Disease specific methods for economic evaluations of breast cancer therapies

ISBN/EAN: 978-94-6108-453-8

Cover design: Jules Calis - www.julescalis.nl

"Woman covering one breast". This simplified yet realistic drawing of the female body stands for the correct representation of the disease of interest in mathematical models used for economic evaluations. Although these models need simplifications, they should primarily reflect reality in a correct way. The breast on the frontpage is covered, thereby representing the current lack of focus on the breast in economic evaluations of breast cancer therapies.

Layout by: Geert Frederix
Printed by: Gildeprint drukkerijen - www.gildeprint.nl
Printed on FSC certified paper

Disease specific methods for economic evaluations of breast cancer therapies

Ziekte specifieke methoden voor economische evaluaties van
borst kanker therapieën

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit Utrecht
op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan,
in gevolge het besluit van het college voor promoties
in het openbaar te verdedigen
op woensdag 12 juni 2013 des middags te 2.30 uur

door

Gerardus Wilhelmus Johannes Frederix

geboren op 8 januari 1985 te Boxmeer

Promotoren: Prof. dr. J.H.M. Schellens
Prof. dr. J.L. Severens

Co-promotor: Dr. A.M. Hövels

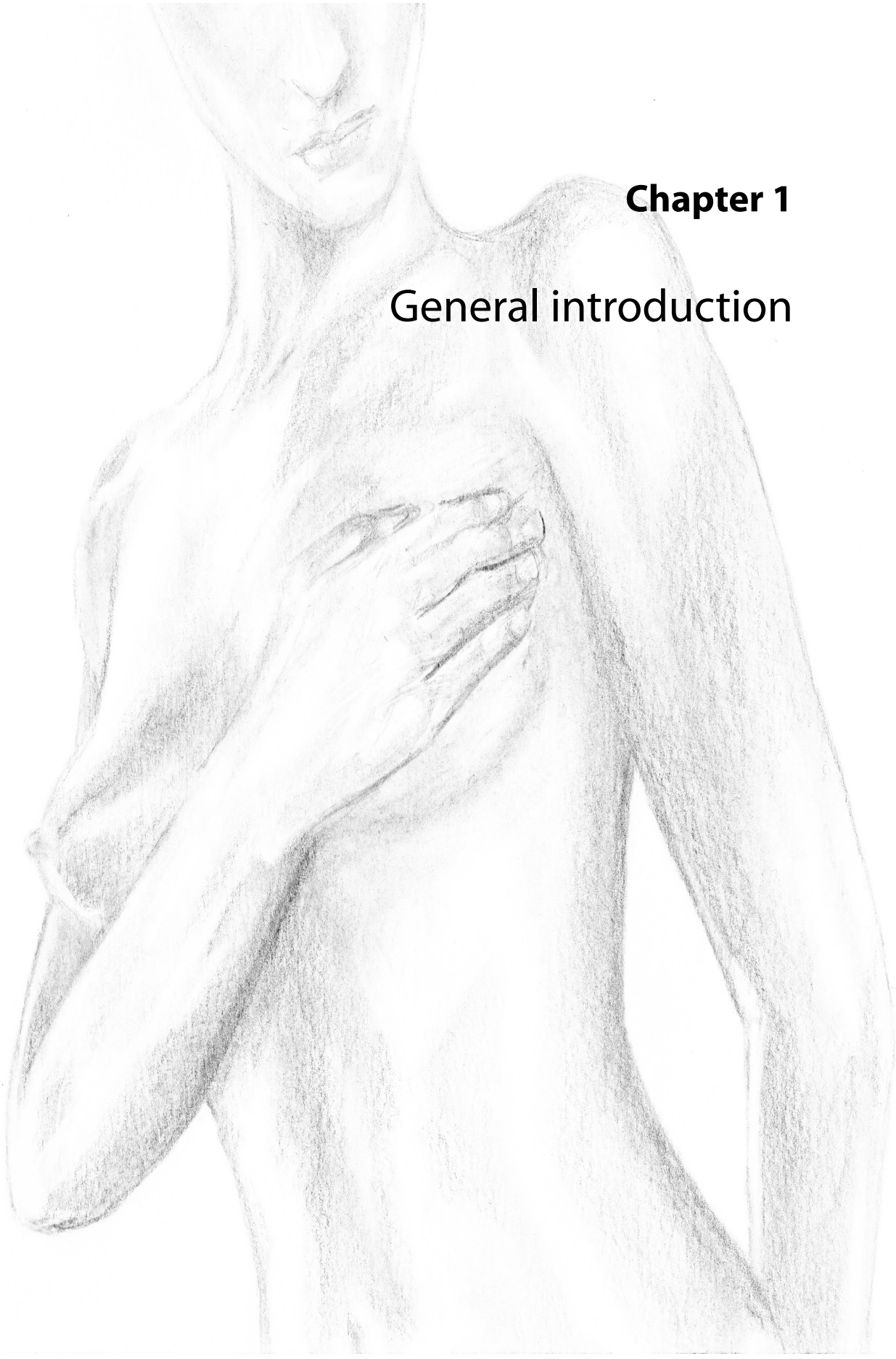
The research described in this thesis was performed at the department of Medical Oncology and at the department of Experimental Therapy of the Netherlands Cancer Institute, Amsterdam, the Netherlands

Publication of this thesis was financially supported by:
Amgen Nederland B.V., Breda, the Netherlands
Boehringer Ingelheim B.V., Alkmaar, the Netherlands
GlaxoSmithKline B.V., Zeist, the Netherlands
Novartis Oncology, Arnhem, the Netherlands
Utrecht Institute of Pharmaceutical Sciences (UIPS), Utrecht, the Netherlands

"All models are wrong, but some are useful"
George E.P. Box (1979)

"Everything should be made as simple as possible, but not simpler"
Albert Einstein (1933)

Contents



Chapter 1

General introduction

General introduction

Worldwide, healthcare costs are swiftly increasing and difficult to control. Of the various factors affecting the increase, i.e. technological advances, aging of the population and drug costs, drug expenditure appears to be the most tangible and therefore a logical target for cost containment. To ensure that healthcare professionals deliver care of the best possible quality and of the best value for money, a large number of health policy decision bodies over the world have incorporated cost-effectiveness analyses (CEAs) in their drug reimbursement decision process[1]. Especially in the field of oncology therapy costs are dramatically increasing over time[2], thereby illustrating the need for CEAs in assisting decision making.

CEAs aim to analyse costs and health-related consequences of at least two alternative treatments for patients and compare these explicitly[3]. The analytical tool to summarise information in CEAs is the Incremental Cost Effectiveness Ratio (ICER), given by the ratio of the difference in costs of two interventions and the difference in effects, and preferably resulting in the cost for one additional Quality Adjusted Life Year (QALY) gained or one additional Life Year (LY) gained. The ICERs are used to determine whether a new intervention represents value for money preferably by comparing the ICER with a country specific cost-effectiveness threshold[4].

A well-known threshold is the one implemented in the United Kingdom by the National Institute for Health and Clinical Excellence (NICE)[5]. Their formal threshold has been set at £30,000 pounds per QALY gained, meaning that therapies having ICERs above this threshold are not considered to be cost-effective, and therefore are often not reimbursed by the National Health Service (NHS). In recent years, additional guidance has come available regarding end-of-life criteria by the NICE, enabling higher thresholds for therapies given during end of life of a patient, which is very relevant for oncology therapies[6]. Although no formal thresholds are implemented in other countries, there is an increased attention in its implementation to enhance objective decision making. In the Netherlands discussions are ongoing on varying the threshold value depending on the burden of the disease of interest, with a maximum threshold of up to €80.000 for very severe diseases[7]. The implementation of thresholds and changes in it's use demonstrate the potential impact of CEAs on reimbursement decisions, it is therefore essential that analyses are of high quality and outcomes are credible, accurate and comparable.

To ensure appropriate quality of CEAs, several guidelines were developed and published several years ago[8-11], with the Drummond guideline in the British Medical Journal (BMJ) as the most widely applied one[8]. These guidelines encompass guidance regarding for

instance choice of perspective, time horizon, discounting and utilities. Regardless of the presence and use of these guidelines, several studies have shown that CEAs differ markedly in quality[12-14]. Common methodological flaws in CEAs relate to study design, data collection and analysis, and interpretation or reporting of results[15].

Another criticized CEA characteristic is the extrapolation of clinical trial data[16]. In many situations, health economists will need to extrapolate data beyond the period observed in the clinical trial, as for instance life years saved is a much more relevant and reliable outcome for economists compared to percentage alive after one year. To do so, several so called decision-analytical models are widely used in CEAs varying from simple to complex models. Concerns have been raised that such models are low in validity due to limited capacity for simulating the complexities of the "real world" by adequately representing disease progression[17]. In addition to "real world" presentation of models, research has demonstrated that it is essential to include country specific parameters to calculate reliable and country specific outcomes[18;19].

Aside from methodological flaws and "real world" presentation of models, decision makers are currently expressing a much bigger interest in real world data to have better indications of uncertainty when making reimbursement decisions[20]. Randomized controlled trials (RCTs), although recognized as the "gold standard", operate in an idealized environment and can only measure outcomes in limited populations. Real world data will enable better generalisability to populations and therefore improves decision making. Recently GlaxoSmithKline has started a large prospective real world trial (Salford Lung Study) with a pre-licence medicine, which is one of the first attempts to inform decision makers upfront with real world data for registration purposes, thereby demonstrating the increasing need and attention for real world data. Although improved generalisability is a major advantage, the main limitation of using real world data is the potential for bias, as observations studies do not meet the methodological rigor of RCTs[20;21]. Real world studies therefore need to be evaluated rigorously to identify sources of bias and confounding and have to be adjusted correctly.

Aims

In this thesis, we aimed to study whether current CEAs in early breast cancer have sufficient quality, whether modelling methods are comparable between published articles, whether they reflect "real world" disease progression and whether disease specific methods are needed. In addition we aimed to assess utility and real world costing data for metastatic breast cancer (MBC) in different countries. Research is presented on various subjects such as, reviewing early breast cancer CEAs, introducing new cost-effectiveness frameworks,

quality of life in MBC and finally real world observational costing studies for MBC from patient population levels.

