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THE IMPORTANCE OF USING STANDARDIZED METHODS TO ESTIMATE UTILITY WHEN CALCULATING QUALITY ADJUSTED LIFE-YEARS

Part 1

BY
LARS ODDERSHEDE

DISSERTATION SUBMITTED 2014

AALBORG UNIVERSITET

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THE IMPORTANCE OF USING STANDARDIZED METHODS TO ESTIMATE UTILITY WHEN CALCULATING QUALITY ADJUSTED LIFE-YEARS

by

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AALBORG UNIVERSITY
DENMARK

Thesis submitted for the qualification of PhD in Health Economics

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CV

Lars Oddershede has an interdisciplinary education from Aalborg University, Denmark. He studied for a Bachelor's degree in Medicine with an Industrial Specialization, which includes courses in physiology, pathophysiology, anatomy, pharmacology, and clinical placements at local hospitals. In 2011, he finished his Master's degree in Medical Market Access. During this two year course he primarily focused on Health Economics with a special emphasis on applied cost-effectiveness analysis of medical devices. A wish to gain a greater insight into the commercial perspective motivated him to do a separate degree in Business Administration next to his PhD studies. After completing his degree in Business Administration in 2013 he started working part-time as a biostatistician at Aalborg University Hospital.

Throughout his research-career, Lars has been especially interested in the application of statistical methods. In acknowledgement that good quantitative methods are merely useful if the data informing the analysis are equally good, his PhD studies focused on how to get optimal estimates of an intervention's effectiveness under non-ideal circumstances.

FOREWORD

If you had told me that one day I would be handing in my PhD thesis in Health Economics during my years as an undergraduate student in Medicine, chances are I would have laughed. Although, I am not sure that my dad would have disputed it.

But things changed when I started my graduate studies in Medical Market Access. Here, Lars Ehlers sparked my interest for Health Economics and for research. During this period I published my first two articles in cooperation with Lars Ehlers. Having tasted blood, I wanted more. With a great sense of gratitude I accepted Lars Ehlers' offer to become a PhD student.

During my time as a PhD student countless people have helped me and for that I am grateful. I owe a special thanks to Jan Jesper Andreasen, Lars Ehlers, and Karin Dam Petersen for supervising me throughout the process. Karin, thank you so much for agreeing to help me when the focus of my research shifted towards your field of expertise.

In addition, special thanks are extended to my co-authors and those who are acknowledged in my papers. Your valuable comments and corrections have been most appreciated.

Also, I am grateful to Mark Sculpher for giving me the opportunity to visit the Centre for Health Economics at University of York. Working alongside you and Simon Walker has been the biggest learning opportunity of my PhD.

On that note, I would like to thank my girlfriend Tessa Bay for her patience. Patience when I suddenly decided I was going to spend five months in the UK. Patience when I spent long hours at the office or in front of the computer at home. And patience when my work-related frustrations left the office along with me and came home to you.

Sabrina Storgaard Sørensen: thank you for all the chats and for your advice. Every PhD student should have as great an office-buddy as you. To the rest of my wonderful colleagues in the Danish Center for Healthcare Improvements: thank you for the discussions and your feedback on my written work.

Last but not least, I want to thank my friend and mentor Søren Lundbye-Christensen. Thank you for having faith in me and for saying the words I will never forget you for: "The first author is merely the useful idiot with a Word document - the real genius is the last author. Someday, Lars, you will also be the last author and be able to do real research". I sure hope so!

I alone am responsible for the final content and any mistakes in the thesis.

Lars Oddershede,

Aalborg, September 2014.

RESUME IN ENGLISH

Resources are scare and healthcare systems must, therefore, prioritize which new technologies should be funded, and which should be rejected. To aid decision makers in their choice, economic evaluations can be conducted to assess the cost-effectiveness of the new technologies. However, the Danish guideline for economic evaluations has no stated preference for the type of economic evaluation and thereby no preference for how effectiveness should be measured.

The present thesis argues that two problems could be solved by updating the Danish guideline for economic evaluations to include a stated preference for measuring effectiveness in terms of quality adjusted life-years (QALYs). Firstly, it would be possible to compare the cost-effectiveness of new technologies across conditions. Secondly, it would make it possible to capture both effects and side effects of new technologies in a single outcome-measure. Therefore, the present thesis explores how to procure optimal estimates of quality of life, i.e. utility, for QALY calculations in different situations, where different data are available.

It is discussed how to procure utility estimates in three situations where different data are available to the analysts. Firstly, the situation where individual patient-level data (IPD) on utility are available from the preferred generic preference-based measured of health, assumed to be the three level version of the EuroQol five dimensions of health questionnaire (EQ-5D). Secondly, the situation where IPD on EQ-5D are unavailable but foreign utilities estimates can be identified in the literature. Thirdly, the situation where analysts neither have IPD on EQ-5D profiles, nor foreign utilities of the EQ-5D, but other measures of health are available.

Using the methodological papers and economic evaluations conducted during the PhD project; the thesis exemplifies why it is important to use standardized methods when calculating QALYs in economic evaluations. If the

Danish decision makers are to use economic evaluations as a tool for prioritizing between new technologies, the QALY estimates must be a reflection of the national preferences for health. As a result, optimal utility estimates can be obtained by applying the national value set to the IPD on EQ-5D profiles. However, this is not an option if IPD on EQ-5D profiles are unavailable. In that situation, foreign utilities of the EQ-5D can be used, but these cannot be applied in a Danish economic evaluation without adjustment. Therefore, a novel method was developed to adjust foreign mean utility values to make them transferable and applicable to the Danish setting. If both IPD on EQ-5D profiles and foreign utilities of the EQ-5D are missing, calculations may be standardized by mapping other measures of health to the EQ-5D. Mapping by statistical association provides accurate predictions of what the incremental QALYs would be, if EQ-5D data had been available.

In summary, the thesis recommends that a shared measure of health, QALYs, is used in order to make the results of the economic evaluations submitted to the Danish Health and Medicines Authorities more comparable across conditions and interventions. An efficient use of the scarce resources could then be obtained by choosing to fund the new technologies which are considered cost-effective.

RESUME PÅ DANSK

Da ressourcerne er begrænsede i sundhedsvæsenet skal der tages stilling til hvilke nye behandlinger der skal tilbydes og hvilke der skal afvises. For at hjælpe beslutningstagerne med deres valg kan omkostningseffektiviteten af de nye behandlinger undersøges ved hjælp af sundhedsøkonomiske evalueringer.

I denne afhandling argumenteres der for, at to typiske problemer ved sundhedsøkonomiske evalueringer kan forhindres ved, at opdatere den danske guideline så den inkluderer en præference for at sundhedsgevinster opgøres i kvalitetsjusterede leveår (QALYs, fra det engelske quality adjusted life-years). For det første ville dette gøre det muligt, at sammenligne omkostningseffektiviteten af nye behandlinger på tværs af sygdomme og interventioner. For det andet ville det blive muligt, at fange både effekter og bivirkninger af nye behandlinger i ét effektmål. Af denne grund undersøges det i afhandlingen hvordan optimale estimater af livskvalitet, til QALY beregningen, kan opnås i forskellige situationer med forskellig data-tilgængelighed.

Gennem brug af den metodeudvikling og de sundhedsøkonomiske evalueringer der er udført, som en del af ph.d. projektet, bliver det eksemplificeret hvorfor det er vigtigt, at anvende standardiserede metoder til at beregne QALYs i sundhedsøkonomiske evalueringer.

Konklusionen på afhandlingen er, at et fælles effektmål, QALYs, bør beregnes på standardiseret vis og anvendes i alle sundhedsøkonomiske evalueringer der indsendes som en del af ansøgningen om tilskud til lægemidler hos Sundhedsstyrelsen.

