise, the empirical distribution can be incorporated directly into the model and the elicited values pooled across all experts using linear pooling.

THE CASE STUDIES

The following section gives a brief overview of the case studies upon which the thesis is based. It will cover the decision problems, the methods applied to address these, and the results of the analyses. It will also discuss the policy implication for the individual case study. For full details of the studies, the reader is referred to the four papers.

Cost-effectiveness of Airsonett Airshower (Paper I)

In patients with extrinsic allergic asthma and continuing or iterated allergen exposure, it is well known that limiting allergen concentration in inhaled air has a beneficial effect. This fact has been shown in studies where patients have moved away from the allergen, e.g. by going to the Alps in the case of dust mite allergy, or stopped exposure to the allergen by removing it, as in cases of domestic animal allergy [45, 46]. However, air cleaning interventions have until now shown little or no effect on patients with perennial allergic asthma [47].

A placebo-controlled cross-over study [48] investigating a treatment, the Airsonett Airshower (AA), using a laminar airflow directed to the breathing zone of patients with perennial allergic asthma, showed an increase in asthma-related quality of life and a decrease in exhaled NO as an indicator of airway inflammation. However, the positive effects of using the AA in addition to standard treatment are also associated with increased treatment costs. As the AA was perceived as rather costly, the county councils in Sweden were reluctant to adopt the treatment.

To establish the cost-effectiveness and value of information (although the value of information was not reported in the published article) of the AA, a decision-analytic model was constructed to compare the treatment alternatives of providing a patient with an AA (Airshower strategy) or a placebo AA. Costs and effects were in the base case extrapolated, estimated over a 5-year time horizon. A Swedish health care perspective was adopted for the analysis.

According to the trial design no changes were made to the standard treatment of asthma, during either the Airshower strategy or the placebo strategy. Scenarios for 13 year time horizon and only providing the treatment to patients with more severe asthma (defined by a score of the mini Asthma Quality of Life Questionnaire (miniAQLQ) equal to or below 5) were also investigated.

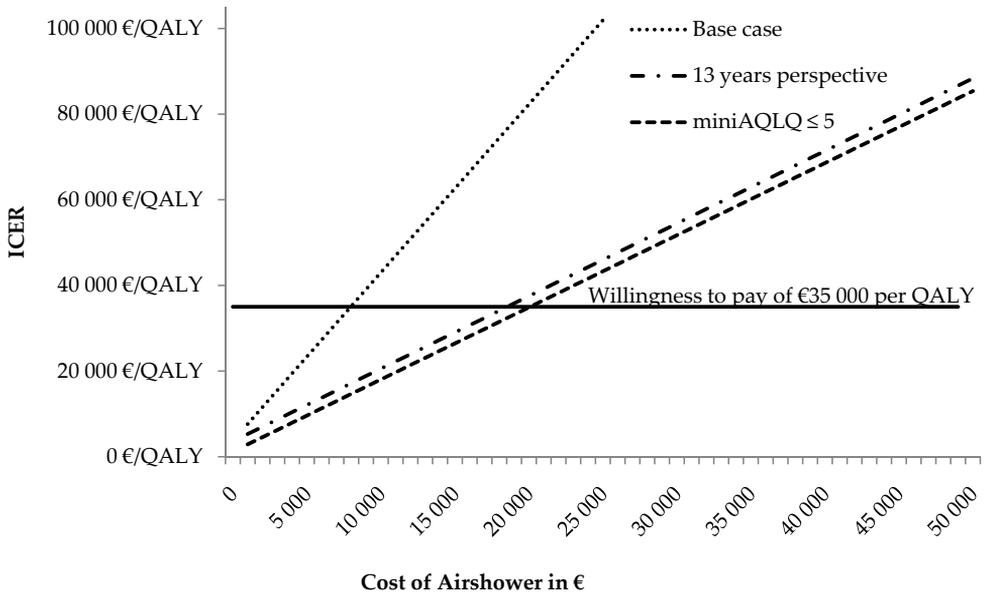
When the cost-effectiveness analysis was about to be finalized the manufacturer withdrew the AA from the open market and would not specify a cost for the AA. Therefore the analysis was performed to identify threshold costs of the device along with different scenarios for €5 000 in a plausible cost scenario; and €15 000 in a high cost scenario.

The exact size of the patient population eligible for AA is unknown (required for the value of information analysis). For example, should only the allergic asthma population with miniAQLQ equal to or below 5 (severe asthma) not having an adequate medication be eligible it would perhaps be 30 000 patients in Sweden in total. However, as even patients with less severe asthma benefits from the AA a larger portion of the estimated 750 000 - 900 000 [49] people with asthma in Sweden could be assumed to have a benefit from research on the AA. An annual population of 10 000 individuals with a ten year time horizon was therefore assumed for the value of information analysis.