Outline of the thesis

This thesis is divided in two different parts, 1) early breast cancer and 2) metastatic breast cancer, thereby reflecting the chronological order of disease progression in breast cancer patients. The first part of this thesis entitled "Early breast cancer" addresses quality of early breast cancer CEAs, the implementation of modelling methods and structures in these CEAs and introduces a relatively new approach for implementing CEAs in the statistical programme R. First in **chapter 2.1**, a literature review is presented describing the quality of endocrine early breast cancer CEAs and the differences in modelling methods and their potential impact on outcome of these CEAs. In **chapter 2.2**, a short perspective is provided, focussing on the outcome of the literature review and the necessity of improving communication between health care professionals and economists. **Chapter 3** focuses on the development and implementation of a framework for CEAs in the statistical programme R. This chapter provides insight into the disadvantages of current methods of cycle length implementation and introduces a new transparent approach to decrease cycle length induced bias on outcome. In **chapter 4** the impact of several structural and parameterization differences in breast cancer CEAs, as published in literature, are addressed by implementing different structures one by one in a pre-defined basic model, making use of the framework explained in chapter 3.

The second part of this thesis entitled "Metastatic breast cancer" has a more applied research perspective, focussing on quality of life assessments and costing studies of human epidermal growth factor receptor 2 (HER-2) positive MBC patients. **Chapter 5** discusses the quality of life and work productivity of HER-2 MBC patients in both the Netherlands and Sweden. Outcomes for both countries are presented, but also implications and differences between countries are discussed that could eventually impact the possibility of exchanging economic data between countries. **Chapter 6** focuses on costing studies in HER-2 positive MBC patients using real world patient level data. In this respect, **chapter 6.1** presents the resource use of MBC patients and total per patient cost for both the Netherlands and Belgium In **chapter 6.2** we link clinical progression of patients to the costs and present MBC health state related costing outcomes over time and the factors contributing to these costs.

Altogether this thesis aims to provide a broad perspective on difference in modelling methods and structures and use of quality of life and real world costing data. Finally, the results of this thesis are summarized and discussed in the **conclusions and perspective**

section. Here, the findings of this thesis are translated into final conclusions and recommendations, including various future perspectives.

References

(1) http://www.ispor.org/htaroadmaps/.

(2) *Uyl-de Groot CA, de Groot S, Steenhoek A. The economics of improved cancer survival rates: better outcomes, higher costs. Expert Rev Pharmacoecon Outcomes Res* ***2010****; 10(3):283-292.*

(3) *Drummond M, Schulpher M, Torrance G, O'Brien B, Stoddart G. Methods for the economic evaluation of health care programmes. Oxford University Press;* ***2005****.*

(4) *McCabe C, Claxton K, Culyer AJ. The NICE cost-effectiveness threshold: what it is and what that means. Pharmacoeconomics* ***2008****; 26(9):733-744.*

(5) http://www.nice.org.uk/.

(6) http://www.nice.org.uk/media/E4A/79/SupplementaryAdviceTACEoL.pdf.

(7) *RVZ. Zinnige en duurzame zorg (Sensible and sustainable Care). Zoetermeer. Raad voor de Volksgezondheid en Zorg (Council for Public Health and Health Care) Report nr. 06/06 (****2006****).*

(8) *Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ* ***1996****; 313(7052):275-283.*

(9) *Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. Int J Technol Assess Health Care* ***2005****; 21(2):240-245.*

(10) *Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess* ***2004****; 8(36):iii-xi, 1.*

(11) *Soto J. Health economic evaluations using decision analytic modeling. Principles and practices--utilization of a checklist to their development and appraisal. Int J Technol Assess Health Care* ***2002****; 18(1):94-111.*

(12) *Neumann PJ, Greenberg D, Olchanski NV, Stone PW, Rosen AB. Growth and quality of the cost-utility literature, 1976-2001. Value Health* ***2005****; 8(1):3-9.*

(13) *Neumann PJ, Fang CH, Cohen JT. 30 years of pharmaceutical cost-utility analyses: growth, diversity and methodological improvement. Pharmacoeconomics* ***2009****; 27(10):861-872.*

(14) *Schwappach DL, Boluarte TA. HEE-GER: a systematic review of German economic evaluations of health care published 1990-****2004****. BMC Health Serv Res 2007; 7:7.*

(15) *Drummond M, Sculpher M. Common methodological flaws in economic evaluations. Med Care* ***2005****; 43(7 Suppl):5-14.*

(16) *Sheldon TA. Problems of using modelling in the economic evaluation of health care. Health Econ* ***1996****; 5(1):1-11.*

(17) *Buxton MJ, Drummond MF, Van Hout BA, Prince RL, Sheldon TA, Szucs T et al. Modelling in economic evaluation: an unavoidable fact of life. Health Econ* ***1997****; 6(3):217-227.*

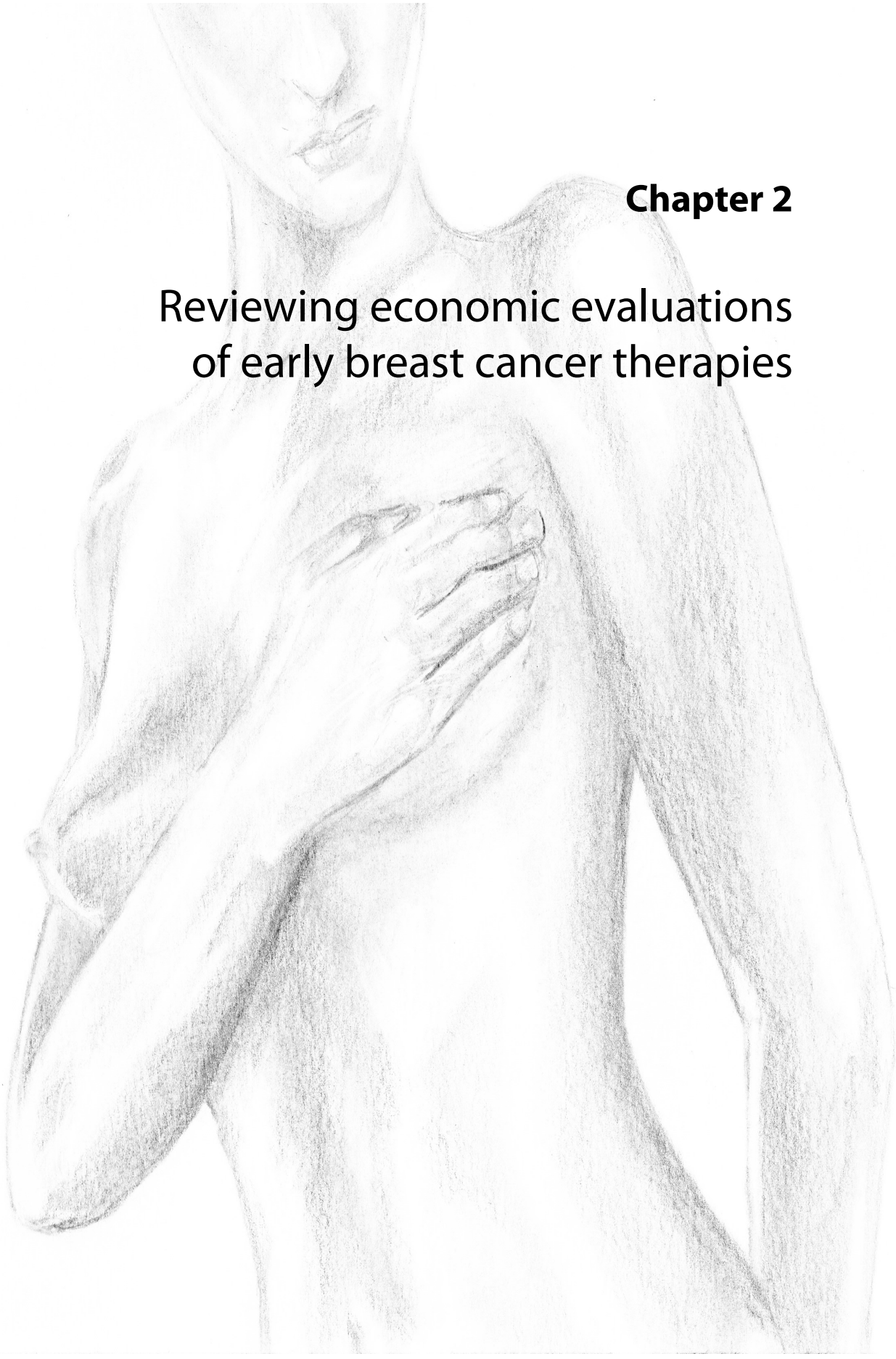
(18) *Drummond MF, Bloom BS, Carrin G, Hillman AL, Hutchings HC, Knill-Jones RP et al. Issues in the cross-national assessment of health technology. Int J Technol Assess Health Care* ***1992****; 8(4):671-682.*

(19) *Knies S, Evers SMAA, Candel MJJM, Severens JL, Ament AJHA. Utilities of the EQ-5D: Transferable or Not? Pharmacoeconomics* ***2009****; 27(9):767-779.*

(20) *Garrison LP, Jr., Neumann PJ, Erickson P, Marshall D, Mullins CD. Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. Value Health* ***2007****; 10(5):326-335.*

(21) *Schneeweiss S, Gagne JJ, Glynn RJ, Ruhl M, Rassen JA. Assessing the comparative effectiveness of newly marketed medications: methodological challenges and implications for drug development. Clin Pharmacol Ther* ***2011****; 90(6):777-790.*

Part I
Early breast cancer



Chapter 2

Reviewing economic evaluations of early breast cancer therapies

Chapter 2.1

Reviewing the cost-effectiveness of endocrine early breast cancer therapies

Influence of differences in modelling methods on outcomes

Gerardus W.J. Frederix
Johan L. Severens
Anke M. Hövels
Jan A.M. Raaijmakers
Jan H.M. Schellens

Value Health. 2012 January; 15(1):94-105

Abstract

Introduction

The purpose of this systematic review is primarily to identify published cost-effectiveness analyses and cost-utility analyses of endocrine therapies for the treatment of early breast cancer. Secondary objective is to identify whether differences in seven modeling characteristics are related to differences in outcome of these cost-effectiveness and cost-utility analyses.

Methods

A systematic literature review was conducted to identify peer reviewed full economic evaluations of endocrine treatments of early breast cancer, published in the English language between 2000 and December 2010. Information from these publications was abstracted regarding outcome, quality and modeling methods.

Results

We identified twenty economic evaluations comprising five different endocrine therapeutic strategies, which are all assessed more then once. The Incremental Cost Effectiveness Ratios (ICERs) of the reported outcomes varied widely for identical therapies. For anastrazole compared to tamoxifen, incremental life years gained even ranged from 0.16 to 0.550 with an incremental cost-effectiveness ratio ranging from €3.958 to €75.331. Incremental QALYs gained ranged from 0.092 to 0.378 with a cost per QALY gained varying from €3.696 to €120.265. These large differences in outcome were related to different modeling methods, with differences in time horizon, and use of a carry over effect as most prominent causes.