PRESENTATIONS AND PUBLICATIONS

The papers presented in Appendices A-F are the product of the PhD project. Most of the studies have either been accepted for presentation or for publication. A summary of presentations and publications is provided below:

The paper entitled "Cost-effectiveness analysis of protease inhibitor monotherapy vs. ongoing triple-therapy in the long-term management of HIV patients" has been accepted for a poster presentation at the *International Society for Pharmacoeconomics and Outcomes Research* 17th Annual European Congress in Amsterdam, November 2014, and for an oral presentation at the *International Congress on Drug Therapy in HIV Infection* in Glasgow, November 2014, and is currently in peer review, see Appendix A.

The paper entitled "Health economic evaluation of single-lead atrial pacing vs. dual-chamber pacing in sick sinus syndrome" is published in the peer reviewed journal *Europace*, see Appendix B[1].

The paper entitled "Adjusting foreign utilities of the EQ-5D-3L increases their transferability" is currently in peer review, see Appendix C.

The paper entitled "Estimation of utility values from visual analog scale measures of health in patients undergoing cardiac surgery" is published in the peer reviewed journal *ClinicoEconomics and Outcomes Research*, see Appendix D[2].

The paper entitled "Endoscopic vein harvesting for coronary artery bypass grafting is safe and reduces postoperative resource consumption" was accepted for oral presentations at the 2014 annual meeting in the *Danish Society of Cardiothoracic Surgery* and at the 6th joint conference of the *Scandinavian Association for Thoracic Surgery* in Gothenburg, September 2014, and has been

accepted for publication in the peer-reviewed *Journal of Cardiovascular Diseases & Diagnosis*, see Appendix E[3].

The paper entitled "Long-term cost-effectiveness of endoscopic vs open vein harvest for coronary artery bypass grafting" was accepted for oral presentation at a discussed session at the 10th world congress in health economics organized by the *international Health Economics Association* in Dublin, July 2014, and is currently in peer review, see Appendix F.

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CHAPTER 1. INTRODUCTION

The PhD thesis which you are about to read is in the field of economic evaluation of health technologies. During the project period, three economic evaluations were performed using quality adjusted life-years (QALYs) as the measure of effectiveness, see appendices A, B[1], and F. Carrying out these economic evaluations gave rise to a series of methodological considerations. All the methodological considerations revolved around a central theme: how could available data be used to obtain the best possible estimates of utility to calculate QALYs in economic evaluations? This thesis compiles these considerations.

The thesis is meant as a helpful tool in the process of updating the Danish national guideline for economic evaluations[4]. Before embarking on the discussion about how Denmark should put the 'Q' in QALY, Chapter 1 will explain why economic evaluations of health technologies are necessary and how these may be carried out.

1.1. WHY ECONOMIC EVALUATIONS ARE NECESSARY

> "The reason economic evaluation is needed is because markets alone do not provide efficient solutions, particularly in health care. However, when free markets don't exist, active decisions have to be made about which health services should be funded given the scares resources available… …The overall aim is to maximize benefits given the resources available"
>
> (Fox-Rushby et al. 2005)[5]

Resources, be it money, people, time, facilities, equipment, or knowledge, are scarce[6]. In the absence of a free market for health care, the government must decide which new health care interventions should be funded and which should be rejected. Randomized clinical trials are considered the golden standard for

providing evidence that a new technology is more efficient than the existing technology. However, the decision to adopt a new technology cannot merely be based on the evidence that it is more efficient than the existing technology as new technologies are frequently also more expensive than the existing. Hence, it is necessary to assess the value-for-money of the new technology to avoid inefficient use of the scarce resources. The value-for-money (cost-effectiveness) of a new intervention is assessed in an economic evaluation which compares the new intervention and its alternatives in terms of costs and consequences[6]. By choosing to fund the interventions which are deemed cost-effective, an efficient use of the scarce resources could be obtained[6].

It does, however, vary to what extent the economic evaluations are used in decision making. The UK National Health Service (NHS) has an advisory body called the National Institute for Health and Care Excellence (NICE) which advises the NHS on how to provide equitable access for all patients to the most clinically effective and cost-effective treatment[7]. To advice the NHS about how to prioritize the scarce resources, NICE assesses and commissions technology appraisals of both new and existing medicines and treatments. In contrast, economic evaluations are used more infrequently in the Danish healthcare system[8].

1.2. ECONOMIC EVALUATIONS OF NEW TREATMENTS IN DENMARK

In Denmark, pharmaceutical companies have the opportunity to submit an economic evaluation as part of the reimbursement application for the Danish Health and Medicines Authorities[9]. As it is optional, rather than a requirement, to submit cost-effectiveness evidence, it is not always done. If the application contaisn an economic evaluation, it is sent to external validation to ensure that the Danish guideline for economic evaluation has been followed. Although other agencies, like NICE, frequently update their guideline, the Danish guideline have remained the

same since they were developed in 1998[4,10]. As a result, the Danish guideline does not state what the preferred outcome-measure should be. Instead, the Danish guideline states, that no single outcome-measure can be used in all economic evaluations[4,10]. As such, the Danish guideline leaves it up to the pharmaceutical companies to choose which type of economic evaluation to perform.

By leaving it up to the pharmaceutical companies to choose how the effectiveness of the treatment is measured, two issues arise: firstly, it becomes difficult to compare the results of one economic evaluation with another, and secondly, it could be questioned whether pharmaceutical companies always choose an outcome-measure which captures both the effects and the side effects of their new product.

This thesis will address how these two issues may be handled by updating the Danish guideline to take a position towards which type of economic evaluation should be preferred.

1.3. TYPES OF ECONOMIC EVALUATIONS

Economic evaluations are typically divided into partial and full economic evaluations. Full economic evaluations assess both the costs and outcomes of two or more interventions for the same condition[6]. Comparative results are then presented using the incremental cost-effectiveness ratio (ICER), which shows the additional cost associated with obtaining an additional unit of health. The three types of full economic evaluations are called: cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis. The main difference between these is the method for valuing health outcomes.

The cost-benefit analysis is consistent with economic theory and provides the result, which the market would produce if one had been operating. This is

frequently referred to as the welfarist approach to economic evaluation of health care interventions and it entails valuing both costs and health oucomes in monetary units. As the current Danish guideline states that a cost-benefit analysis should only be submitted along with either a cost-effectiveness analysis or a cost-utility analysis, it is not considered likely to become the preferred type of economic evaluation when updating the guideline. Consequently, the cost-benefit analysis will not be discussed further in this thesis.

Where welfarism relies on the premise that social welfare is a function of individual utility, extra-welfarism relies on the assumption that social welfare can be measured on other information, such as health[11]. The extra-welfarist would argue that economic evaluations should be conducted to help allocate the health care budget and hence the resources consumed should be compared to the health outcomes. As such, both cost-effectiveness analysis and cost-utility analysis are conducted from an extra-welfarist approach as they measure value in terms of health outcomes.

In a cost-effectiveness analysis, the effectiveness is measured in a single clinical or health-related outcome relevant to all interventions being compared[5]. Examples of such outcome-measures could be 'Cases detected', 'Life-years gained', or 'Episode-free days'[6]. The main limitation of the cost-effectiveness analysis is that it only considers a single outcome and that outcome may only be applicable to the interventions being compared. This causes two problems. Firstly, the results may not be useable for comparison across other interventions and disease-areas[5]. Secondly, by using a single outcome-measure it is impossible to capture both effects and side effects of a new technology.