Results (Paper I)

The result of the base-case analysis showed that the Airshower strategy resulted in a mean gain of 0.25 QALYs per patient, and had an ICER below €35 000, as long as the cost of the AA was below €8 200. The sensitivity scenario with a 13-year perspective led to a gain of 0.59 QALYs, with an ICER below €35 000, as long as the cost of the AA was below €18 760. The scenario analysing only the data of the patients with miniAQLQ values equal to or below 5, i.e. those with more severe asthma, resulted in a mean gain of 0.594 QALYs. In this scenario the ICER will not be higher than €35 000 before the cost of the AA exceeds €20 100 (Figure 2).

Figure 2. Relationship between cost of Airsonett and cost-effectiveness results



When performing the analysis for a cost for the AA of €5 000, the ICER was €22 418, €11 670, and €10 007, respectively, for the base case, 13 years, and miniAQLQ values equal to or below 5 scenario. Corresponding results for the €15 000 cost resulted in ICERs of €62 644, €28 619, and €26 847. The results of the probabilistic sensitivity analysis are shown in the cost-effectiveness acceptability curve (Figure 3), thus showing the probability that AA treatment is cost-effective over a range of willingness-to-pay values for both the €5 000 and €15 000 alternatives.

Despite high probability of being cost-effective, given current evidence, the value-of-information analysis revealed that there was substantial value in performing more research. As seen in Figure 4 the value of information given a willingness to pay for a QALY of €35 000 for the base-case analysis with a cost of €5 000 would be approximately €500 000 000.

Figure 3. Cost-effectiveness acceptability curve for Airshower.

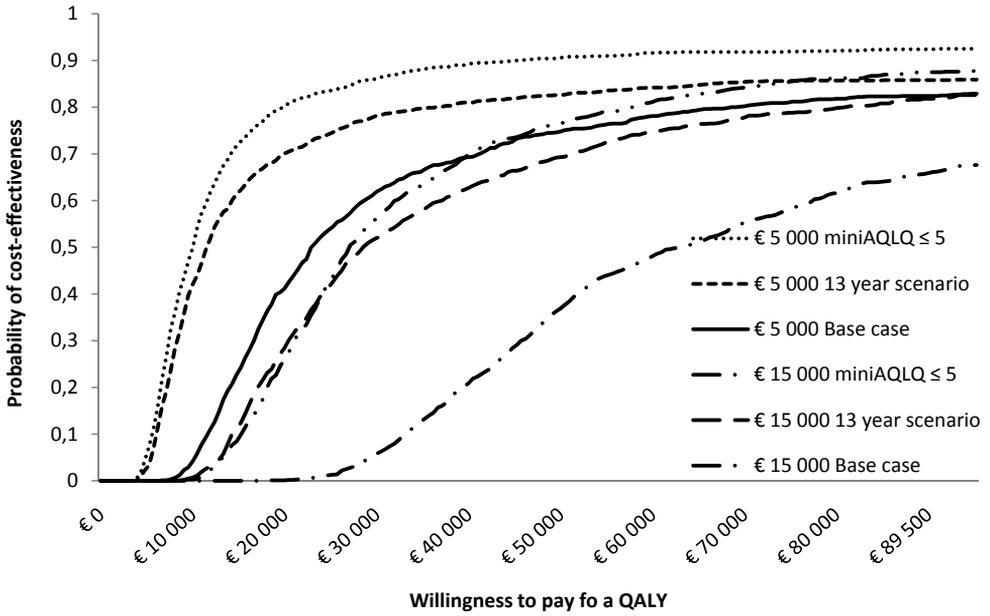
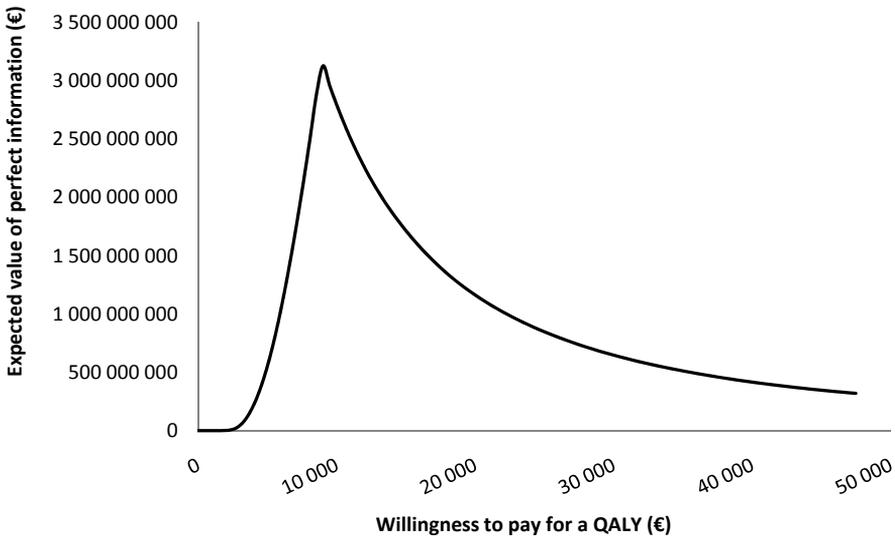


Figure 4. Value of further research for Airshower.