Conclusion

Despite similar comparators and logical differences due to transferability issues the outcomes of the included studies varied widely. To increase comparability, and transparency of pharmacoeconomic evaluations, standardization of modeling methods for different therapeutic groups/diseases and the availability of a detailed and complete description of the model used in the evaluation is advocated. Recommendations for standardisation in modelling treatment strategies in early breast cancer are presented.

Introduction

Breast cancer is the most common cancer among women in the western world[1]. The primary aim for treatment of early breast cancer is to reach cure by intensive local and systemic treatment[2]. Currently, the major therapies for early breast cancer are surgery, radiotherapy, chemotherapy, endocrine therapy and immunotherapy. New technologies in cancer therapies may improve patients' survival and quality of life, but such improvements come at substantial costs. Therefore, health care financing and reimbursement of expensive anti-cancer drugs[3,4] is an often discussed topic in an era of cost containment.

Reimbursement of cancer therapy in Europe is part of the social system and the decisions regarding reimbursement usually are the responsibility of the government or healthcare insurance companies. First step in the reimbursement procedure for drugs is the approval for market authorization in Europe by the European Medicines Agency (EMA) www.ema.europa.eu/. A positive benefit risk balance of the drug is needed for this approval. Subsequently, each European country applies its own assessment and/or appraisal procedure for reimbursement of this new drug. Usually therapeutic benefit is the most important consideration for these national appraisals, but more and more also pharmacoeconomic evaluations are part of the reimbursement evaluation. A complete overview of all existing European guidelines on economic evaluations can be found on www.ispor.org.

Currently the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom is the only institute in Europe that links policy decisions directly to these ICERs[5]. In this process, the ICER for each therapy is compared to a threshold value, which is generally accepted as having an upper limit of £20.000 and 30.000 in case of life saving interventions. Other European countries use these outcomes at this moment only as a guidance in policy decisions[6]. Such decisions made by policy makers and researchers of these reimbursement agencies are crucial for patient groups in all countries. Therefore, decisions should be based on solid evidence, abstracted from high quality studies, especially when ICERs are directly linked to policy decisions as in the United Kingdom. In this respect, the credibility of cost-effectiveness studies can be decreased by an unexplained and wide variation in ICERs, seen in recent pharmacoeconomic evaluations.

In the published literature two systematic reviews of cost-effectiveness studies for endocrine therapies in early breast cancer can be found[7,8]. Their main conclusion is that aromatase inhibitors are cost-effective alternatives to current or previous standard therapies for the treatment of early breast cancer. Besides, Annemans[9] published a review about methodological issues in evaluating the cost-effectiveness of aromatase inhibitors

in early breast cancer, in which he concluded that there is a need for improvement regarding several modelling methods applied i.e. recurrence rate, patient subtypes and model calibration. Although these reviews provide useful overviews of cost-effectiveness issues of endocrine therapies, none of them provide causal insight into the relationship of modeling methods and reported differences in outcome of similar endocrine therapies. Therefore, this review will focus on cost-effectiveness outcome and the mathematical models used in economic evaluations of endocrine therapy in early breast cancer, which therapy is intended to improve cure rate in estrogen- and/or progesterone receptor positive disease[10].

The purpose of this systematic review is primarily to identify published cost-effectiveness analyses and cost-utility analyses of endocrine therapies, which are recommended by the European Society of Medical Oncology (ESMO) for the treatment of early breast cancer. Secondary objective is to identify whether the differences in seven modeling characteristics, as described in the review by Annemans, are related to differences in outcome of these cost-effectiveness and cost-utility analyses.

Methods

Study design

A systematic literature review was conducted to identify peer reviewed full economic evaluations of endocrine treatments of early breast cancer, published in the English language between 2000 and December 2010. Only those treatments of which ≥ 2 studies were available were included in order to make a comparison regarding methods betweens studies possible.

Treatment recommendations for early breast cancer with endocrine therapy were obtained from the site of the European Society of Medical Oncology (ESMO)[2].

Search strategy

To identify all cost-effectiveness (CE) and cost-utility (CU) analyses on early breast cancer drugs we exploded medical subject heading "adjuvant" and "breast" We used different strategies in each database to identify cost-effectiveness analyses. For our PUBMED/ MEDLINE and additional EMBASE search, we added the exploded medical subject heading "costs and cost analysis". The following (shortened) search string was used ('adjuvant' [all fields] OR 'early' [all fields] OR ('primary' [all fields] AND ('breast cancer'[all fields]) AND ('cost'[all fields] OR economic'[all fields]. In the NHS EED, we limited the search to "breast and cancer" to be sure no hits will be missed. The complete search string is made

available in the appendix. References of retrieved publications and of relevant overview publications were checked to identify additional studies.

Study selection

The abstracts and titles of the resulting hits were checked by one author (G.F) for the following inclusion criteria: (i) The article was published between 2000 and 2010; (ii) the article was published in English, because papers in English are accessible to academic readers all over the world; (iii) The study population consisted of patients diagnosed for adjuvant treatment of breast cancer; (iv) The study focused on endocrine therapies recommended by ESMO for the treatment of early breast cancer; (v) Focus of the study was on determining the cost-effectiveness or cost-utility (as defined in Drummond[11]) of drug treatment. Studies on diagnostics, radiotherapy or surgery were excluded; (vi) Information on the ICER had to be presented or it had to be possible to calculate it from the published data; If a study did not meet the inclusion criteria, the study was excluded and the reason recorded. Only the first reason for exclusion was recorded.

Data extraction

We developed a data extraction sheet in Excel, which was discussed extensively with all authors to obtain all relevant data. Information was extracted from each included study on: author, publication year, country of the study, comparator, perspective of analysis, source of clinical probabilities, discount rate, time horizon, natural units of effect (CE analysis), utilities (CU analysis), costs, and ICERs. The ICERs presented in the assessments were converted to the year 2010 by using the Consumer Price Index of the country of interest[12]. Subsequently the 2010 prices were converted to international Dollars by using the Purchase Power Parity (2009)[13], which is a economic technique used to determine the relative values of two currencies. Finally international Dollars were converted to Euros by using February 2011 values.

Modelling characteristics

The included articles will be assessed using the following seven aspects (**table 1**) which were selected from the review by Annemans et al. These seven aspects were selected because Annemans demonstrated a large variation in choice of these characteristics in his review. Furthermore, it appears from several studies that these parameters have the largest absolute impact on the ICER[14-20].

Besides the differences in methodological characteristics, study sponsorship might also influence the outcome. All incorporated articles will be checked whether they were sponsored by the manufacturer of the drug.

Methodological quality

The methodological quality of the included studies was determined using the CHEC list[21]. This list contains 19 items that were selected in a Delphi process by 23 experts in the field of health economics and is used for the assessment of the quality of pharmacoeconomic evaluations[22]. This checklist is originally developed for assessing economic evaluations alongside clinical trials. To increase it's relevance we added six items for the assessment of modeling studies. These items were retrieved from a study published by Soto et al[23] and were incorporated in our checklist after extensive discussions with all authors.

Table 1. Methodological aspects of interest

1	Time horizon
2	Hazard rate
3	Incidence of recurrence
4	Carry-over effect
5	Adverse events
6	Patient subtypes
7	Cost of the intervention

All publications were assessed independently by two or more reviewers. After the first assessment of all publications by GF, other authors (AH, JLS and JHMS) reviewed approximately 1/3 of all publications each. Differences between reviewers were discussed; when no agreement was reached by the two reviewers a third author was consulted. The findings from the comparison of the results were used to determine whether it is feasible for one reviewer to score quality with this checklist in an accurate and consistent manner.

All articles were assessed using the following characteristics; no details given, complete details given in text, not clearly stated within text, references given and not applicable.

Results

Study selection

The total PubMed search resulted in 386 hits, total NHSEED search resulted in 114 hits. In addition we searched in 881 EMBASE hits for additional papers, but did not identify unique papers. A first selection of publications on title and abstract resulted in the elimination of studies using the exclusion criteria. This selection resulted in 32 unique papers in total (**figure 1)**. Abstracts and full text of these 32 papers were screened again to determine whether the paper evaluated an original cost-effectiveness/cost-utility study

of an endocrine therapy. Reviews, editorials, posters, abstracts and studies that involved drugs of no interest where excluded. A total of twenty publications matched all criteria. These twenty economic evaluations comprise of five different endocrine therapeutic strategies, which are all assessed more then once (**figure 2**).

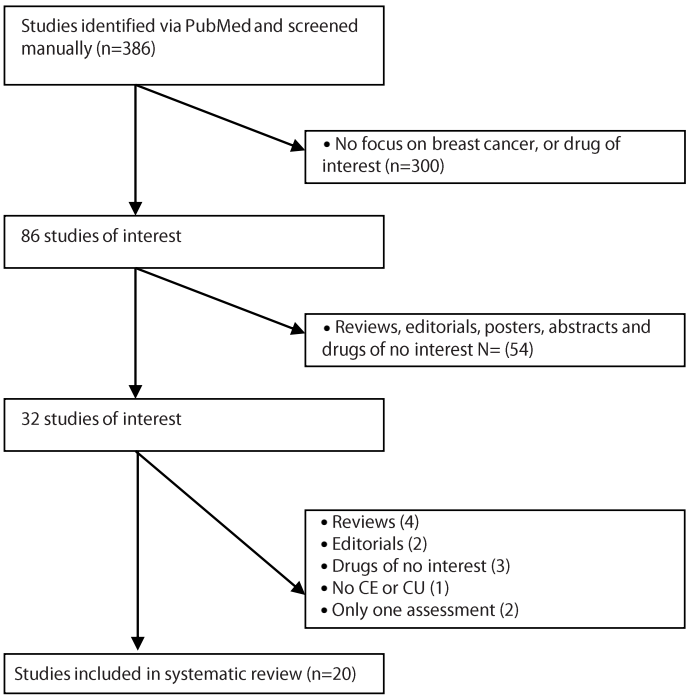


***Figure 1**. Decision tree of included and excluded studies, with reasons for exclusions*

CE = Cost-Effectiveness
CU= Cost-Utility

The effectiveness and safety of each endocrine strategy is evaluated in different phase III clinical trials. Each author used clinical data available from the published trials in mathematical modeling to calculate ICERs for their economic evaluations.

Quality of pharmacoeconomic evaluations

As assessed based on the CHEC and Soto list, a majority of evaluations >15 have included correct descriptions of the model, included model data sources, appropriately assessed costs and included deterministic and probabilistic sensitivity analyses. We believe these characteristics are the most essential characteristics of this quality assessment.