The cost-utility analysis offers a solution for these two issues by measuring the outcome in terms of quality adjusted life-years (QALYs). A QALY is defined as a year lived in full health and, therefore, QALYs are estimated by multiplying the length of life by the utility, or the health-related quality of life[6]. The terms utility and health-related quality of life are not interchangeable. Utilities must be elicited

under uncertainty, i.e. using standard gamble methods, while many instruments measuring health-related quality of life rely on other methods[6]. The terms are, however, frequently used as if they were interchangeable and the papers in Appendices A, B[1], C, D[2], and F are no exception. As economic evaluations, which measure health outcomes in terms of QALYs, are frequently referred to as cost-utility analyses, in the chapters to come the term utility will be used. As QALYs capture both effects and side-effects of healthcare interventions on both life expectancy and quality of life, it provides a generic measure of health for economic evaluations[6]. As such, comparison across interventions and disease-areas becomes possible if health is measured in QALYs. This makes cost-utility analysis an appealing approach to assess the cost-effectiveness of new technologies in Denmark. The notion that cost-utility analysis should be the preferred type of economic evaluation in Denmark was also raised in a recent report containing ten solutions for the fiscal challenges of the Danish healthcare system:

> "… in many respects it would be absurd to think in terms of a cost-benefit ratio. The relevant approach would be a cost-utility approach based on quality adjusted life years."
>
> (Pedersen et al. 2011)[8]

The calculation of QALYs in economic evaluations requires good utility estimates obtained from generic questionnaires with a preference-based valuation of health states[6]. If the Danish guideline for economic evaluations is to recommend the use of QALYs as the preferred outcome-measure, a practical question arises: how should utility be estimated?

1.4. MEASURING UTILITY FOR ECONOMIC EVALUATIONS IN DENMARK

In order for the Danish healthcare system to compare results between cost-utility analyses, it is essential to use the same instrument for estimating patients' utility. This is referred to as setting the 'reference case' for a generic preference-based instrument by NICE[12]. Choosing the reference case instrument requires considerations about validity across different patient groups, reliability, ease of administration, and popularity abroad. Examples of such generic preference-based instruments would be the EuroQol 5 dimensions of health questionnaire (EQ-5D)[13], the Short-Form 6 dimensions of health questionnaire, the 15 dimensions of health questionnaire, The Health Utilities Index questionnaires, and many more. The three level version of the EQ-5D questionnaire (EQ-5D-3L) contains the following five dimensions at three levels of severity: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The answers to the five questions of the EQ-5D, the EQ-5D-3L profile, are converted into the EQ-5D index[14], which will be referred to as a utility value in the present thesis. This is done by using weights from a value set (previously referred to as a 'tariff'[14,15]). The weights are obtained by elicitation of health preferences through a time trade-off (TTO) exercise in a large sample of the general population. While elicitation methods are a highly relevant topic when discussing how to measure utility in economic evaluations, it is beyond the scope of the present thesis and will therefore not be addressed any further.

A five level version of the EQ-5D questionnaire (EQ-5D-5L) is also available[16]. However, the value set for the five level version is currently a crosswalk from the three level value set[17], and the three level version, therefore, remains the most widely used. Hence, when referring to the EQ-5D in this thesis the questionnaire in question is the EQ-5D-3L.

Currently there are Danish value sets for the EQ-5D and 15D and one of these might therefore be considered as the preferred instrument[18,19]. There are two important cases to be made regarding the choice between the 15D and the EQ-5D: 1) The EQ-5D preference weights were elicited using TTO[19], i.e. a choice-based method representing social value[15], while the 15D preference weights were obtained using a non-choice-based method of preference elicitation[18], and 2) the EQ-5D is more frequently used on an international level[20,21]. The latter issue becomes important if national utility data for a particular health state cannot be found and must be valued using the results from foreign studies. Hence, it would be preferable to use the same instrument as the majority of values from other instruments are not considered comparable[6,11]. The main arguments against using the EQ-5D would include: concerns about its generic nature[22], concerns about its discriminative ability, and methodological arguments for using standard gamble for preference-elicitation rather than TTO. Other instruments might have a larger discriminative ability than the EQ-5D and be valid over a larger range of conditions, i.e. truly generic, but none has currently found as wide an application and acceptance as the EQ-5D.

Throughout this thesis it will, therefore, be assumed that in an updated Danish guideline, the reference-case for economic evaluations would be a cost-utility analysis using the EQ-5D to measure utilities. Therefore, optimal utility estimates for these cost-utility analyses would require individual patient-level data (IPD) on EQ-5D, when treatment options are compared in clinical trials. Availability of such IPD would allow the national value set to be applied and, hereby, the cost-effectiveness results would be a reflection of national preferences for health. Such ideal conditions for estimating utilities are, however, not always present. Analysts may face situations where IPD on EQ-5D profiles are unavailable, but foreign utilities, or other measures of health, are available. The remainder of the thesis will therefore address how to obtain optimal utility measures under ideal and non-ideal conditions. The hypothesis is that utility estimates obtained using non-standardized methods will bias the cost-effectiveness result, i.e. the results will not

reflect the national preferences for health, while standardization of the methodology will provide unbiased results.

1.5. DEFINING THE RESEARCH QUESTION

As explained above, there are several arguments for performing cost-utility analyses to assess the cost-effectiveness of new health technologies in Denmark. Likewise, there are several arguments for using the EQ-5D as the reference case instrument for measuring utility for QALY calculations. Assuming that the Danish Health and Medicines Authority will update the national guideline for economic evaluations to include a preference for cost-utility analyses, and utility measures from the EQ-5D, the research question is:

HOW CAN AVAILABLE DATA BE USED TO PROCURE OPTIMAL UTILITY ESTIMATES FOR THE CALCULATION OF QUALITY ADJUSTED LIFE-YEARS IN THE ASSESSMENT OF COST-EFFECTIVENESS OF NEW HEALTHCARE INTERVENTIONS?

Calculation of QALYs under non-ideal conditions is generally considered technically challenging and, therefore, NICE recently funded four technical support documents[23–26] on this matter to compliment the NICE "guide to the methods of technology appraisal"[12].

1.5.1. DELIMITATION OF THE RESEARCH QUESTION

Several other subjects would be equally relevant to address. Examples of such topics might include discussions about: the preferred perspective of the economic evaluations submitted to the Danish Health and Medicines Authorities, whether the EQ-5D should be the preferred instrument, how to elicit preference-weights, and what the opportunity cost might be in terms of cost per QALY. These issues will

not be addressed in the present work. Instead, the NICE reference-case will be applied to hold all other matters equal[12]. Hence, the present thesis will only elaborate on how to obtain optimal utility estimates for Danish cost-utility analyses.

1.6. READING INSTRUCTIONS

The thesis is meant as a helpful tool in the process of updating the Danish national guidelines for economic evaluations. The intention with this thesis is to exemplify why it is important to use standardized methods for estimating utility, when health outcomes are measured in terms of QALYs.

As mentioned in the beginning of the introduction, this thesis is a compilation of methodological considerations, which arose when performing the three economic evaluations presented in Appendices A, B[1], and F. These methodological considerations are summarized in Chapter 2-5. These chapters generally follow the same structure:

X.1 A brief introduction to the chapter will explain why you (a reader assumed to be a health economist working with economic evaluations) should care about the content of that chapter and which papers from the appendices are relevant to that specific chapter.

X.2 Then a brief introduction to the condition and the interventions investigated in the cost-utility analysis will follow. Here, the reader is encouraged to pause from reading the thesis and read the paper(s) relevant to the chapter, before continuing with the section named “The comparison”.

X.3 Includes an exemplification of why it is important to use standardized methods to ensure that the results of one Danish economic evaluation can be compared to another.

X.4 The lessons learned from considering the methodological issues, which arose when performing the economic evaluations, are summarized in a preliminary conclusion.

The preliminary conclusions are subsequently used to provide some recommendations for estimating health outcomes in terms of QALYs in economic evaluations conducted from the perspective of the Danish healthcare system.

Each of the papers presented in Appendices A-F[1–3] should be viewed as independent pieces of work. As such, the first table in a new paper will be named Table 1. The details of reference number 1 in a paper cannot be found in the literature list of the thesis, but must be found in the reference list of that paper. Likewise, at the first use of an abbreviation in a paper, the abbreviation is spelled out; however, it cannot be found in the glossary of the thesis.

Appendix G contains declarations of authors' contributions. These are mandatory to include when submitting a thesis, which contains articles with multiple authors at the Faculty of Social Sciences at Aalborg University.

Enjoy!