Implications for policy (Paper I)

There is no formal regulatory body in Sweden issuing specific guidance on funding of non-pharmaceutical technologies, unless they are evaluated specifically by the National Board of Health and Welfare; thus, no specific guidance on Airsonett Airshower have been issued. Several of the county councils have been reluctant to finance the AA, primarily due to the cost of this device. The results of the present analysis do, however, show that, as long as the cost of the AA is below €8 200, the ICER would be below a threshold of €35 000.

Based on the base-case analysis, choosing not to adopt the AA, given current evidence, implies that each patient suitable to benefit from an AA would forego 0.25 QALYs over a 5-year period. For an estimated eligible patient population of 10 000 patients per year, 2 500 QALYs would be foregone. Given a cost for the AA of €5 000 and a willingness to pay for a QALY of €35 000, this would result in a loss in net benefit of €31 455 000

Although current evidence suggests that the AA should be adopted, the value-of-information analysis revealed that further information on the AA would have a substantial value. Acquiring more information is most likely cost-effective. A multinational randomized trial with a larger patient sample than the study underpinning this cost-effectiveness analysis is due to be presented in June 2010. Initiating further research before the model is updated with these results is, therefore, not likely to be cost-effective.

However, as current evidence suggests that patients with allergic asthma would benefit from the use of the AA, and that it would be cost-effective, patients should perhaps have received this treatment pending the results of the new study. This is especially true since this is a reversible treatment that could easily be discontinued if future evidence should indicate a change of decision.

Cost-effectiveness of C-Leg (Paper II & III)

Transfemoral amputation significantly reduces the patient's potential for living an active life. Therefore, the introduction of the microprocessor-controlled knee, the C-Leg, about ten years ago was coupled with great expectations of a possibility of regaining some of this potential. This knee unit offered a microprocessor-controlled swing and stance phase, and was therefore assumed to increase the functional level of the prosthetic users.

The treatment alternatives in the field of prosthetics are often not well supported by evidence [50], but since its introduction, some studies have shown beneficial results for the C-Leg compared to the conventional non-microprocessor-controlled knee (NMK) units. Advantages observed are negotiation of stairs and hilly terrain, decreased frequency of stumbles and falls, decreased difficulty in multitasking, and higher satisfaction [51], lower rate of oxygen consumption [52], and biomechanical advantages such as decrease in hip-work production, lower peak hip-flexion moment at terminal stance, and enhanced smoothness of gait [53]. In terms of costs the C-Leg is substantially more costly compared to the non-microprocessor-controlled alternatives.

No published evidence regarding quality of life and costs for the C-Leg or non-microprocessor-controlled knee units was available at the time of the study. However, decision-makers still had to make recommendations regarding the provision of the C-Leg. The county councils in Sweden have taken different approaches as some are providing the C-Leg, whereas, others are not [unpublished data by Gustav Tinghög, Linköping University]. It appears that one reason for the different approaches is the considerably higher cost of the C-Leg compared to NMK. Therefore, a decision-analytic model was constructed to estimate the costs and health outcomes of the C-Leg and non-microprocessor-controlled knees. In the absence of published data, experts' or patients' opinion (single mean values from each) was used for many of the model parameters (Paper II) to estimate the cost-effectiveness of providing patients with the C-Leg. The mean values and the variance between the experts/patients were used to assign distributions for the parameters in the model.

Appropriate characterization of the uncertainty in input parameters is important for both cost-effectiveness and value of information analyses based on decision modelling. Therefore it was further explored how the use of formal expert elicitation could influence the results (Paper III). To achieve this, a formal expert elicitation exercise was undertaken for 11 input parameters. Point estimates, and the associated uncertainty around the point estimates were derived from 11 experts. The model used in Paper II was then reanalysed with parameter values from the formal elicitation. The elicitation was performed using a facilitator lead Excel based questionnaire. The questionnaire utilized a histogram approach to elicit the experts' beliefs about the mean value and uncertainty for each parameter.

To explore the added value of performing an expert elicitation the decision model was run for both the original set of data and the new elicited data. The implications for cost-effectiveness and research recommendation from the two sets of parameter values were then compared.

Results (Paper II & III)

The analysis from Paper II resulted in a mean incremental cost for the C-Leg of €7 657 and 2.38 incremental quality-adjusted life-years gained, yielding a cost per quality-adjusted life-year gained of €3 218 (Table 1). The uncertainty surrounding the cost-effectiveness of a C-Leg strategy was low for common values of willingness to pay for a QALY. If, for instance, the decision-maker has a willingness to pay €35 000 per QALY, the probability of C-Leg being cost-effective is 0.97.