Therefore, the overall quality of pharmacoeconomic evaluations of adjuvant endocrine breast cancer therapies appeared to be good.

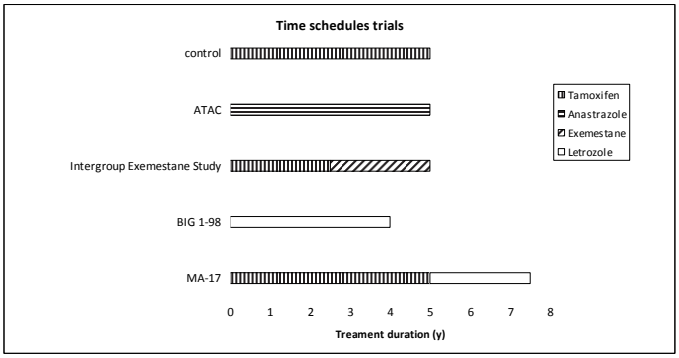


Figure 2. *Overview of time schedules and treatment duration of clinical trials applied in the pharmacoeconomic evaluation of endocrine therapies in early breast cancer (ATAC[24], Intergroup Exemestane Study[25], BIG 1-98[26] and MA-17[27]*

However in the majority of studies a limited health care payer perspective instead of the societal perspective was used and the discussion and conclusion section, parts on generalizability and ethical questions were often lacking. The results of these assessments are provided in **table 2**.

After this, all publications were analyzed for differences in modeling methods and outcomes.

Outcomes

Costs and outcomes of the twenty selected publications are provided in **table 3**.

We identified eleven cost-effectiveness analyses of anastrazole compared with, the until then, standard treatment tamoxifen[14-16;28-35]. All studies used the ATAC trial[24] to obtain transition probabilities, and were performed from a health care payer perspective. Incremental life years gained ranged from 0.16[30] to 0.550[28] with an incremental cost-effectiveness ratio ranging from €3.958[32] to €75.331[29]. Incremental QALYs gained ranged from 0.092[34] to 0.378[32] with a cost per QALY gained varying from €3.696[32] to €120.265[29]. Comparable studies were performed in four different countries. Two studies in Belgium calculated ICERs of €3.696[32] and €18.672[33] per QALY gained, two studies in the US found ICERs of €61.250[30] and €16.338[14] per QALY gained, two studies in the UK calculated ICERs of €8.566[31], €13.793[31] and €18.264[15] per QALY gained. Finally two studies in Canada calculated costs of €16.915[16], €18.264[16], €18.294[34] and €44.386[34] per QALY gained respectively.

Table 2. Quality of econonomic evaluations

		References																			
		32	31	28	14	16	33	34	35	15	30	29	18	17	42	41	40	38	37	36	39
	Research question, perspective and time horizon																				
1	Does a well defined objective exist? Is it clear, explicit and answerable?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2	Are competing alternatives described?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	nc	nc	✓	✓	✓	✓
3	Is a societal perspective used?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4	Is it justified why the narrower perspective is valid?	-	-	-	-	-	-	-	-	-	-	✓	-	-	-	-	-	-	-	-	-
5	Is a life time horizon taken into account?	-	✓	✓	✓	✓	-	-	-	✓	-	-	✓	-	✓	✓	✓	✓	-	✓	✓
6	Are reasons for another time horizon incorporated?	-	-	-	na	na	-	-	✓	na	✓	✓	na	✓	na	na	na	-	✓	na	na
	Type and description of the model																				
7	Is the type of model used in the study stated clearly?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	✓	✓	✓
8	Are details of the model given?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
9	Is the design of the model appropriate and does it include the correct health states?	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	✓	✓	✓	✓	-	✓	✓	✓	✓	✓
	Model data sources																				
10	Are the sources of all values credible and accurate?	✓	✓	-	✓	nc	✓	✓	✓	✓	✓	✓	✓	✓	✓	nc	nc	✓	✓	✓	✓
11	Are assumptions incorporated into the model clearly stated?	✓	✓	-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Outcomes and probabilities																				
12	Are all important and relevant outcomes for each alternative identified (LY or QALYs gained)?	✓	✓	-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
13	Are the probabilities that outcomes happen clearly stated?	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
14	Are outcomes measured appropriately?	✓	✓	-	✓	✓	nc	nc	✓	✓	✓	✓	✓	✓	✓	✓	nc	✓	✓	nc	✓
15	Are outcomes valued appropriately?	nc	✓	-	✓	✓	nc	nc	nc	nc	✓	✓	nc	✓	✓	✓	nc	nc	✓	nc	✓

Table 2. Continued. Quality of econonomic evaluations

		References																			
		32	31	28	14	16	33	34	35	15	30	29	18	17	42	41	40	38	37	36	39
	Costs																				
16	Are all important and relevant costs for each alternative identified?	✓	✓	-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
17	Are all costs measured appropriately in physical units?	-	✓	-	✓	-	nc	nc	nc	nc	-	✓	nc	-	nc	-	-	nc	✓	nc	✓
18	Are costs valued appropriately?	-	✓	✓	✓	✓	✓	nc	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	nc	✓
19	Are all future costs and outcomes discounted appropriately?	-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Incremental analysis and sensitivity analysis																				
20	Is an incremental analysis of cost and outcomes of alternatives performed?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
21	Is a one-way sensitivity analysis performed?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-
22	Is a probalistic sensitivy analysis performed?	-	✓	✓	✓	✓	-	-	✓	✓	-	-	✓	✓	✓	✓	✓	✓	-	-	✓
	Discussion and conclusions																				
23	Do the conclusions follow from the data reported?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
24	Does the study discuss the generalizability of the results to other settings and patient/client groups?	-	-	✓	-	-	-	-	✓	✓	-	-	-	✓	✓	✓	✓	✓	-	✓	-
25	Does the article indicate that there is no potential conflict of interest of study researcher (s) and funder (s)?	-	-	✓	-	✓	-	-	-	-	✓	-	-	✓	-	-	-	-	-	-	-
26	Are ethical and distributional issues discussed appropriately?	-	-	-	-	-	-	-	-	-	✓	-	-	-	-	-	-	-	-	-	-

- = no details given
✓ = complete details given in text
nc = not clearly stated within text, references given
na= not applicable

Two analyses also compared anastrazole with a combination of tamoxifen and exemestane[33;34]. Both studies used the Intergroup Exemestane Study[25] to obtain probabilities with a health care payer perspective. For the analysis of anastrazole vs. tamoxifen and exemestane[33;34], QALYs gained varied between 0.016[34] and -0.02[33]. Costs of these QALYs varied between €178.270[34] and a dominated outcome[33].

Three pharmacoeconomic analyses of letrozole were selected based on our criteria[17;18;31]; all three analyses compared letrozole with tamoxifen and used data from the same source, i.e. the BIG 1-98 trial[26]. In all three analyses the healthcare payer perspective was used. Incremental life years gained ranged from 0.350[31] to 0.510[31] and incremental QALYs ranged from 0.343[17] to 0.520[31]. The additional life years and QALYs cost ranged from €7.741[31] to €17.220[18] per LY and from €7.592[31] to €18.409[18] per QALY gained respectively.

Cost effectiveness of switching to exemestane after 2-3 years of therapy with tamoxifen compared to continuing tamoxifen was determined in five selected studies[29;36-39]. All studies used the Intergroup Exemestane Study[25] and one also used the SEER-Medicare data[38] to obtain probabilities, two analyses used the healthcare payer perspective[29;37], and for two it was unclear[36;38], however, because only direct costs were included, we assumed that a healthcare payer perspective was used. Incremental life years gained varied between 0.103[37] and 1.046[29] and incremental QALYs gained varied between 0.120[37] and 0.566[29]. Cost of one life year gained was found to vary between €8.451[38] and €46.072[29] and the cost of one QALY gained varied between €12.871[38] and €72.112[29].

The outcome of addition of tamoxifen to exemestane was studied in two of the selected publications[33;34]. Both analyses compared giving tamoxifen and exemestane with giving tamoxifen alone, and used the Intergroup Exemestane Study[25] with a healthcare payer perspective. Incremental QALYs gained varied between 0.076[34] and 0.251[33] and the cost of one QALY gained varied between €4.650[33] and €16.513[34].

Besides these pharmacoeconomic analyses of letrozole, three analyses of extended letrozole were selected[40-42]. All analyses have compared letrozole (after 5 years of tamoxifen) with no extended adjuvant therapy by using the MA17[27] trial to obtain transition probabilities. Two of these analyses used a health care payer[41;42] perspective, and for one analysis it was not stated[40]. However, because only direct costs were included we assumed that this analysis was performed from a health care payer perspective. Incremental life years gained varied between 0.202[41] and 0.332[41] and incremental QALYs gained between 0.182[41] and 0.360[42]. Cost of one life year gained was found to be between €13.345[42] and €26.467[41], the cost of one QALY gained varied between €13.189[42] and €29.469[41].

Methodological differences

The following sections show the base-case methods and assumptions that were applied in the twenty economic analyses with regard to the seven selected methodological aspects (**table 3**).

Time horizon

The individual studies applied a time horizon of 7.5[37], 10 [29;34], 20 [29;30;32-34], 25 [14;15;35], 30 [17;18;40], 35 [38], 40 [42], 50 years[31] or lifetime[16;28;36;39;41] (see **table 3** for an overview per therapy group).

Hazard rate for recurrence

The hazard rate for recurrence is one of the essential differences between two adjuvant therapies. Within the analyses a wide variation was observed in the use of the hazard ratio. The use of hazard ratios varied from the use of a disease free survival hazard ratio (which includes background mortality in addition to death due to breast cancer)[16-18;29;33;34;36], recurrence free survival hazard ratio (does not include background mortality and includes breast cancer recurrence and deaths due to recorded recurrence)[14;15;28;35]and even outcome specific hazard ratios for different types of recurrence are used[30-32;37;40;42].

Incidence of recurrence

The majority of authors considered a time dependent recurrence risk, and used recurrence rates which varied over time[14-18;28;29;31;35-38;40]. Several other authors applied a constant probability of recurrence, in which the recurrence rate stays at the same level up to the end of the model[28;30;32-34;41]. Breast cancer mostly recurs within the first 2-3 years after initiation of therapy, with a peak at about 2 years[19;43]. For women with strong ER+ or PR+ tumours breast cancer often recurs after a period of ten years from initial treatment stop[44;45].

Carry-over effect

In the latest updates of several trials carry-over effects (effects of treatment that persist after treatment has been stopped) were confirmed for several years after treatment cessation[46;47]. Five analyses of interest did not use a carry-over effect[29;31;36;37;40;42], several others used a carry over effect of 5 years[14-18;32-35;41] and one analysis used a carry over effect which lasts for the entire life-span of the patient[28] **(table 3**).