CHAPTER 2. THE MOTIVATIONAL CASE

2.1. AN INTRODUCTION TO THE CASE

The aim of Chapter 2 is to familiarize the reader with the issues of economic evaluations valuing health outcomes in terms of QALYs under non-ideal circumstances. Section 2.3 exemplifies how much the results of two economic evaluations may deviate when non-standardized methods are used.

This chapter will clarify why the remaining chapters of the thesis will discuss how methods, for measuring utility for economic evaluations, could be standardized in Denmark.

2.2. THE CONDITION AND THE INTERVENTIONS

A frequent type of cardiovascular disease is arteriosclerosis of the coronary arteries. This is a chronic disease which is characterized by abnormal thickening and hardening of the arteries that supply the heart with nutrients and oxygen[27]. While arteriosclerosis is a normal part of the ageing process, it is worsened by genetic predisposition, smoking, hypertension, diabetes, hypercholesterolemia, and a sedentary lifestyle[28]. As coronary arteriosclerosis develops, patients' risk of angina, myocardial infarction, and mortality increases. Treatment of the condition involves management of risk factors through lifestyle changes and medicine and, in later stages, percutaneous coronary intervention or coronary artery bypass grafting (CABG). CABG is the preferred treatment for multi-vessel coronary artery disease[29]. CABG is a surgical treatment for coronary artery disease involving opening of the chest wall to allow access to the heart, see Figure 2-1.

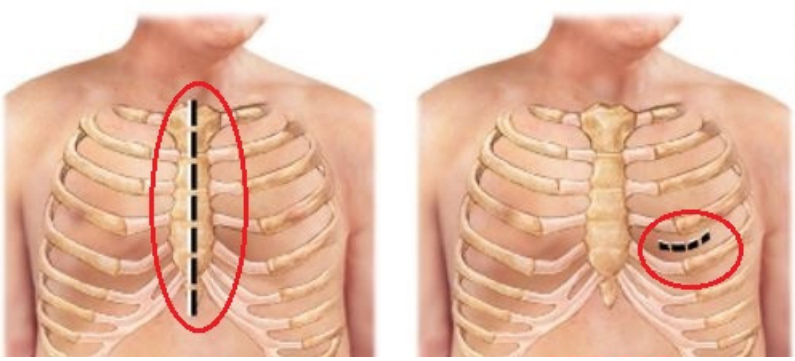

Figure 2-1: Incision in the chest to obtain access to the heart. On the lefthand side a sternotomy - on the righthand side the minimally invasive direct coronary artery bypass. Illustration from[30].

When access is obtained, the surgical team may choose to bypass the blocked coronary arteries, to allow oxygen and nutrients to reach the affected heart muscles, by reattaching the patient's left and right internal mammary arteries to the coronary circulation below the blockage, or to use an arterial/venous conduit[31]. The radial artery is used as a conduit in a mere 5.5% of bypass procedures[32].

In the majority of patients, the left internal mammary artery is connected to the left anterior descending coronary artery, while saphenous vein grafts are used to connect, or graft, healthy arteries to the remaining blocked coronary arteries, see Figure 2-2.

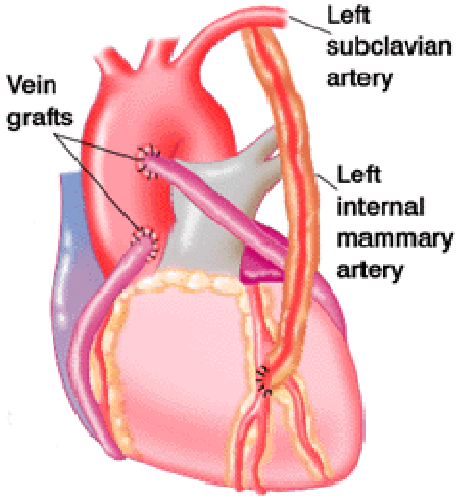

Figure 2-2: Triple bypass of the coronary blood flow using the left internal mammary artery to the left anterior descending coronary artery and two venous grafts as conduits. Illustration from[33].

Because the greater saphenous vein is still frequently used as a conduit, the manner in which it is obtained receives a lot of attention. Previously, this process involved harvesting the vein using an open vein harvesting (OVH) technique, with a single continuous skin incision. However, today the majority of vein harvesting procedures are performed using an endoscopic vein harvesting (EVH) technique[3,34–36]. The two economic evaluations being compared in the following section have both investigated the short-term cost-effectiveness of EVH compared to OVH for CABG[37,38].

2.3. THE COMPARISON

Because both studies estimated the cost-effectiveness in terms of cost per QALY under non-ideal circumstances, these offer a great motivational case. The two studies applied slightly different methodologies; the first study generated a decision analytic model aimed at calculating cost per QALY[38], whereas the second study

was a piggy-back cost-effectiveness analysis of a randomized controlled trial, which calculated both cost per purulent infection avoided and cost per QALY[37]. The studies considered slightly different types of resource consumption and this resulted in two quite different estimates of mean incremental costs, see Table 2-1.

Table 2-1: Results of two economic evaluations comparing endoscopic vein harvesting to open vein harvesting for patients undergoing coronary artery bypass grafting[37,38].

Analysis	Incremental Cost* ($ USD)	Incremental Effect* (QALYs)	ICER ($/QALY)	Probability of being cost-effective at $50,000 per QALY
Oddershede et al.[37]	$217.14	0.00273	79,391	>1%
Rao et al.[38]	$458.74	0.0231	19,859	95.6%

*ICER – incremental cost-effectiveness ratio; QALY – quality adjusted life-years. USD – United States Dollar. * Increments were calculated as endoscopic vein harvesting minus open vein harvesting.*

Both studies shared a problem – they were unable to identify preference-based measures of health for the EVH group. Therefore, both studies estimated the utility gain from evidence that EVH decreases pain intensity and increases postoperative mobility, compared to OVH. As this was done based on the analysts and clinicians judgments, it is not surprising that they did not arrive at the same estimate. It is, however, very surprising how different the estimates were. Oddershede et al.[37] arrived at an estimate, which was almost a tenth of Rao et al.[38]. Needless to say,

such a difference may have a massive impact on the cost-effectiveness results and cause analysts to arrive at different decisions, which is exactly what happened in this case: Rao et al.[38] estimated EVH to be cost-effective, while Oddershede et al.[37] did not.

2.4. PRELIMINARY CONCLUSION

The reservation towards QALY estimates based on analysts' and clinicians' judgment, i.e. judgment mapping, can easily be summarized:

> "The main criticism of this approach is its arbitrariness."
>
> (Brazier et al. 2007)[11]

Through this motivational example, it is evident that standardized methods must be applied if the study is intended to inform a decision about allocation of scarce resources. Furthermore, the motivational case supports the first part of the hypothesis: cost-effectiveness results can be biased if non-standardized methods are used to calculate QALYs. The remaining chapters will, therefore, focus on how to avoid biased QALY estimates through the use of standardized methods.

In the motivational case, the QALY calculations could have been standardized by "mapping" based on the statistical association between the measures of health at hand, and the EQ-5D[39]. 0 will return to the matter of how this non-ideal situation could be handled, whereas the following Chapter will exemplify why it is ideal to have IPD on EQ-5D profiles.

CHAPTER 3. WHEN PATIENT-LEVEL EQ-5D DATA ARE AVAILABLE

3.1. AN INTRODUCTION TO THE CASE

The case presented in Chapter 2 served to illustrate how health outcomes, measured in QALYs, are difficult to value in the absence of utility data in the literature. The case put forward in the present chapter serves to show how easily an estimate of health outcomes measured in QALYs can be obtained when IPD of EQ-5D profiles are available. The economic evaluation presented in this chapter was performed during a stay abroad at the Centre for Health Economics (University of York, UK) and as such it was conducted from the perspective of the UK NHS and Personal Social Services. The comparison in section 3.3 will show how IPD used to obtain the UK estimate of incremental QALYs may be reused to obtain a Danish estimate.