Table 1. Results of the cost-effectiveness analysis for C-leg in Paper I.

| | Total cost/ patient (€) | Effectiveness QALY | Incremental cost per patient (€) | Incremental effectiveness QALY | Incremental cost/QALY (€) | Prob C/E (€35 000) |
|-------|----------------------------|-----------------------|--|--------------------------------------|---------------------------------|-----------------------|
| C-Leg | 25 146 | 5.98 | 7 657 | 2.38 | 3 218 | 0.97 |
| NMK | 17 488 | 3.60 | | | | |

Abbreviations: NMK, Non-microprocessor-controlled knee; QALY, Quality-adjusted life-year; Prob C/E, Probability of cost-effectiveness.

The sensitivity scenarios performed did not result in cost-effectiveness ratios that substantially would change the estimated cost-effectiveness of the C-Leg strategy. However, the quality of life associated with each prosthesis during a year appeared to have some impact on the cost-effectiveness. When analysing

the scenario with equal quality of life for both treatment strategies, the resulting cost per QALY was found to be €23 524. Despite this rather unfavourable assumption, the C-Leg is still below general acceptable thresholds of cost-effectiveness.

In Paper III, all 11 experts completed all questions and the elicitation took approximately 1 hour per expert to complete. None of the experts reported any difficulties completing the questionnaire and all found the format of the elicitation clear and comprehensible. However, several of the experts reported difficulties answering the questions due to the uncertainty related to the technology per se.

In general, the elicited priors suggest that the effect of the C-Leg in the original analysis (Paper II) might have been overestimated, particularly as the difference in both QALYs and number of problems between the two treatment alternatives (both highly influential on the results) were rated as smaller than the values used in the original analysis. There was rather large heterogeneity between the experts, as can be seen in Figure 5, showing the elicited distributions for 5 of the 11 experts for the parameter 'Hours needed to make a prosthesis with C-Leg' (The additional 6 experts were excluded from the figure to make it less crowded but had similar distributions). The combined distribution of all experts for the same parameter can be seen in Figure 6. This and the distribution for the parameter 'Number of problems per year with the NMK' (Figure 6) also shows the wider distribution seen in the elicited priors, as compared to the data used in Paper II. This increased uncertainty was seen in all parameters, except 'How many days does a problem last', where the distribution was narrower for the elicited parameters compared to the original data.

Figure 5. Comparison of elicited distributions from 5 experts.

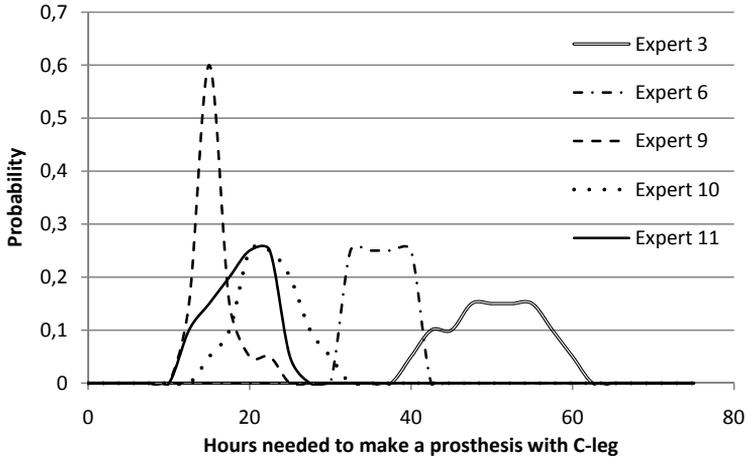
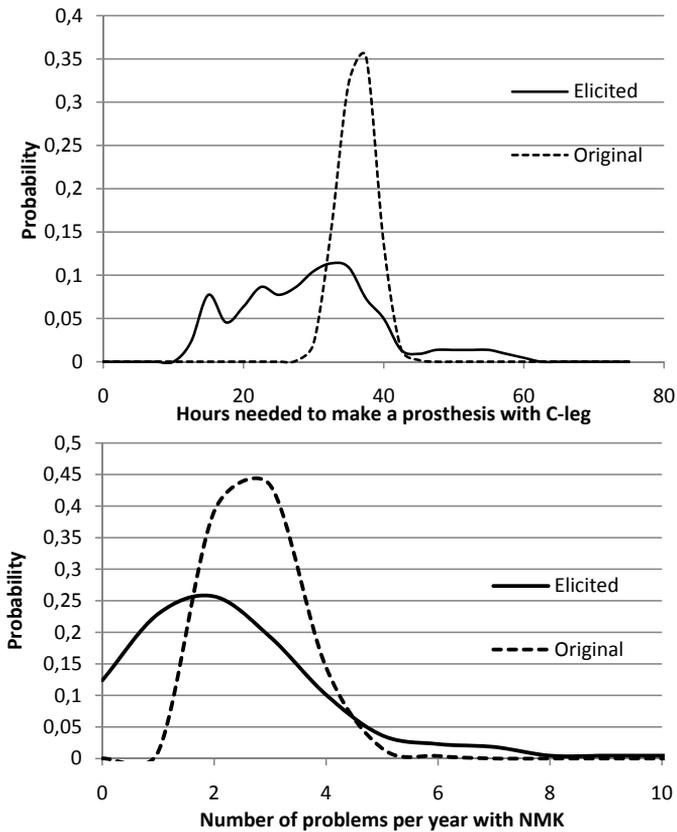


Figure 6. Comparison of two distributions of original and elicited priors.