Adverse events

Sensitivity analyses have shown that the inclusion of adverse events has a strong impact on ICERs. A wide variety of adverse events was included in the models of interest, with fractures, venous thromboembolism, vaginal bleeding and endometrial cancer as the most abundant ones. One study only included hip fractures and osteoporosis[40] and another study only included fractures[42]. Two studies did not present the adverse events in

detail[28;32], and one study did not use any adverse events in the model[41].

Patient subtypes
One study sub-divided patients in node negative and node positive groups[41] for base-case calculations. One other study calculated ICERs for ER+ and ER- patients for the analysis of exemestane vs. continuing tamoxifen[38]. All other studies did not use any patient subtypes in their base-case analyses.

Cost of the intervention
Price differences per day between the intervention and the comparator varied from €2.53 to €5.46 for anastrazole vs. tamoxifen, €-0.23 to €-0.64 for anastrazole vs. tamoxifen + exemestane, €3.10 to €4.64 for letrozole vs. tamoxifen, €3.58 to €5.71 for extended letrozole vs. no extended adjuvant therapy, €2.94 to €6.37 for exemestane vs. continuing tamoxifen and €3.52 to €4.18 for tamoxifen + exemestane vs. tamoxifen alone (**table 3**).

Discount rates could also be considered to have large impact, but because all countries considered in our review have guidelines for the application of a discount rate[6], the relationship between the results and the discount rate is driven by these country specific requirements. Unfortunately, no undiscounted numbers were given in the majority of studies, and therefore the influence of discount rates could not be analysed in detail.

Two of all twenty incorporated articles were non-pharmaceutical company-sponsored studies[30;33].

As well as the diversity seen in the modelling methods, a large diversity was seen in the choice of health states and cycle length used in the Markov models. Furthermore, instead of the usual head to head comparisons, several articles compared treatments by using indirect comparison[31;33;34;48]. These indirect comparisons refer to a comparison of different healthcare interventions using data from separate studies. In addition, several studies used data from clinical trials [26] in which patients could switch from control to study treatment. To answer the question of what would have been the survival experience of two patient groups in the absence of a cross-over, authors in the BIG 1-98 trial applied the Inverse Probability of Censoring Weighted (IPCW) method, to remove the bias caused by treatment cross-over.[49] At last, overall survival was driven off of recurrence in all studies because of the absence of overall survival data.

Table 3. *Overview of outcomes and modelling characteristics of endocrine economic evaluations, in order of increasing cost-effectiveness*

Intervention	Author	Country	Life Years gained*	QALYs gained*	Incremental costs (€)†	Cost per LY gained (€)†	Cost per QALY gained (€)†	Time Horizon (years)	Hazard Ratio	Absolute incidence of recurrence	Carry over effect	Adverse events	Patient subtypes	Difference in cost of the intervention (€)
Anastrazole vs. tamoxifen	[32]	Belgium	0.353	0.378	1,397	3,958	3,696	20	Outcome specific	Constant	5 years	Yes	none	2.53
	[31]	UK	0.350	0.360	3,084	8,810‡	8,566‡	50	Outcome specific	Time dependent	none	Yes	none	2.86
	[28]	Brasil	0.550	NA	9,929	17,920	NA	Lifetime	0.74	Constant	lifetime	Yes	none	-
	[31]	UK	0.250	0.260	3,535	14,125§	13,793§	50	Outcome specific	Time dependent	5 years	Yes	none	2.86
	[14]	US	0.221	0.257	4,206	14,140	16,338	25	0.74	Time dependent	5 years	Yes	none	4.22
	[16]	Canada	0.194	0.218	3,688	19,028‖	16,915‖	Lifetime	0.83	Time dependent	5 years	Yes	none	3.31
	[33]	Belgium	NA	0.231	4,314	NA	18,672	20	0.83	Constant	5 years	Yes	age in sensitivity analysis	3.54
	[34]	Canada	NA	0.227	4,110	NA	18,097	20	0.83	Constant	5 years	Yes	age in sensitivity analysis	3.05
	[16]	Canada	0.192	0.208	3,797	19,745¶	18,264¶	Lifetime	0.83	Time dependent	5 years	Yes	none	3.31

Table 3. Continued. *Overview of outcomes and modelling characteristics of endocrine economic evaluations, in order of increasing cost-effectiveness*

Intervention	Author	Country	Life Years gained*	QALYs gained*	Incremental costs (€)†	Cost per LY gained (€)†	Cost per QALY gained (€)†	Time Horizon (years)	Hazard Ratio	Absolute incidence of recurrence	Carry over effect	Adverse events	Patient subtypes	Difference in cost of the intervention (€)
Anastrazole vs. tamoxifen	[35]	Germany	0.290	0.320	6,303	21,732	19,473	25	0.76	Time dependent	5 years	Yes	None	5.46
	[15]	UK	0.230	0.244	5,370	23,273	21,971	25	0.74	Time dependent	5 years	Yes	none	4.27
	[34]	Canada	NA	0.092	4,041	NA	43,907	10	0.83	Constant	5 years	Yes	age in sensitivity analysis	3.29
	[30]	US	0.160	0.123	5,406	32,763	61,250	20	Outcome specific	Constant	5 years	Yes	none	4.44
	[29]	Spain	0.535	0.285	20,537	38,387	72,060	20	0.83	Constant	none	Yes	none	5.32
	[29]	Spain	0.182	0.114	13,710	75,331	120,265	10	0.83	Constant	none	Yes	none	5.32
anastrazole vs. tamoxifen + exemestane	[34]	Canada	NA	-0.017	2,883	NA	Dominated	20	0.70	Constant	5 years	Yes	age in sensitivity analysis	-0.23
	[33]	Belgium	NA	-0.020	3,145	NA	Dominated	20	0.70	Constant	5 years	Yes	age in sensitivity analysis	-0.64
	[34]	Canada	NA	0.016	2,804	NA	178,270	10	0.70	Constant	5 years	Yes	age in sensitivity analysis	-0.23
letrozole vs. tamoxifen	[20]	UK	0.510	0.520	3,948	7,741	7,592	50	Outcome specific	Time dependent	5 years	Yes	none	3.49

Table 3. Continued. *Overview of outcomes and modelling characteristics of endocrine economic evaluations, in order of increasing cost-effectiveness*

Intervention	Author	Country	Life Years gained*	QALYs gained*	Incremental costs (€)†	Cost per LY gained (€)†	Cost per QALY gained (€)†	Time Horizon (years)	Hazard Ratio	Absolute incidence of recurrence	Carry over effect	Adverse events	Patient subtypes	Difference in cost of the intervention (€)
letrzole vs. tamoxifen	[20]	UK	0.350	0.360	4,504	12,869	12,477	50	Outcome specific	Time dependent	none	Yes	none	3.49
	[35]	Canada	0.368	0.343	5,130	13,942	14,969	30	0.70	Time dependent	5 years	Yes	age in sensitivity analysis	3.10
	[34]	US	0.440	0.409	7,525	17,220	18,409	30	0.70	Time dependent	5 years	Yes	age in sensitivity analysis	4.65
extended letrozole vs. no extended therapy	[42]	UK	0.320	0.360	4,728	13,345	13,189	40	Outcome specific	Time dependent	none	Yes	none	4.49
	[41]	Canada	0.332	0.290	4,929	14,869#	16,993#	Lifetime	0.48 node-, 0.61 node+	Constant	5 years	No	100% node positive patients	3.58
	[41]	Canada	0.267	0.236	5,139	19,263**	21,796**	Lifetime	0.48 node-, 0.61 node+	Constant	5 years	No	50 % node positive and 50% node negative patients	5.71

Table 3. Continued. *Overview of outcomes and modelling characteristics of endocrine economic evaluations, in order of increasing cost-effectiveness*

Intervention	Author	Country	Life Years gained*	QALYs gained*	Incremental costs (€)†	Cost per LY gained (€)†	Cost per QALY gained (€)†	Time Horizon (years)	Hazard Ratio	Absolute incidence of recurrence	Carry over effect	Adverse events	Patient subtypes	Difference in cost of the intervention (€)
extended letrozole vs. no extended therapy	[40]	US	0.320	0.338	7,827	24,427	23,183	30	Outcome specific	Time dependent	5 years	Yes	n-, n+ and age in sensitivity analysis	3.58
	[41]	Canada	0.202	0.182	5,351	26,467††	29,469††	Lifetime	0.48 node-, 0.61 node+	Constant	5 years	No	100% node negative patients	3.58
exemestane vs. continuing tamoxifen	[38]	US	0.390	0.260	3,333	8,451‡‡	12,871‡‡	35	Outcome specific	Time dependent	none	Yes	ER+ only	4.07
	[37]	Canada	0.103	0.120	1,849	17,995	15,477	7.5	Outcome specific	Time dependent	none	Yes	none	2.94
	[38]	US	0.330	0.220	3,411	10,312§§	15,584§§	35	Outcome specific	Time dependent	none	Yes	ER+ and Er-	4.07
	[36]	Sweden	0.220	0.160	2,443	11,193	15,760	Lifetime	0.69	Time dependent	none	Yes	none	3.11
	[39]	Germany	0.249	0.238	3,942	15,840	15,840	Lifetime	Unknown	Constant	none	Yes	none	-
	[29]	Spain	1.046	0.566	23,091	22,075	40,796	20	0.68	Constant	none	Yes	none	6.37
	[29]	Spain	0.360	0.230	16,586	46,072	72,112	10	0.68	Constant	none	Yes	none	6.37

Table 3. Continued. *Overview of outcomes and modelling characteristics of endocrine economic evaluations, in order of increasing cost-effectiveness*

Intervention	Author	Country	Life Years gained[x]	QALYs gained[x]	Incremental costs (€)[†]	Cost per LY gained (€)[†]	Cost per QALY gained (€)[†]	Time Horizon (years)	Hazard Ratio	Absolute incidence of recurrence	Carry over effect	Adverse events	Patient subtypes	Difference in cost of the intervention (€)
	[33]	Belgium	NA	0.251	1,168	NA	4,650	20	0.70	Constant	none	Yes	age in sensitivity analysis	4.18
tamoxifen + exemestane vs. tamoxifen	[34]	Canada	NA	0.244	1,226	NA	5,034	20	0.70	Constant	none	Yes	age in sensitivity analysis	3.52
	[34]	Canada	NA	0.076	1,260	NA	16,513	10	0.70	Constant	none	Yes	age in sensitivity analysis	3.52