3.2. THE CONDITION AND THE INTERVENTIONS

Human immunodeficiency virus (HIV-1) is an infectious disease. The virus leads to depletion of different types of cells of the immune system, specifically the CD4+ T cells. As the number of CD4+ T cells decline, the immune system fails and the body becomes increasingly susceptible to opportunistic infections. Over time, these opportunistic infections become life-threatening and may be accompanied by development of cancers[40].

The current standard-of-care treatment for patients living with HIV-1 is combination antiretroviral therapy (ART), usually consisting of three drugs: two nucleoside reverse transcriptase inhibitors with either a non-nucleoside reverse transcriptase inhibitor or a protease inhibitor[41,42]. An increasing pool of evidence suggests that protease inhibitor monotherapy (PIM) may be sufficient to maintain

complete virological suppression for patients who have achieved sustained virological suppression[43]. A recent trial randomised 587 HIV-1 infected patients who had achieved sustained virological suppression to a strategy of Protease Inhibitor monotherapy Versus Ongoing Triple-therapy (the PIVOT trial) and found PIM non-inferior to ongoing triple-therapy (OTT) in terms of preserving future drug options[44]. Likewise, the PIM strategy was shown to be no different than OTT in terms of safety and could, therefore, be considered a treatment option in the long-term management of HIV-1 infected patients[44]. While the PIM strategy might require a stricter regimen of follow-up than the OTT, it is likely to reduce ART drug costs substantially. If the PIM strategy is also comparable to OTT in terms of QALYs gained this may make PIM cost-effective compared to OTT. However, the cost-effectiveness of PIM is unknown[43]. The objective of the case-study presented in Appendix A was to investigate the cost-effectiveness of a strategy of switching to PIM compared to continuing OTT in HIV-1 infected patients.

A detailed description of the methods used to perform the economic evaluation can be found in the methods section of the paper in Appendix A.

3.3. THE COMPARISON

The base-case in the economic evaluation was a within-trial analysis. IPD on consumption of health care resources and ART use were used to calculate costs. QALY calculations were based on IPD of EQ-5D profiles. The EQ-5D profiles were converted into utilities using the UK value set[45]. The base-case analysis handled missing values of costs and utilities by means of multiple imputation, and, as a supplementary sensitivity analysis, a complete-case analysis was conducted. Regression methods were used to adjust costs and QALYs for baseline covariates in both the base-case analysis and the complete-case analysis. Results are summarized in Table 3-1.

Table 3-1: Results from Appendix A (value set from United Kingdom applied to the EQ-5D profiles)

Analysis	Incremental* cost (£)	Incremental* effect (QALY)	ICER (£/QALY)	Probability of being cost-effective at £20,000 per QALY
Base-case	-£6,424.11 [a]	0.0051 [a]	Dominant	100%
Complete-case	-£6,417.15 [b]	-0.0227 [c]	282,641 **	100%

*EQ-5D – EuroQol five dimensions of health questionnaire; ICER – incremental cost-effectiveness ratio; m – number of imputations; n – number of patients; OTT – ongoing triple therapy; PIM - protease inhibitor monotherapy; QALY – quality adjusted life-years; * Increments were calculated as PIM minus OTT; **ICER in southwest quadrant of the cost-effectiveness plane; [a]PIM (n=296, m=20) & OTT (n=291, m=20); [b]PIM (n=266, m=0) & OTT (n=254, m=0); [c]PIM (n=142, m=0) & OTT (n=130, m=0);*

The incremental QALYs presented in Table 3-1 reflect the UK valuation of health states, in line with current UK guidelines for cost-effectiveness analysis[12]. If this economic evaluation had been conducted from the perspective of the Danish health care system it would be reasonable to apply the Danish value set. When the Danish value set is applied to the EQ-5D profiles the mean utility becomes a reflection of how the Danish general population values health, and as an extension, how the general population values a particular health gain. When IPD, of EQ-5D profiles, are readily available to the analyst another value set can easily be applied. The cost-effectiveness results obtained from using the Danish value set are shown in Table 3-2.

It is striking that the present study found the incremental QALY in the UK base-case to be 1.5 times larger than the Danish base-case. This is in agreement with what a Swedish study found when applying the Danish and the UK value sets to the same IPD in a group of rheumatoid arthritis patients[46].

Table 3-2: Results when applying value set from Denmark to the EQ-5D profiles from Appendix A.

Analysis	Incremental* cost (£)	Incremental* effect (QALY)	ICER (£/QALY)	Probability of being cost-effective at £20,000 per QALY
Base-case	-£6,420.60 [a]	0.0034 [a]	Dominant	100%
Complete-case	-£6,417.15 [b]	-0.0220 [c]	292,035 **	100%

*EQ-5D – EuroQol five dimensions of health questionnaire; ICER – incremental cost-effectiveness ratio; m – number of imputations; n – number of patients; OTT – ongoing triple therapy; PIM - protease inhibitor monotherapy; QALY – quality adjusted life-years; * Increments were calculated as PIM minus OTT; **ICER in southwest quadrant of the cost-effectiveness plane; [a]PIM (n=296, m=20) & OTT (n=291, m=20); [b]PIM (n=266, m=0) & OTT (n=254, m=0); [c]PIM (n=142, m=0) & OTT (n=130, m=0).*

When comparing the UK base-case analysis of incremental QALYs to the Danish base-case analysis the interpretation requires caution. The reason is that the missing utility values were handled by two separate imputation-models and differences in the incremental QALYs could, therefore, be attributable to the multiple imputation of missing values, rather than to differences in valuation between countries. As such, the difference between the incremental QALY in the UK and Danish complete-case may be the most appropriate way to exemplify how a nation's valuation of health affects the results of an economic evaluation. The difference in the incremental QALYs can seem minute in the present case, but this is merely because PIM is very cost-saving compared to OTT. Had the incremental cost been a tenth of what it is in the present case, the implications of a difference in the incremental QALY would be much greater.

3.4. PRELIMINARY CONCLUSION

As such, it is important to use the Danish value set in economic evaluations conducted from the perspective of the Danish healthcare system whenever IPD on EQ-5D profiles are available. An unbiased reflection of the Danish preferences for health can only be obtained by using the national value set to estimate the incremental effectiveness. Consequently, it is easy to obtain unbiased QALY estimates when IPD on EQ-5D profiles are available but, unfortunately, this is not always the case.

CHAPTER 4. WHEN PATIENT-LEVEL EQ-5D DATA ARE UNAVAILABLE BUT FOREIGN EQ-5D UTILITIES ARE AVAILABLE

4.1. AN INTRODUCTION TO THE CASE

Economic evaluations are only occasionally used to inform decision making in the Danish healthcare system and the clinical trials, therefore, rarely collect IPD on EQ-5D profiles. However, such data may have been collected in foreign studies. In 0 it was explained why the optimal solution for a Danish economic evaluation would be to use the IPD on EQ-5D profiles from a foreign study and apply the Danish value set to these data. However, it may not always be possible for analysts to obtain IPD from foreign studies. In such situations the mean utility of the EQ-5D, valued by a foreign value set, will have to be used.

Evidence does, however, suggest that foreign utilities may not be transferable to a Danish setting[15,46–54]. Analysts are advised to adjust utilities before applying them in economic evaluations[47]. However, if IPD on EQ-5D profiles cannot be obtained there are no published methods for adjusting mean utilities across countries. Therefore, a novel method for adjusting mean utilities of the EQ-5D between countries was developed, see Appendix C. In section 4.3 we investigate the importance of performing adjustments by using the results of the economic evaluation presented in Appendix B[1].

4.2. THE CONDITION AND THE INTERVENTIONS

The normal heart rhythm is generated in the sinus node in the atrium of the heart. From there, the signal travels through the heart while causing the atriums and ventricles of the heart to contract at an appropriate pace[27]. In patients suffering from arrhythmias, the conduction system is disturbed. This causes irregular rhythms and/or decreased pumping ability which can lead to an array of health issues ranging from unpleasant heart palpitations, through dizziness to stroke, heart failure, and death[27].