The updated analysis with the elicited parameters resulted in a higher ICER, €13 625 compared to €3 258 for original analysis (Table 2). This is the result of both a decreased cost of the NMK strategy and a decreased incremental gain in QALY for the C-Leg strategy. However, referring to a threshold of €35 000, the C-Leg strategy would still be seen as cost-effective based on expected cost-effectiveness.

Table 2. Results comparing the cost-effectiveness of original and elicited parameters.

| | | Cost (€) | QALY | ICER (€) | Prob C/E (€35 000) | EVI (€35 000) |
|----------|-------|----------|------|----------|--------------------|---------------|
| Original | C-Leg | 25 146 | 5.94 | 3258 | 0.97 | 355 100 |
| | NMK | 17 488 | 3.59 | | | |
| Elicited | C-Leg | 25 418 | 5.33 | 13 625 | 0.70 | 5 987 444 |
| | NMK | 14 071 | 4.50 | | | |

Abbreviations: NMK, Non-microprocessor-controlled knee; QALY, Quality-adjusted life-year; ICER, Incremental cost-effectiveness ratio; Prob C/E, Probability of cost-effectiveness; EVI, Expected value of information.

With respect to decision uncertainty and the value of further research, the increased uncertainty of the elicited values resulted in a higher value of further research to inform the decision. With a threshold of €35 000 the C-Leg strategy would have a probability of being cost-effective of 0.70 with the elicited values compared to the 0.97 from the original analysis. The value of information analysis showed that, based on the elicited parameters, the total value of further research would be €5 987 444. This value of further research is significantly higher than the value of further research of €355 100 for the analysis based on the original estimates.

Implications for policy (Paper II & III)

Similar to the AA, no national guidance has been issued with regard to use of the C-Leg. At the time of our analysis, several county councils were reluctant to provide the C-Leg to their patients, due to the extra cost of the knee compared to the non-microprocessor-controlled alternatives. Based on the results from both the original analysis and the analysis with parameters obtained by expert elicitation, providing the C-Leg would be deemed cost-effective, based on a willingness to pay for a QALY of €35 000. Implementing the C-Leg, therefore, seems to be warranted, in light of current evidence.

The value of further research was significantly different between the two analyses. Based on the analysis performed in Paper II, it would most likely not be cost-effective to commission further research with regard to the C-Leg, but the increased uncertainty conveyed when basing the analysis on expert elicitation in Paper III suggests that further research could be considered cost-effective. In this respect, it might be problematic that several of the county councils have already started to provide the C-Leg, removing some of the incentive for the manufacturer to undertake further research. But the results from this analysis indicate that patients would actually miss out on QALYs if provided with a NMK, and would even do so if included in a trial. Therefore, it would be of interest to further investigate exactly which parameters that would be most important to gain further knowledge about, and if this knowledge can be sampled at reasonable cost (both in money and health foregone). Should it turn out to be knowledge that does not require a controlled trial, patients could receive the C-Leg, base on current results, but impose a condition on manufacturers to provide further evidence.

Cost-effectiveness of screening for hypertrophic cardiomyopathy (Paper IV)

Hypertrophic cardiomyopathy (HCM) is seen as the leading cause of sudden cardiac death (SCD) among young athletes [54]. Sudden death among young people is always tragic and followed by questions on how to prevent further events, and SCD due to HCM is no exception. A demand for screening to prevent SCD has therefore been raised, and several countries have already introduced pre-participation cardiovascular screening to identify individuals active in sport suffering from HCM. The United States and Italy have been two of the most prominent countries performing pre-participation screening [55, 56]. In Italy, with more than 25 years of experience, it has been shown that pre-participation screening has the potential to save lives [57].

However, the potential gain from screening has to be balanced against the risk of false-positive findings, excluding healthy individuals from sport and reducing their quality of life. It is essential to take the quality of life into account when evaluating new health programmes in order to capture the larger panorama of health and well-being thought to be important and meaningful to individuals.