Note: Exchange rate: 1 € = 1.35 US Dollar

Time horizon= the length of the period in which costs and outcomes will be considered
LYs won= (LYs gained by drug of interest) – (LYs gained by comparator)
QALYs won= (QALYs gained by drug of interest) – (QALYs gained by comparator)
Incremental costs= (total costs treatment with drug of interest) – (total costs treatment with comparator)
Cost per LY= (Incremental costs) / (LYs gained)
Cost per QALY= (Incremental costs) / (QALYs gained)
Dominated = effectiveness of treatment is lower and treatment costs are higher
Adverse events= adverse events included in analysis
Absolute incidence of recurrence= risk of recurrence after therapy (constant or time dependent)
Carry over effect= inclusion and duration of effect after treatment cessation
Patient subtypes= use of patient subtypes within analysis
Daily cost therapeutic= daily cost of the intervention
Daily cost comparator= daily cost of the comparator
Difference in cost of the intervention = (daily cost of the intervention) – (daily cost of the comparator)

[a] *3 year interim analysis*
[b] *5 year interim analysis*
[c] *No Carry over effect*
[d] *5 year carry over effect*
[e] *50% node positive and 50% node negative patients*
[f] *100% node negative patients*
[g] *100% node positive patients*
[h] *ER positive and ER unknown patients*
[i] *ER positive only*
[j] *LYs and QALYs gained are presented as stated within the articles*
[k] *Original costs are converted to Euros (February 2011)*
[L] *Unable to calculate daily cost from the article*
n- = node negative patients
n+ = node positive patients
ER- = Estrogen receptor negative patients
ER+ = Estrogen receptor positive patients

Impact variation

The following sections demonstrate the possible impact of the variation in methodological characteristics on the ICER. The impact of these characteristics is obtained from sensitivity analyses or base case analyses, therefore outcomes in these examples are not adjusted with the current inflation rate. Differences in inclusion of adverse events and incidence of recurrence was not tested separately in sensitivity analyses within the evaluations of interest, therefore no examples are given.

Time horizon

In several selected publications a sensitivity analysis on time horizon was performed, which showed large effects on ICERs[16;29;30;38]. In addition to these sensitivity analyses, several authors have performed base case analyses with a ten and twenty year time horizon[29;34]. In the analysis by Skedgel et al[34] ICERs varied from €43.907 for ten years to €18.097 per QALY gained for twenty years, corresponding to a decrease of 59%. Lux et al.[35] have shown the impact of the time horizon using a 10, 15, 20 and 25 year time horizon, which resulted in ICERs of respectively €44.676, €27.185, €22.776 and €21.069 per QALY gained.

Hazard rate for recurrence

Skedgel et al[33] have tested the influence of the use of a disease free survival hazard ratio and a recurrence free survival hazard ratio. The analysis based on the disease free survival hazard ratio resulted in an ICER of €19.982 and the analysis based on the recurrence free survival hazard ratio resulted in an ICER of €11.338 which corresponds to a decrease of 43%.

Carry-over effect

A few authors have tested the influence of a carry-over effect in their sensitivity analyses, and found a strong decrease of the ICER employing a carry-over effect[8;31;33;34]. For instance, the sensitivity analysis performed by Skedgel et al.[34] has shown that the inclusion of a carry over effect results in a decrease in ICER of approximately 38%. As well as these sensitivity analyses, a few authors have included base case analyses with or without a carry over effect, with ICERs varying from €13.793 per QALY gained without a carry over effect to €8.566 per QALY gained with a carry over effect up to 5 years[31], which also corresponds in a decrease of 38% of the ICER.

Patient subtypes

Several of the selected papers provided information about patient subtypes, for which especially the effect of age was shown in sensitivity analyses[17;18;33;34;40]. A combination of node negative and node positive patients had a cost of €21.796 per QALY gained, the cohort of 100% node negative patients a cost of €29.469 and the cohort of 100% node

positive patients a cost of €16.993. In the other study a cost of €15.584 for ER+ and €12.871 for ER- patients per QALY gained was calculated[38]. Cost effectiveness of letrozole therapy is more favorable in younger postmenopausal women, with cost varying from €12.338 for 50 year old patients to €80.718 for 70 year old patients[17].

Cost of the intervention
Sensitivity analyses performed in a few articles of interest, showed a strong improvement of the ICER when using lower costs[30;36;38]. For instance, Lundkvist et al. [36] have incorporated cost of tamoxifen and exemestane in their sensitivity analysis. Varying the cost of exemestane to 75% of the original cost results in a 55% decrease of the ICER compared to using 125% of the original cost.

Sponsorship
Both non-pharmaceutical company sponsored studies calculated higher ICERs when compared to the average outcomes of all other studies. Respectively €18.097 (20 year analysis)[33], €43.907 (10 year analysis[33]) and €61.250[30] per QALY gained.

Discussion

We identified twenty publications about cost-effectiveness estimates of endocrine therapies in early breast cancer that met our inclusion criteria. These included thirteen studies of anastrazole[14-16;28-34], three of letrozole[17;18;31], three of extended letrozole[40-42], five of exemestane[29;36-38], and two involved tamoxifen in combination with exemestane[33;34]. In general the quality of these analyses appeared to be good, and all analyses adhered to the general guidelines of pharmacoeconomic evaluations. There were several articles which accounted for all influential methodological characteristics, but we believe the article by Mansel et al.[15] could be identified as a high quality assessment. Apart from including all methodological characteristics, this article also incorporated a short cycle length (3 and 6 months) and used a transparent way of publishing all assumptions and probabilities. However, in the analyses of interest a wide variation in outcomes for several similar therapies appeared, in spite of the use of the same trial data (**table 2**). Hence, the large variations in outcome must be caused by differences in approach and modelling methods between studies.

Three analyses with ICERs above the threshold defined by NICE of £30.000 in the anastrazole vs. tamoxifen group calculated low numbers of LYs and QALYs gained. One analysis used a time horizon of ten and twenty years, a hazard ratio of 0.83, a constant risk of recurrence and no carry over effect[29;30;34]. The other used a time horizon of twenty years, a constant

risk of recurrence and a carry over effect of 5 years[30]. As stated in pharmacoeconomic guidelines over the world, time horizon of studies should be long enough to capture all relevant costs and outcomes[6]. Too short time horizons fail to capture the full costs and consequences of chronic disease management. As a result an underestimated effect of treatment was seen in analyses with a short time horizon, especially in two analyses with a ten year time horizon[29;34]. As ER+ and PR+ breast cancer often relapses after a period of ten years from initial treatment a time horizon of ten years is considered too short. The use of a constant risk of recurrence results in the use of a too high recurrence rate over several years, because the majority of relapses in early breast cancer occur in the first two years after diagnosis[19;43;50] and for ER+ and PR+ tumors after a period of ten years from the end of the initial treatment stop[44;45]. Therefore, the use of a constant probability underestimates the effect of the intervention, and overestimates the ICER. The use of no carry over effect assumes the effect of the drugs of interest is directly halted at the moment of treatment stop and thereby underestimates the effect of treatment. In combination with a high incremental cost, effect-underestimating modelling methods lead to the calculation of high ICERs. One twenty year analysis had an unexplained high number of LYs and QALYs gained[29;32]. This is in spite of the use of a twenty year time horizon, a constant risk of recurrence and no carry over effect. This analysis also calculated very high ICERs, which was caused by the high country specific costs. One other analysis calculated very low ICERs[32], which was caused by the low incremental costs. These low incremental costs are due to the fact that costs are incurred solely during the first five years in this analysis. The large incremental costs in the other analysis are unexplained. The calculations based on the Brazilian situation[28] resulted in a very high number of LYs gained compared to outcomes in other studies. This could be related to the combination of modeling characteristics within this analysis. The Brazilian study includes a lifetime time horizon, a recurrence free survival hazard ratio of 0.74 and inclusion of a lifetime benefit of anastrazole. All three characteristics have shown to cause an increase in LYs gained and a decrease in ICERs in several sensitivity analyses.

Two studies performed from a Belgian perspective calculated a 1.5 fold difference in the number of QALYs gained. The incremental cost difference in both studies could be explained by the difference in costs of the intervention. The only difference in the pre-defined seven characteristics was seen in the inclusion of specific HRs for local and distant recurrence by one study. However, because one analysis[33] based the amount of local and distant recurrences on the proportion of both types in the ATAC trial, they also have incorporated different chances for both recurrences. Therefore, this could not be the cause of the large discrepancy in QALYs gained. Other modeling differences between both studies must be present which are related to this discrepancy in outcome. Both US studies calculated a two fold difference in QALYs gained, which could be caused by

underestimation of the effect of anastrazole in one study using a constant probability[30] and a HR for DSF (0.83) compared to outcome specific hazard ratios in the other analysis. Between the UK studies a difference was seen when the carry over effect was included. Due to this carry over effect one study calculated more QALYs gained, and therefore an improved ICER was seen. The other difference between the UK studies was caused by the difference in incremental costs, possibly due to the difference in medication price.

A short time horizon and a constant probability were also used in the analysis that revealed a cost of €178.270 per QALY gained for anastrazole vs. tamoxifen + exemestane[34]. However, the low number of QALYs gained in this analysis was caused by the small difference in effect of both therapies. The only varying outcome between the analyses of letrozole vs. tamoxifen was caused by the use of a carry over effect. When introducing a carry over effect up to five years, the number of LYs and QALYs gained increased, resulting in a more favourable ICER[31].

In contrast to these outcomes, the high ICER seen in the analysis of extended letrozole vs. no extended therapy was caused by differences in effect between patient cohorts. The selection and effectiveness of adjuvant systemic treatment relies heavily on pathological nodal status, tumor grade, tumor size and ER status[2]. As a result, therapy for some women may prove very effective and cost-effective, and for others no significant positive effects are seen. In this analysis extended letrozole is less effective in node negative patients. Due to that a less favorable cost-effectiveness ratio was calculated.

The highest ICERs in the exemestane vs. continuing tamoxifen group[29] are above all caused by the large incremental costs. Both analyses (10 and 20 year time horizon) calculated high numbers of LYs and QALYs gained in comparison to other studies, which is remarkable because of the use of a short time horizon, constant risk of recurrence and no carry over effect. No explanations for the high incremental costs and high number of LYs and QALYs gained were given in this publication. Differences between both US based studies are related to the difference in effect of interventions between both patient cohorts. Exemestane was more effective in the cohort with ER positive patients only, which decreased the ICER.

Finally, the only difference seen between the analyses of tamoxifen + exemestane vs. tamoxifen was the low number of QALYs gained when using a ten year time horizon in comparison to both twenty year time horizons. The differences in ICERs between studies performed in Canada and Belgium is related to differences between jurisdictions, because for both analyses the same model was used.