In patients suffering from the arrhythmia called sick sinus syndrome, bradycardia (a slow heart rate) should be treated with either a single-lead atrial pacemaker (AAIR) or a dual-chamber pacemaker (DDDR). In sick sinus syndrome, cardiac pacing is mainly used to obtain relief from the symptoms[55], and to avoid the development of systemic thromboembolism[56]. Following the publication of the Danish multicenter randomized trial on AAIR versus DDDR in sick sinus syndrome (the DANPACE trial)[57], DDDR pacing has been recommended as the standard treatment option[55]. However, this recommendation was controversial from a health economic point of view. Although DDDR pacing reduces the costs of reoperations[57], the DDDR device costs are higher than AAIR device costs[58]. Furthermore, no studies had reported a comparison of the resource consumption for AAIR pacing vs. DDDR pacing. To aid decision-making, an economic evaluation was developed using pooled IPD from three randomized controlled trials, comparing DDDR pacing with AAIR pacing for sick sinus syndrome patients with preserved atrioventricular conduction. The full study can be found in Appendix B[1].

4.3. THE COMPARISION

The economic evaluation in Appendix B[1] used UK utilities of the EQ-5D for the health states in the Markov model. In the present section, the published results are

compared to the results, which would be obtained if the utilities had been adjusted to represent the Danish preference for health using the method in Appendix C. The method presented in Appendix C was developed to adjust German or Dutch utilities to the UK setting. By applying the Danish[19] and the UK[45] value sets to the same estimation dataset and plotting them against each other it is possible to obtain a formula for adjusting UK utilities of the EQ-5D to the Danish setting:

*Danish utility = 0.7831 * UK utility + 0.2057*

The impact of using foreign utilities in the economic evaluation in Appendix B is assessed by inserting the Danish mean utilities instead. The results of the comparison are presented in Table 4-1.

Table 4-1: Cost-effectiveness results from Appendix B[1] for Risk Group 2 in the adjusted pooled approach using UK utilities and utilities adjusted to the Danish setting.

Analysis	Incremental* cost (£)	Incremental* effect (QALY)	ICER (£/QALY)	Probability of being cost-effective at £20,000 per QALY
UK utilities	-£3,855.65	-0.170	22,709 **	50.7%
UK utilities adjusted to a Danish setting	-£3,855.65	-0.179	21,504 **	50.6%

*ICER – incremental cost-effectiveness ratio; QALY – quality adjusted life-year; UK – United Kingdom; * Increments were calculated as dual-chamber pacing minus single-lead atrial pacemaker; **ICER in southwest quadrant of the cost-effectiveness plane;*

In Table 4-1 it is seen that UK utilities adjusted to Danish preferences for health yielded a slightly different result than originally published[1]. The original model used UK utilities from a catalogue of utilities for chronic conditions[59] and found an incremental QALY of -0.170. This was done under the assumption that the cultural similarities between Denmark and the UK made it possible to use mean UK utilities when Danish utilities were not available[49]. While Denmark and the UK may have comparable cultures, their value sets are very different. In fact, the utilities obtained from the Danish value set is more comparable to those obtained from the US value set, than to utilities from the UK value set, see Figure 4-1.

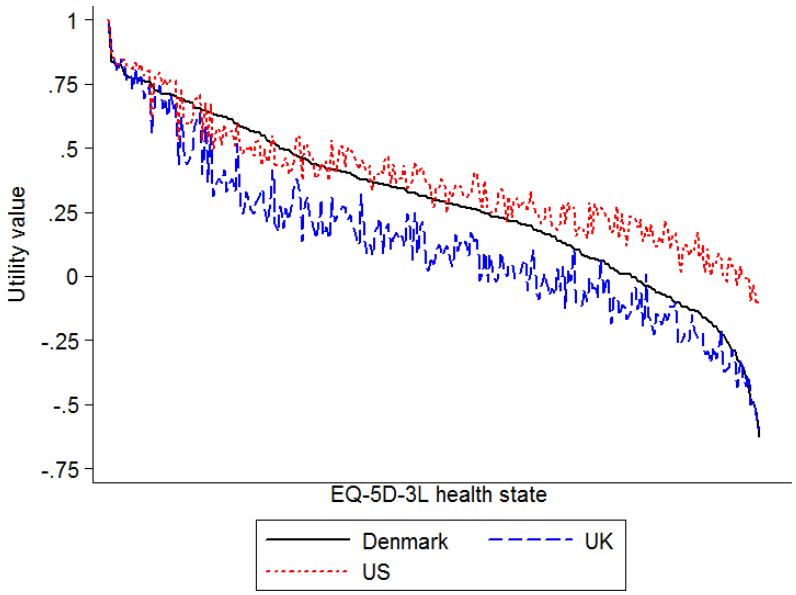

Figure 4-1: Comparison of the time trade-off value sets for Denmark, the United Kingdom (UK) and the United States (US). The graphs show the utility values obtained when applying the value sets to the 243 health states of the three leveled version of the EuroQol five dimensions of health questionnaire (EQ-5D-3L). Health states are ordered so that the x-axis runs from the least severe health state (11111) to the most severe health state in the Danish value set (33333).

The red line, the US utility values, runs much closer to the black line, the Danish utility values, than the blue line, the UK utility values. As such, US utilities for chronic conditions[60,61] are a closer reflection of Danish preference for health, than UK utilities[59], and could have been applied instead. Or better yet: Danish utilities for chronic conditions, which are being developed[62].

4.4. PRELIMINARY CONCLUSION

It is not all that surprising that application of foreign utilities in a Danish decision analytic model will yield different results than one would have obtained using national utility values. This was shown in section 3.3 by applying UK and Danish value sets to the same IPD for a HIV trial and the same has been shown in a rheumatoid arthritis trial by others[46].

What is new and interesting is that it is possible to adjust foreign mean utilities of the EQ-5D to national preferences for health. The paper presented in Appendix C showed a novel method for this. A method, which seems to be working but also a method that needs further development before it can become a part of routine practice when transferring foreign utilities. The method could benefit from being developed using a larger number of mean index scores with a larger range than the estimation dataset used in Appendix C.

Adjusting foreign utilities to make them reflect national preferences for health has great potential. It will enable countries, such as Denmark, which frequently face difficulties in finding national utility estimates from the relevant patient population, to use foreign values more readily. Furthermore, the synthesis of EQ-5D utilities for NICE submissions could potentially include more estimates as the foreign estimates could be adjusted to reflect UK preferences for health. This would increase precision, as NICE recommends pooling the relevant estimates in the same manner as aggregate clinical data[25].

CHAPTER 5. WHEN PATIENT-LEVEL AND AGGREGATE EQ-5D DATA ARE UNAVAILABLE – BUT OTHER MEASURES OF HEALTH ARE AVAILABLE

5.1. AN INTRODUCTION TO THE CASES

Economic evaluations inform decision makers on how to allocate scarce resources to obtain the maximum amount of value-for-money. Therefore, a shared measure of 'value' (QALYs) *must* be used in all economic evaluations to facilitate comparison between all interventions for all conditions. As an extension of this argument, the estimates of utility *must* be obtained using a single shared instrument. However:

> "Key trials or studies often do not use one of the generic preference-based measures, but have used a non-preference-based health or quality of life measure. This situation is far from ideal, but surprisingly common. "
>
> (Brazier et al. 2007)[11]

Because utility data from the preferred instrument, assumed to be EQ-5D in this thesis, is not always accessible, a shared standard for handling this would be useful. Section 5.1.1 will address which methods could be used to handle the situation where IPD on EQ-5D profiles is not available. In section 5.2 the results of non-standardized methods will be compared to the method, which may be used when IPD on EQ-5D profiles are not available: mapping.