When this evaluation began, there was no organized screening programme for HCM in Sweden. However, due to a number of sudden cardiac deaths that attracted much attention in the media, the National Board of Health and Welfare initiated work to issue policy guidance. Cost-effectiveness of a screening intervention for identifying HCM was therefore estimated, using a decision-analytic model. Costs and health outcomes, in terms of life-years and QALYs, were determined for a lifetime perspective of a onetime pre-participation screening intervention at the age of twelve years for athletes participating in competitive sport. The decision-analytic model was also used to estimate the value of further research, with regard to implementation of screening (although the value of information is not reported in the manuscript).

There was a particular lack of evidence regarding sensitivity and specificity of echocardiography, which is the cornerstone for clinical diagnosis of manifest HCM. To be able to formally address the uncertainty about these parameters,

distributions for sensitivity and specificity were elicited from 4 experts using the same methods as applied in Paper III. However, in this paper the Excel based questionnaire was distributed via e-mail to the experts.

Results (Paper IV)

Compared with no screening, the screening strategy was associated with a mean incremental cost of €93 and a mean incremental gain of 0.0005 life-years, yielding a cost per life-year gained of €196 205. Taking the quality of life into account in the analysis showed that the screening strategy was associated with a loss of 0.034 QALY compared with no screening. This indicates that the screening strategy is dominated by the non-screening strategy (i.e. more costly and less effective). The probability of the screening being cost-effective for conventional values of willingness to pay for a life-year or a QALY was low (below 1% employing a willingness to pay for a health outcome of € 35 000). Due to this low probability of screening being cost-effective the value of further research was very low.

Sensitivity scenarios

The results of running several sensitivity scenarios showed that the decision whether to implement a screening programme could be affected by different assumptions (Table 3). However, when investigating the impact of the specificity of echocardiography, alteration of this parameter in the range between 0.98 and 1 would not change the ICER substantially. Similarly, varying sensitivity did not generate any substantial differences in the ICER. With respect to gender, there was a substantial difference in life-years gained, but differences were not found that would indicate a different conclusion in males or females, as the ICER was still well above common values of willingness to pay, using life-years as health outcome, and the screening strategy was dominated with regard to cost per QALY.

Table 3. Results of sensitivity scenarios.

| | Incremental cost (€) | Incremental QALY | Incremental life- years | ICER | |
|---|-------------------------|---------------------|----------------------------|------------------|----------------|
| | | | | Cost/QALY (€) | Cost/LY (€) |
| Specificity echocardiography* | | | | | |
| 0.8 | 109 | -0.071 | 0.0005 | Dominated | 230 756 |
| 0.9 | 94 | -0.0038 | 0.0005 | Dominated | 199 481 |
| 1 | 79 | -0.004 | 0.0005 | Dominated | 168 207 |
| Sensitivity echocardiography* | | | | | |
| 0.8 | 92 | -0.034 | 0.0004 | Dominated | 229 587 |
| 0.9 | 92 | -0.034 | 0.0005 | Dominated | 204 574 |
| 1 | 93 | -0.035 | 0.0005 | Dominated | 184 564 |
| Sensitivity and specificity of echo = 1 'the perfect test' | 79 | -0.005 | 0.0005 | Dominated | 158 266 |
| Gender | | | | | |
| <u>Female</u> | 92 | -0.032 | 0.00001 | Dominated | 1 824 968 |
| <i>Prevalence 1/1099</i> | | | | | |
| <i>Increased mortality due to HCM 0.0001</i> | | | | | |
| <u>Male</u> | 93 | -0.035 | 0.0008 | Dominated | 110 230 |
| <i>Prevalence 1/383</i> | | | | | |
| <i>Increased mortality due to HCM 0.0007</i> | | | | | |
| Cost of added life years | 93 | -0.034 | 0.0005 | Dominated | 195 4 |

Abbreviations: QALY, quality-adjusted life-years; LY, life-year; Echo, echocardiography; HCM, hypertrophic cardiomyopathy
* Base case sensitivity = 0.94, specificity = 0.91.

Implications for policy (Paper IV)

As the background to the evaluation of the cost-effectiveness of screening for hypertrophic cardiomyopathy in young athletes was the National Board of Health and Welfare's wish to issue national guidance, it has had a direct implication for current Swedish policy on HCM screening [58]. Given that the analysis clearly pointed out that screening for HCM would be either very costly per life-year gained or could result in a net loss of QALY, the national board did recommend against publicly funded screening. However, the National Board of Health and Welfare did not recommend against screening performed within the sport associations. Based on the current analysis, this would actually lead to loss in QALY, regardless of whether the screening is paid for by the government or the sport associations. As there is, to the author's knowledge, no inventory of the sport associations currently offering this type of screening, nor is it known at what age screening is offered, it is

difficult to estimate the consequences of such a screening. Based on the current analysis, if screening were introduced to 12-year-olds competing in sport, it would lead to a loss of 2 648 QALYs per cohort of 12-year-olds participating in competitive sport in Sweden today. Accompanied by the cost incurred and a willingness to pay €35 000 per QALY, screening would lead to loss of total net benefit of €102 664 107.