Furthermore, it was remarkable to see that both non-pharmaceutical company sponsored analyses calculated lower numbers of QALYs and LYs gained and indirectly a higher ICER in the anastrazole vs. tamoxifen group. These outcomes confirm the conclusions made by Jang et al.[51] that economic evaluations funded by a pharmaceutical company are less likely to reach unfavorable conclusions, but it must be kept in mind, that it this case it only occurred in two analyses, and that non-pharmaceutical company sponsored studies also calculated high ICERs.

Limitations

There are some limitations of this systematic review that must be addressed. First, this review included only fully published studies between 2000 and December 2010 written in the English language, which may have omitted some earlier cost-effectiveness analyses. Second, there are several factors that limit the transferability of study results to other countries[52;53]. We only converted foreign currencies to Euro's with help of current quotations and inflation rates. Therefore we did not take into account several important transferability factors like for example prices, practice variation, life expectancy and disease spread[54]. As well as differences in methodology, these factors may have caused discrepancies between outcomes of the studies of interest. At last, we did not use the checklist made by Philips et al[55]. We believe this checklist is too comprehensive for our quality assessment. Therefore we used the combination of CHEC and Soto et al.[23] to assess the included articles on their quality.

Conclusions

Based on these findings we conclude that there is a wide variation in the calculated ICERs of endocrine therapy analyses, between and even within several countries, in spite of the use of similar clinical trials for data input. Apart from cultural differences between countries, several large differences in reported ICERs are caused by choice of modelling methods. This is especially demonstrated in the large differences between outcomes of similar countries, in which transferability characteristics do not play any role.

To improve the comparability of future pharmacoeconomic evaluations of early breast cancer, and to decrease the diversity in modelling choices, an optimal model, with standardized, clinically relevant, modelling methods is necessary. A standard model was already advocated by Annemans in his publication two years ago, but in literature not much progression on standard models was made afterwards.

Any standard model should reflect a coherent theory and the underlying biological

process of a disease[55]. Regarding the seven characteristics analysed, to a large extend we confirmed the findings of Annemans et al: a standard model for the assessment of breast cancer treatment should at least take into account the following characteristics; a lifetime time horizon to capture all relevant costs and outcomes, a hazard ratio based on recurrence free survival, inclusion of a time dependent risk of recurrence which has a better representation of the course of the disease, the use of a carry over effect based on the latest trial updates and if relevant, patient subgroups in sensitivity analysis (age, ER+, ER-). We specified and extended the recommendations made by Annemans regarding adverse events and costs of the intervention: not only accounting for adverse events in detail, but more specifically those adverse events should be included that could cause death (endometrial cancer, thromboembolic events and hip fracture) are very costly (i.e. spine fracture, vaginal bleeding, biphosphonate treatment) or have a serious impact on the quality of life (endometrial cancer, thromboembolic events and hip fracture). Cost of the intervention must be transparently specified and impact should be tested in the sensitivity analysis. In addition to the conclusions regarding the seven methodological characteristics, we also recommend that both deterministic and probabilistic sensitivity analysis must be included in the evaluation. (**Table 4**)

Table 4. *Summary of recommendations for cost-effectiveness models in adjuvant breast cancer*

item ***7 characteristics according to Annemans (2008)***	**options (based on review)**	**recommendations**
Time horizon	Short (10-15 years) Mediocre (15- 25 years) Long (>25 years)	To capture all relevant costs and outcomes it is essential to use a **life-long time horizon.**
Carry over effect *(effect of treatment persists when treatment is halted)*	Not included Included	A carry over effect is an important characteristic for several hormonal therapies. Therefore, if relevant, a **carry over effect should be included** in the economic analysis
Hazard ratio	Disease free survival Recurrencw free survival Outcome specific*	The rate of recurrence is an essential characteristic for the outcome. The **recurrence free survival hazard ratio** should be included in the base-case analysis. When possible, the impact of other hazard ratio's should be assessed in the sensitivity analysis.
Incidence of recurrence	Constant over time Time dependent	Inclusion of a **time dependent incidence of recurrence** has a better representation of the course of the disease†
Adverse events	none selected all possible	All adverse events, which could **cause death** (endometrial cancer, thromboembolic events and hip fracture) very **costly events** (i.e. spine fracture, vaginal bleeding, biphosphonate treatment) and events which have a **serious impact on quality of life** (endometrial cancer, thromboembolic events) should be included.

Table 4. Continued. *Summary of recommendations for cost-effectiveness models in adjuvant breast cancer*

item	options (based on review)	recommendations
Patient subtypes/ subgroups	none Age ER+/ER-	Clinical effectiveness of a therapy is often different between subtypes and subgroups of patients. Therefore additional analyses of subtypes **(ER+/ER-) and subgroups (Age)** is essential
Cost of the intervention	not specified specified	Due to the large impact of therapeutic costs on the outcome, it is essential to **explicitly report the cost** of the intervention
Additional model characteristics		
Health states	A large variety of health states were included in the models	The markov model must at least include a **disease free, local recurrence, metastatic disease, background mortality death state and a disease related death state**. Use of additional health states should be justified, and where possible the impact on the outcome should be stated.
Cycle length	3 months 3-12 months 1 year	Recurrences are very relevant for the outcome and can occur continuously over time, therefore a short cycle length will have a better representation of the course of the disease . A cycle length of **3 months** should be used, which represents the time when patients are seen in a hospital. Longer cycle lengths should be justified.
Mortality modelling	overall survival based on recurrence	If no long term survival data is present for the study, it is recommended **to base overall survival on** recurrence. Applied literature for transition from recurrence to death should be relevant for the studied setting.
Indirect comparisons	yes no	**Indirect comparisons are feasible**, but should be justified and checked for the following characteristics: 1) Justification for indirect comparison 2) Identification and selection of clinical trial and/or meta analyses 3) Provide clear description of methods 4) Present the characteristics of the included trials that may cause heterogeneity 5) Provide details on how heterogeneity and adjustment for effect modifiers (i.e. patient characteristics, measurement of outcomes and protocol requirements) among trials is handled
Cross-over effect between therapies	not justified	A criticial assessment of clinical trial data is needed to assess whether clinical trial data is cross-over free. The **IPCW method** is recommend to obtain cross-over free data. Other methods could be appropriate but should be justified in the article.

Furthermore, because several other differences in model results could not be related to the seven characteristics assessed, we additionally make recommendations regarding standardization of health states, cycle length and other important assumptions. More specifically, the Markov model must at least include a disease free, local recurrence, metastatic disease, background mortality death state and a disease related death state. Use of additional health states should be justified, and where possible the impact on the outcome should be stated. Cycle length should be as short as possible to adequately represent the chronic disease pathway in which series of events occur through time. In discretized models a cycle length of 3 months is recommended, longer cycle lengths should be justified. Overall survival should be driven of off recurrence, and where possible this should be validated with mature overall survival data. Furthermore, in the absence of head to head trials, adjusted indirect comparisons, as performed by Karnon et al. are possible. But these have to be performed with some restraint because, empirical evidence indicates that results of adjusted indirect comparisons are usually, but not always, similar to those of direct comparison trials[56]. Therefore, outcomes should be interpreted cautiously and economic evaluations using adjusted indirect comparisons should be checked for justification, clear descriptions of methods, whether they present characteristics of the included trials and provide details on how heterogeneity and adjustment for effect modifiers (i.e. patient characteristics, measurement of outcomes and protocol requirements) among trials is handled. At last, to our opinion, economic models need cross-over free data that are not biased by a cross over design to calculate cost-effectiveness. Treatment cross over from one to another therapy is often necessary on ethical ground, but it leaves the scientific audience with an uncertainty about whether the therapy does offer a survival advantage. We recommend authors of economic evaluations to have a critical assessment whether clinical trial data is cross-over free, and how this cross-over free data is generated. The IPCW method is recommended because it can provide important additional evidence to guide therapeutical choices[57]. Other methods could be appropriate, but should be justified.

In addition to all these methodological characteristics, deterministic and probabilistic sensitivity analysis must be included both in the evaluation and where possible all characteristics assessed in this review should be tested within these sensitivity analyses.

In this review we only included Markov models in our analysis, and therefore models based on Discrete Event Simulation (DES) were omitted. In a recent article Caro et al. have recommended that DES is the preferred option in health economics[58]. Although this was recommended, Markov models do generate reliable outcomes in the assessment of the costs-effectiveness of the adjuvant treatment of breast cancer, and do not need huge amounts of individual data. Therefore Markov models are well suited and a valid option

for economic evaluations of adjuvant breast cancer therapies.

These conclusions confirm, specify and extend the conclusions made by Annemans previously. By suggesting the use of a standardized format, future pharmacoeconomic evaluations of breast cancer therapies will be more consistent and only depend on country related differences. Therefore these transparent and standardized models could be used by decision-makers all over the world, which will increase the usefulness, credibility, comparability and will decrease the possible influence of study sponsorship of cost-effectiveness outcomes.

Acknowledgements

The authors wish to thank Prof. Dr. Lieven Annemans from the I-CHER Interuniversity Centre for Health Economics Research, UGent and VUB, Ghent, Belgium, for providing his comments on the final table of recommendations.

References

(1) *Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin **2005**; 55(2):74-108.*

(2) *Kataja V, Castiglione M. Primary breast cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol **2009**; 20 Suppl 4:10-14.*

(3) *Dedes KJ, Matter-Walstra K, Schwenkglenks M, Pestalozzi BC, Fink D, Brauchli P et al. Bevacizumab in combination with paclitaxel for HER-2 negative metastatic breast cancer: an economic evaluation. Eur J Cancer **2009**; 45(8):1397-1406.*

(4) *Le QA, Hay JW. Cost-effectiveness analysis of lapatinib in HER-2-positive advanced breast cancer. Cancer **2009**; 115(3):489-498*

(5) *Eichler HG, Kong SX, Gerth WC, Mavros P, Jonsson B. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? Value Health **2004**; 7(5):518-528.*

(6) *Hjelmgren J, Berggren F, Andersson F. Health economic guidelines--similarities, differences and some implications. Value Health **2001**; 4(3):225-250.*

(7) *Karnon J. Aromatase inhibitors in breast cancer: a review of cost considerations and cost effectiveness. Pharmacoeconomics **2006**; 24(3):215-232.*

(8) *Younis T, Rayson D, Dewar R, Skedgel C. Modeling for cost-effective-adjuvant aromatase inhibitor strategies for postmenopausal women with breast cancer. Ann Oncol **2007**; 18(2):293-298.*

(9) *Annemans L. Methodological issues in evaluating cost effectiveness of adjuvant aromatase inhibitors in early breast cancer: a need for improved modelling to aid decision making. Pharmacoeconomics **2008**; 26(5):409-423.*

(10) *Tamoxifen for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet **1998**; 351(9114):1451-1467.*

(11) *Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for the economic evaluation of health care programmes. 2nd ed. **1997**. New York:*

Oxford University Press.