5.1.1. MAPPING AND OTHER WAYS OF OBTAINING UTILITY ESTIMATES IN THE ABSENCE OF EQ-5D DATA

Different approaches could be suggested: utility values obtained from other preference-based instruments could be used, a vignette could be developed and valued, additional EQ-5D data could be collected, or non-preference-based measures of health could be mapped to the EQ-5D. The process of mapping can best be explained in the following way:

> "Mapping is the development and use of an algorithm (or algorithms) to predict health-state utility values using data on other indicators or measures of health. The algorithm can be applied to data from clinical trials, other studies or economic models containing the source predictive measure(s) to predict utility values…"
>
> (Longworth et al. 2011)[26]

Concerns could be raised with all approaches. Other preference-based measures of health might measure different aspects of utility, even if these are called generic instruments, see Figure 5-1.

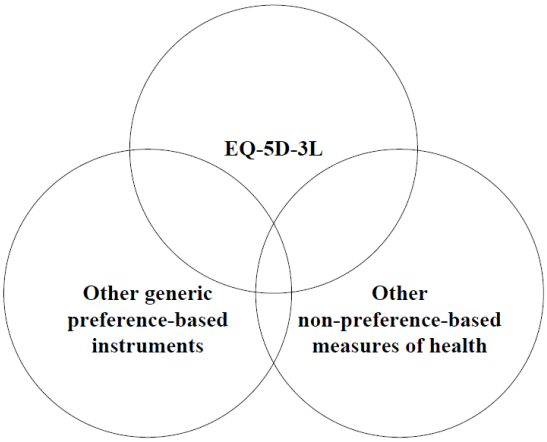

Figure 5-1: Utility measured by various instruments. Aspects that are measured frequently overlap but the extent to which these overlap may vary.

If different aspects are measured it makes it more probable that changes in overlapping dimensions with the EQ-5D are valued differently. Therefore, it becomes problematic to interpret the ICER obtained from an economic evaluation that used another generic preference-based instrument in relation to other economic evaluations that applied the EQ-5D.

A concern, which is frequently raised regarding the use of vignettes, is whether the vignette can be constructed to reflect the clinical evidence and the uncertainty surrounding the outcome of the treatment. On top of this concern, ICERs obtained from economic evaluations using vignettes are equally difficult to interpret.

Collecting additional data is always an excellent solution; however, it is usually also a very expensive and time-consuming solution. This leaves mapping.

Mapping is, however, limited by the assumption that the EQ-5D covers all the important aspects of health covered by the non-preference-based measures of health. This may be the case for some non-preference-based measures of health, but not for others, as illustrated by the slightly overlapping circles in Figure 5-1. Another issue with mapping is whether a mapping-algorithm is available or feasible to produce[11]. Recently it became easier to determine the availability of appropriate mapping-algorithms after the launch of a database which contains readily available mapping-algorithms[63]. A mapping-algorithm could be considered appropriate if it is able to predict the EQ-5D utility, valued by the preferred value set, from the available non-preference-based measures of health. If an appropriate mapping-algorithm can be obtained, the process of mapping has been shown to produce a valid estimate of the incremental QALY[64], but also, to underestimate the uncertainty in the incremental QALY[65]. If the mapping-algorithm is not appropriate it is likely that it cannot successfully predict the EQ-5D utility[66]. In the presence of multiple mapping-algorithms it may be prudent to conduct sensitivity analyses investigating the importance of choice of mapping-algorithm[66]. However, it has been shown to be unimportant whether the mapping-algorithm is designed to map

the non-preference-based measures of health to the EQ-5D responses or directly to the utility value[67]. As such, mapping using a statistical algorithm should only be viewed as a second-best solution to IPD on EQ-5D profiles.

5.2. THE CONDITION AND THE INTERVENTIONS

The comparison of mapping, using a mapping-algorithm based on the statistical association of outcomes, to the non-standardized method of mapping based on clinicians or experts' judgment (judgment mapping), is based on the condition and interventions presented in section 2.2. Readers are encouraged to spend a second refamiliarizing themselves with the interventions, if necessary.

5.3. THE COMPARISON

The comparison in 0 is divided in two. The first part (section 5.3.1) compares the results of a previous economic evaluation by Oddershede et al.[37] to the results that could have been obtained if one of the two mapping-algorithms[2,68], which are now available, had been applied to the IPD. The second part (section 5.3.2) compares the use of the two available mapping-algorithms on aggregate data to the results of the economic evaluation by Rao et al.[38] who mapped aggregate data without a mapping-algorithm.

5.3.1. MAPPING IPD USING A MAPPING-ALGORITHM VERSUS JUDGMENT MAPPING

In section 2.3, the lack of a mapping-algorithm meant that the two economic evaluations arrived at very different estimates of the incremental QALY. Since the publication of these economic evaluations, two mapping-algorithms have been

published[2,68]. The mapping-algorithm presented in Appendix D^2 was developed for the purpose of predicting the Danish EQ-5D utility value from non-preference-based measures of health measured on visual analogue scales (VAS) for CABG patients. Hence, this mapping-algorithm was specifically designed for the purpose. The mapping-algorithm presented in Appendix D^2 explained as much as 65% of the variability in the Danish EQ-5D utility, which is quite high compared to mapping-algorithms in general[39]. The second mapping-algorithm that has become available maps pain measured on a VAS to the UK EQ-5D utility in shoulder patients[68]. No other dimensions of health were included in the mapping-algorithm and, hence, it merely explained approximately 10% of the variation in the UK utility value. As such, this second mapping-algorithm serves as an example of the importance of using an appropriate mapping-algorithm.

In Table 5-1 the results of the previous economic evaluation by Oddershede et al.[37] are presented along with the results which would have been obtained with the two mapping-algorithms that are available now[2,68].

Table 5-1: Cost-effectiveness results when IPD of non-preference-based measures of health are mapped based on judgment and based on statistical mapping-algorithms

Analysis	Incremental Cost* ($ USD)	Incremental Effect* (QALYs)	ICER ($/QALY)	Probability of being cost-effective at $50,000 per QALY
Judgment mapping of IPD from Oddershede et al.[37]	$217.14 **	0.00273	79,391	>1%
Mapping IPD from Oddershede et al.[37] using mapping-algorithm from Appendix D[2]	$222.46 **	0.00269	82,791	>1%
Mapping IPD from Oddershede et al.[37] using mapping-algorithm from Maund et al.[68]	$222.46 **	0.00120	185,693	>1%

*ICER – incremental cost-effectiveness ratio; IPD – individual patient-level data; QALY – quality adjusted life-year; USD – United States Dollar; * Increments were calculated as endoscopic vein harvesting minus open vein harvesting. ** Stata's "set seed" function was not used to generate the incremental cost published in Oddershede et al.[37] and the new bootstrap analysis, therefore, produced a slightly different mean incremental cost.*

It is seen that the incremental QALY estimated in the previous economic evaluation[37] closely resembles the estimate obtained when using the mapping-

algorithm presented in Appendix D. This is merely a coincidence. The original results were not mapped using a mapping-algorithm based on the statistical association of outcomes, but by judgment mapping, and section 2.3 clearly showed the variability in estimates of incremental QALYs obtained by judgment mapping. As such, the results presented in Table 5-1 cannot be used as an argument of the validity of mapping without a mapping-algorithm. However, a rather large difference between the estimate obtained from the mapping-algorithm presented in Appendix D[2] and the estimate obtained using the mapping-algorithm developed by Maund et al.[68]. This stresses that mapping is a valid second-best approach only if an appropriate mapping-algorithm is available.