A recently published study estimating the cost-effectiveness of screening for 16 different cardio-vascular diagnoses, including HCM, has come to a different conclusion with regard to the cost-effectiveness of screening to prevent SCD in the United States [59]. The authors conclude that screening would save 0.0024 life years per individual screened at a cost of \$199, yielding a cost-per life-year saved of \$76 100. More interestingly they conclude, on the contrary to our analyses, that screening will lead to a gain of 0.0018 QALY. It is, however, unclear from the article how false positive results impact their analysis as no estimates of sensitivity and specificity are given for echocardiography. In addition, as they only present the results on an aggregated level for all diagnoses. Hence the negative results for screening shown in our study with regards to HCM may have been observed in the study from the United States as well, but could be hidden behind very positive effects of screening on other diagnoses than HCM. The divergent result indicates that introducing screening with a broader perspective of diagnosis in mind might be valuable to explore.

GENERAL DISCUSSION

As stated in the introduction, concerns have been raised that many health technologies would not be considered for funding based on standard methods of cost-effectiveness, due to scarcity of evidence. However, as argued here and elsewhere [4, 60], scarce evidence per se should not be a hindrance to perform cost-effectiveness analyses. As long as the amount and quality of evidence used for the analysis are properly characterized, scarce evidence does not necessarily need to be an obstacle. Overall it could be argued that the case studies in this thesis themselves provide some evidence that conducting economic evaluations using the proposed analytic framework is feasible even when evidence is scarce. It was shown that cost-effectiveness could be comprehensibly estimated for all three cases, and inform decisions on whether or not to utilize the technologies. The results showed that, given current information, both C-Leg and AA could be seen as cost-effective whereas screening for HCM would not. In both the case of C-Leg and AA it was also shown that conducting further research could be cost-effective.

Based on current practise of use of evidence for cost-effectiveness in Sweden, and other countries, it is very likely that the technologies dealt with in the case studies would not have been evaluated at all due to the scarcity of evidence underpinning them. In this context it is important to consider the consequences of not evaluating a technology due to scarce evidence. In most cases, this implies that current clinical practice is maintained, leading to the costs and consequences associated with current clinical practice. This is unfortunate, and a clear consequence of such reasoning is that it will inevitably lead to arbitrary adoption of health technologies, making it difficult to allocate resources optimally. As shown from the case studies this can lead to a considerable amount of health being foregone. Rather than precluding technologies due to scarce evidence, making informed decisions utilizing the proposed framework for cost-effectiveness analysis, would therefore seem appropriate.

Utilizing the methodological framework applied in this thesis, rather than making decisions ad hoc, also has the potential to elucidate effects of the treatments perhaps not earlier considered as important. By clearly structuring the decision at hand, course of events and how these impact the overall result often become clearer. Examples from the case studies are the effect of taking

quality of life into account when screening for HCM, and the effect of number of problems with the prosthetic knee on quality of life with regard to C-Leg. In the case of screening for HCM, the previous studies had only focused on the possibility of saving life. When using decision modelling that synthesizes evidence from several sources, including quality of life, it is clear that failing to consider the impact of screening on quality of life could lead to a faulty assumption about the positive clinical effect of screening. Similarly, all studies previously investigating the effect of the C-Leg, compared to non-microprocessor-controlled knees, had focused on the improved physical function. When analysing the cost-effectiveness of C-Leg compared to non-microprocessor-controlled knees, the results showed that an important factor not earlier considered was the decreased number of problems encountered with the C-Leg. This aspect had been overlooked previously but appeared as an important parameter once the decision problem had been structured in more detail with a decision-analytic model.

So as argued here the case studies show some proof of the feasibility of performing cost-effectiveness analyses even when evidence is scarce and for technologies that are seldom evaluated with regards to cost-effectiveness. However, even if the framework of economic evaluations cannot be seen as a hindrance for economic evaluation of these technologies there are still methodological aspects that would need to be examined further, within the framework. Such a methodological area is for example, as pointed out earlier [2], how to incorporate the incremental development of devices. An advantage of using decision analytic model as a basis for decision with regard to this is however that it can be easily updated. If a new version of the device is presented and new functionalities added, or new evidence becomes available as in the case of C-Leg, the cost-effectiveness given the new evidence can be easily estimated.