5.3.2. MAPPING AGGREGATE DATA USING A MAPPING-ALGORITHM VERSUS JUDGMENT MAPPING

Previous economic evaluations of EVH vs OVH for CABG have applied a short time-horizon[37,38]. In many instances, and especially for interventions in chronic conditions, a lifetime horizon would be more appropriate[69]. Especially in the case of EVH vs OVH the short time horizon became an issue as the long-term EVH graft patency was questioned in an observational study[70]. Although it seems evident that EVH is not associated with an increased mortality[34], the uncertainty lingers in the clinical community and causes the initiation of new randomized clinical trials[71,72]. Because of the uncertainty surrounding long-term outcomes recent reviews called for a more rigorous cost-effectiveness analysis[73,74]. To be able to compare EVH to OVH in terms of lifetime costs and outcomes, it was necessary to conduct a systematic review with meta-analysis. Previous meta-analyses had defined the comparators (and outcomes) different from one and another, and none had used the definitions which we believed to be appropriate[75–84]. Therefore, a new meta-analysis was conducted, see the paper in Appendix E[3]. The meta-analysis pooled data on resource consumption, long-term clinical endpoints relevant to decision analytic modeling, and short-term clinical endpoints to enable mapping of the short-

term utility gain from using EVH. Based on the summary statistics from the meta-analysis in Appendix E[3], a Markov model was constructed to allow modeling of short-term and life-time costs and QALYs. The summary statistics of short-time non-preference-based measures of health, from the meta-analysis in Appendix E[3], were mapped using the generalized least squared mapping-algorithm number two from Appendix D[2]. The methods and full results of the economic evaluation of lifetime costs and QALYs are presented in Appendix F.

The present comparison is merely a comparison of how short-term estimates of the incremental QALY could be obtained using mapping methods. Three approaches could be used. Firstly, the summary statistics from the meta-analysis, in Appendix E[3], could be mapped using an appropriate mapping-algorithm[2]. Secondly, the summary statistics from the meta-analysis, in Appendix E[3], could be mapped using a mapping-algorithm[68] considered inappropriate for the analysis in Appendix F. Thirdly, the aggregate summary data could have been mapped by judgment as it was in the study by Rao et al.[38]. The results from the three approaches are summarized in Table 5-2.

Table 5-2: Aggregate data, from the meta-analysis in Appendix E[3], mapped using two mapping-algorithms[2,68], compared to judgment mapping of aggregate data.

Analysis	Incremental Costs ($ USD)	Incremental Effect (QALYs)	ICER ($/QALY)	Probability of being cost-effective at $50,000 per QALY
Rao et al.[38]	$458.74	0.0231	19,859	95.6%
Mapping aggregate data from the meta-analysis in Appendix E[3] using the mapping-algorithm developed in Appendix D[2]	$849.78 *	0.0048	178,866 *	17.0%
Mapping aggregate data from the meta-analysis in Appendix E[3] using the "Model 1" mapping-algorithm from Maund et al.[68]	$849.78 *	0.0029	297,601 *	10.0%

*ICER – incremental cost-effectiveness ratio; QALY – quality adjusted life-year; * The incremental costs were converted from Pounds Sterling (£) to US dollars (USD $) using a conversion rate of 1.6804 $ per £.*

A great variation is seen in the three estimates of incremental QALY in Table 5-2. The difference is largest when comparing the result which Rao et al.[38] obtained by judgment mapping, to mapping using a mapping-algorithm based on

the statistical association of outcomes. In other words, standardized methods will produce more consistent results than unstandardized methods. In contrast to section 5.3.1, the results in Table 5-2 suggest that an inappropriate mapping-algorithm is better than judgment mapping.

5.4. PRELIMINARY CONCLUSION

A number of valuable lessons emerges from the process of developing a mapping-algorithm (Appendix D^2), systematically reviewing and pooling the aggregate data (Appendix E^3), and using the summary measures to estimate the life-time cost-effectiveness of EVH (Appendix F). Firstly, the process of mapping was more reliable than judgment mapping, even when applying a mapping-algorithm[68] considered inappropriate for the present analysis. Secondly, it would dramatically increase the usability of mapping-algorithms if these were: a) developed to map EQ-5D responses or b) accompanied by an appendix where a number of different value sets had been applied to the EQ-5D responses. Thirdly, it is a time-consuming exercise and should only be applied if utilities of the EQ-5D cannot be obtained in other ways. Nonetheless, it should be viewed as the best way to handle the absence of IPD on EQ-5D profiles and mean utilities of the EQ-5D. A comparison between all interventions for all conditions can only be facilitated if a single shared instrument is used to measure utility. As such, it is necessary to use the reference case instrument, assumed to be EQ-5D in this thesis, to measure differences in utility, or, to predict the differences in utility using a mapping-algorithm that predicts utilities of the EQ-5D from other measures of health.

Therefore, the take home message is: whenever a trial is initiated, either observational or randomized, IPD on EQ-5D profiles should be collected. By doing so, time-consuming mapping-exercises may be avoided.

CHAPTER 6. CONCLUSION

The current Danish guideline for economic evaluations submitted to the Danish Health and Medicines Authorities do not take a position towards the preferred type of economic evaluation. In Section 1.2 the two main issues with this was identified as: firstly, incomparability of economic evaluations, and secondly, choosing an outcome-measure that captures both the effects and side effects of treatments.

It was argued that updating the Danish guideline to include a stated preference for cost-utility analyses would solve these issues, if the utility estimates, used in the analyses, were obtained by the means of standardized methods. Therefore, the present thesis investigated, through methodological studies and case-studies, how the available data could be used to procure optimal utility estimates for QALY calculations.

The results indicate that if economic evaluations are to be used to inform decision makers of the cost-effectiveness of new technologies, it is not only necessary to have a stated preference for cost-utility analysis, but also to include thorough instructions for estimating utility. The present thesis showed that estimates of incremental QALYs are unlikely to be an unbiased reflection of national preferences for health if standardized methods for estimating utility have not been applied.

First of all, it should be noted that an update of the Danish guideline for economic evaluations is long overdue! Several advances have been made, within health economics, since 1998 and the national guideline should be updated to reflect this.

If the Danish Health and Medicines Authorities choose to update the national guideline for economic evaluations to include a preference for cost-utility analyses, they should include instructions on estimating utilities. The key to making

the results comparable and relevant to the Danish setting is to request that standardized methods be applied in all evaluations of new technologies. Amongst other things, it would be important to standardize which generic preference-based instrument to use, how to apply foreign utilities in Danish economic evaluations, and how it should be handled if utility data are not available to the analyst. The present thesis suggested standardized methods for handling the latter two in the papers presented in Appendix C and Appendix D.

While the conclusion of this thesis addresses which initiatives the Danish Health and Medicines Authorities might take to improve the usefulness of the economic evaluations submitted to them, the advice also has a more universal ring to it. All economic evaluations may benefit from applying standardized methods such as e.g. those developed and advocated for in this thesis.

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GLOSSARY

15D – 15 dimensions of health questionnaire

ART – Antiretroviral therapy

CABG – Coronary artery bypass grafting

CD4+ – Cluster of differentiation 4

EQ-5D – EuroQol 5 dimensions of health questionnaire

EVH – Endoscopic vein harvesting

HIV – Human immunodeficiency virus

ICER – Incremental cost-effectiveness ratio

IPD – Individual patient data

NHS – National Health Service

NICE – National Institute for Health and Care Excellence

OTT – Ongoing triple therapy

OVH – Open vein harvesting

PIM – Protease inhibitor monotherapy

QALY – Quality adjusted life-year

SF-6D/SF-12/SF-36 – Short form health questionnaires

TTO – Time trade-off

VAS – Visual analogue scale

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SUMMARY

Resources are scare and healthcare systems must, therefore, prioritize which new technologies should be funded, and which should be rejected. To aid decision makers in their choice, economic evaluations can be conducted to assess the cost-effectiveness of the new technologies.

The present thesis argues that two problems could be solved by updating the Danish guideline for economic evaluations to include a stated preference for measuring effectiveness in terms of quality adjusted life-years (QALYs). Firstly, it would be possible to compare the cost-effectiveness of new technologies across conditions. Secondly, it would make it possible to capture both effects and side effects of new technologies in a single outcome measure. Therefore, the present thesis explores how to procure optimal estimates of quality of life, i.e. utility, for QALY calculations in different situations, depending on which data are available.

Using the methodological papers and economic evaluations conducted during the PhD project; the thesis exemplifies why it is important to use standardized methods when calculating QALYs in economic evaluations.

The thesis recommends that a shared measure of health, QALYs, is used in order to make the results of the economic evaluations submitted to the Danish Health and Medicines Authorities more comparable across conditions and interventions.

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