Both the estimation of cost-effectiveness and the value of further research are dependent on the correct characterization of uncertainty [61]. With this in mind the difference in results between Paper II and III does highlight an important matter for performing cost-effectiveness analysis when evidence is scarce. Failing to adequately characterize the uncertainty might have a substantial effect on the interpretation of the results. Utilizing only mean values from experts does not seem to properly account for the experts' true uncertainty about the quantity of interest. The case study described here illustrates the limitation of using ad-hoc elicitation of estimates of means, in

terms of characterising the level of uncertainty in experts' beliefs. When experts' were allowed to fully express their uncertainty regarding the model parameters, all expressed high levels of uncertainty for all elicited parameters. No expert expressed a belief that suggested they were fully certain of the value of a particular elicited parameter. Therefore failing to account for this uncertainty could underestimate the value of further research. As noted from the difference between Paper II and III, the decision with regard to implementation of C-leg or not could be changed from "implement without further research" to "implement but conduct more research". Not capturing the uncertainty properly, could therefore lead to value of research forgone. Making use of formal expert elicitation when evidence is scarce therefore seems to be adequate to fully capture the uncertainty, and thus the value of further research when other evidence is missing.

Even if the use of formal expert elicitation to estimate parameters for cost-effectiveness analysis has been limited, formal expert elicitation is shown to adequately capture the experts' beliefs [41]. However, although the method has been shown to capture the experts' uncertainty of the parameters, it is important to acknowledge that it does not capture the inherent risk of bias accompanied with the use of experts. By performing the elicitation with a consistent methodology it is of course hoped that the risk of bias is minimized, but we can of course not validate experts' beliefs because they are essentially unknown. Techniques exist (such as calibration) that try to get a handle on how accurate elicited beliefs are, however, these are not without their problems [13]. Further research on the methodological uncertainty of using experts could therefore be warranted.

It has been noted in previous work, utilizing expert elicitation to characterize uncertainty in models, that the use of elicitation can be rather time consuming [25]. In both Paper III and IV the formal elicitation approach for obtaining input parameters proved feasible to perform within reasonable time limits. The format of the elicitation was also considered to be comprehensible for the experts. Especially the elicitation performed in Paper IV, where the elicitation was distributed via e-mail, proved that performing elicitation when evidence is missing would be fully applicable under normal timeframes for an economic evaluation. If a facilitator on site is to be used, as in Paper III, it is substantially more time consuming, specifically if expert from different geographical areas are to be used. However, all in all the time needed to perform elicitations such

as those performed in this thesis could not be seen as an argument for refraining from performing elicitation when evidence is scarce.

The case studies in this thesis show that it is feasible to perform cost-effectiveness analysis for technologies not commonly evaluated in terms of cost-effectiveness, and where evidence is scarce. It is important to remember that currently there is no formal demand for cost-effectiveness analyses in Sweden and many other countries, except for pharmaceuticals. This leads to a situation where the decision on whether or not to implement a new technology highly relies on the county councils or even individual prescribers, and the cost, rather than the cost-effectiveness, of the technology. Both the AA and C-Leg are examples of this but where the cost-effectiveness analysis showed that they could be considered cost-effective given current information. Investigatory work on a Swedish national benefit board for non-pharmaceutical health technologies is, however, currently ongoing [62]. If such a system was to be implemented, it is important to consider whether the demands for evidence should also change. Should an amendment be made to generally demand randomized controlled trials (RCT) even for non-pharmaceutical technologies, or should we maintain the same requirements of evidence as we have today, but with the added requirement of cost-effectiveness analysis? The former would lead to an increased number of RCTs, and thus, evidence higher up on the hierarchy of evidence with regard to clinical effect. However, as the current situation of not requiring such studies for clinical effectiveness will most likely prevail, it is important to make an as informed decision as possible given current information. As shown in this thesis, there is no direct hindrance to carry out cost-effectiveness analyses even under these circumstances. It could even be seen as a tool for identifying situations where more evidence is cost-effective and important to collect, and thus promote a shift towards more clinical trials even for non-pharmaceutical technologies where specifically needed.

CONCLUSIONS

- Adding the Airsonett Airshower treatment to optimized standard therapy for adolescents with perennial allergic asthma would generate additional QALYs at a reasonable cost, compared with placebo.
- The C-Leg appears to yield positive health outcomes at an acceptable cost, given current information. Further research does, however, appear to be worthwhile, in terms of cost-effectiveness.
- Screening young athletes for hypertrophic cardiomyopathy is not likely to yield survival benefits at a cost normally considered to be cost-effective, and if quality of life is considered in the analysis, screening is associated with higher costs and a loss of QALYs. Thus, based on the present findings, a strategy of screening young athletes for hypertrophic cardiomyopathy is unlikely to be cost-effective.
- The case studies in this thesis indicate that the framework for economic evaluations in health care is feasible to use, even for health technologies not commonly evaluated with cost-effectiveness analysis. The character of the technology per se should not exclude the technology from being evaluated with regard to costs.
- Expert elicitation shows promise of being an adequate method of characterizing uncertainties when evidence is scarce, and allowing the value of further research to be determined.
- In conclusion, this thesis shows that scarcity of evidence should not preclude the use of cost-effectiveness analysis. On the contrary, in such cases it is probably more important than ever to use a framework that enable us to define key parameters for a decision problem and identify available evidence in order to determine cost-effectiveness given current information and provide guidance on further data collection.

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