(12) *http://global-rates.com/economic-indicators/inflation/inflation.aspx.*

(13) *http://stats.oecd.org/Index.aspx?datasetcode=SNA_TABLE4.*

(14) *Locker GY, Mansel R, Cella D, Dobrez D, Sorensen S, Gandhi SK. Cost-effectiveness analysis of anastrozole versus tamoxifen as primary adjuvant therapy for postmenopausal women with early breast cancer: a US healthcare system perspective. The 5-year completed treatment analysis of the ATAC ('Arimidex', Tamoxifen Alone or in Combination) trial. Breast Cancer Res Treat* ***2007****; 106(2):229-238.*

(15) *Mansel R, Locker G, Fallowfield L, Benedict A, Jones D. Cost-effectiveness analysis of anastrozole vs tamoxifen in adjuvant therapy for early stage breast cancer in the United Kingdom: the 5-year completed treatment analysis of the ATAC ('Arimidex', Tamoxifen alone or in combination) trial. Br J Cancer* ***2007****; 97(2):152-161.*

(16) *Rocchi A, Verma S. Anastrozole is cost-effective vs tamoxifen as initial adjuvant therapy in early breast cancer: Canadian perspectives on the ATAC completed-treatment analysis. Support Care Cancer* ***2006****; 14(9):917-927.*

(17) *Delea TE, El Ouagari K, Karnon J, Sofrygin O. Cost-effectiveness of letrozole versus tamoxifen as initial adjuvant therapy in postmenopausal women with hormone-receptor positive early breast cancer from a Canadian perspective. Breast Cancer Res Treat* ***2008****; 108(3):375-387.*

(18) *Delea TE, Karnon J, Sofrygin O, Thomas SK, Papo NL, Barghout V. Cost-effectiveness of letrozole versus tamoxifen as initial adjuvant therapy in hormone receptor-positive postmenopausal women with early-stage breast cancer. Clin Breast Cancer* ***2007****; 7(8):608-618.*

(19) *Coates AS, Keshaviah A, Thurlimann B, Mouridsen H, Mauriac L, Forbes JF et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. J Clin Oncol* ***2007****; 25(5):486-492.*

(20) *Wheler J, Johnson M, Seidman A. Adjuvant therapy with aromatase inhibitors for postmenopausal women with early breast cancer: evidence and ongoing controversy. Semin Oncol* ***2006****; 33(6):672-680.*

(21) *Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. Int J Technol Assess Health Care* ***2005****; 21(2):240-245.*

(22) *van der Roer N, Goossens ME, Evers SM, van Tulder MW. What is the most cost-effective treatment for patients with low back pain? A systematic review. Best Pract Res Clin Rheumatol* ***2005****; 19(4):671-684.*

(23) *Soto J. Health economic evaluations using decision analytic modeling. Principles and practices--utilization of a checklist to their development and appraisal. Int J Technol Assess Health Care* ***2002****; 18(1):94-111.*

(24) *Baum M, Buzdar A, Cuzick J, Forbes J, Houghton J, Howell A et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. Cancer* ***2003****; 98(9):1802-1810.*

(25) *Coombes RC, Kilburn LS, Snowdon CF, Paridaens R, Coleman RE, Jones SE et al. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet* ***2007****; 369(9561):559-570.*

(26) *Thurlimann B, Keshaviah A, Coates AS, Mouridsen H, Mauriac L, Forbes JF et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med* ***2005****; 353(26):2747-2757.*

(27) *Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med* ***2003****; 349(19):1793-1802.*

(28) *Fonseca M, Araujo GT, Saad ED. Cost-effectiveness of anastrozole, in comparison with tamoxifen, in the adjuvant treatment of early breast cancer in Brazil. Rev Assoc Med Bras* ***2009****; 55(4):410-415.*

(29) *Gil JM, Rubio-Terres C, Del Castillo A, Gonzalez P, Canorea F. Pharmacoeconomic analysis of adjuvant therapy with exemestane, anastrozole, letrozole or tamoxifen in postmenopausal women with operable and estrogen receptor-positive breast cancer. Clin Transl Oncol **2006**; 8(5):339-348.*

(30) *Hillner BE. Benefit and projected cost-effectiveness of anastrozole versus tamoxifen as initial adjuvant therapy for patients with early-stage estrogen receptor-positive breast cancer. Cancer **2004**; 101(6):1311-1322.*

(31) *Karnon J, Delea T, Barghout V. Cost utility analysis of early adjuvant letrozole or anastrozole versus tamoxifen in postmenopausal women with early invasive breast cancer: the UK perspective. Eur J Health Econ **2008**; 9(2):171-183.*

(32) *Moeremans K, Annemans L. Cost-effectiveness of anastrozole compared to tamoxifen in hormone receptor-positive early breast cancer. Analysis based on the ATAC trial. Int J Gynecol Cancer **2006**; 16 Suppl 2:576-578.*

(33) *Skedgel C, Rayson D, Dewar R, Younis T. Cost-utility of adjuvant hormone therapies with aromatase inhibitors in post-menopausal women with breast cancer: upfront anastrozole, sequential tamoxifen-exemestane and extended tamoxifen-letrozole. Breast **2007**; 16(3):252-261.*

(34) *Skedgel C, Rayson D, Dewar R, Younis T. Cost-utility of adjuvant hormone therapies for breast cancer in post-menopausal women: sequential tamoxifen-exemestane and upfront anastrozole. Breast Cancer Res Treat **2007**; 101(3):325-333.*

(35) *Lux MP, Wockel A, Benedict A, Buchholz S, Kreif N, Harbeck N et al. Cost-effectiveness analysis of anastrozole versus tamoxifen in adjuvant therapy for early-stage breast cancer - a health-economic analysis based on the 100-month analysis of the ATAC trial and the German health system. Onkologie **2010**; 33(4):155-166.*

(36) *Lundkvist J, Wilking N, Holmberg S, Jonsson L. Cost-effectiveness of exemestane versus tamoxifen as adjuvant therapy for early-stage breast cancer after 2-3 years treatment with tamoxifen in Sweden. Breast Cancer Res Treat **2007**; 102(3):289-299.*

(37) *Risebrough NA, Verma S, Trudeau M, Mittmann N. Cost-effectiveness of switching to exemestane versus continued tamoxifen as adjuvant therapy for postmenopausal women with primary breast cancer. Cancer **2007**; 110(3):499-508.*

(38) *Thompson D, Taylor DC, Montoya EL, Winer EP, Jones SE, Weinstein MC. Cost-effectiveness of switching to exemestane after 2 to 3 years of therapy with tamoxifen in postmenopausal women with early-stage breast cancer. Value Health **2007**; 10(5):367-376.*

(39) *Braun S, Mittendorf T, Menschik T, Greiner W, der Schulenburg JM. Cost Effectiveness of Exemestane versus Tamoxifen in Post-Menopausal Women with Early Breast Cancer in Germany. Breast Care (Basel) **2009**; 4(6):389-396.*

(40) *Delea TE, Karnon J, Smith RE, Johnston SR, Brandman J, Sung JC et al. Cost-effectiveness of extended adjuvant letrozole therapy after 5 years of adjuvant tamoxifen therapy in postmenopausal women with early-stage breast cancer. Am J Manag Care **2006**; 12(7):374-386.*

(41) *El Ouagari K, Karnon J, Delea T, Talbot W, Brandman J. Cost-effectiveness of letrozole in the extended adjuvant treatment of women with early breast cancer. Breast Cancer Res Treat **2007**; 101(1):37-49.*

(42) *Karnon J, Delea T, Johnston SR, Smith R, Brandman J, Sung J et al. Cost effectiveness of extended adjuvant letrozole in postmenopausal women after adjuvant tamoxifen therapy: the UK perspective. Pharmacoeconomics **2006**; 24(3):237-250.*

(43) *Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet **2005**; 365(9453):60-62.*

(44) *Chen RC, Lin NU, Golshan M, Harris JR, Bellon JR. Internal mammary nodes in breast cancer: diagnosis and implications for patient management -- a systematic review. J Clin Oncol **2008**; 26(30):4981-4989.*

(45) *Fisher B, Jeong JH, Bryant J, Anderson S, Dignam J, Fisher ER et al. Treatment of lymph-node-negative, oestrogen-receptor-positive breast cancer: long-term findings from National Surgical Adjuvant Breast and Bowel Project randomised clinical trials. Lancet* ***2004****; 364(9437):858-868.*

(46) *Forbes JF, Cuzick J, Buzdar A, Howell A, Tobias JS, Baum M. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol* ***2008****; 9(1):45-53.*

(47) *Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ et al. Efficacy of letrozole extended adjuvant therapy according to estrogen receptor and progesterone receptor status of the primary tumor: National Cancer Institute of Canada Clinical Trials Group MA.17. J Clin Oncol* ***2007****; 25(15):2006-2011.*

(48) *Lonning PE. Comparing cost/utility of giving an aromatase inhibitor as monotherapy for 5 years versus sequential administration following 2-3 or 5 years of tamoxifen as adjuvant treatment for postmenopausal breast cancer. Ann Oncol* ***2006****; 17(2):217-225.*

(49) *BIG 1-98 Collaborative Group. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. New England Journal of Medicine* ***2011****; 361:766-776, 2009.*

(50) *Saphner T, Tormey DC, Gray R. Annual hazard rates of recurrence for breast cancer after primary therapy. J Clin Oncol* ***1996****; 14(10):2738-2746.*

(51) *Jang S, Chae YK, Haddad T, Majhail NS. Conflict of interest in economic analyses of aromatase inhibitors in breast cancer: a systematic review. Breast Cancer Res Treat* ***2010****; 121(2):273-279.*

(52) *Drummond M, Barbieri M, Cook J, Glick HA, Lis J, Malik F et al. Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report. Value Health* ***2009****; 12(4):409-418.*

(53) *Boulenger S, Nixon J, Drummond M, Ulmann P, Rice S, de Pouvourville G. Can economic evaluations be made more transferable? Eur J Health Econ* ***2005****; 6(4):334-346.*

(54) *Welte R, Feenstra T, Jager H, Leidl R. A decision chart for assessing and improving the transferability of economic evaluation results between countries. Pharmacoeconomics* ***2004****; 22(13):857-876.*

(55) *Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. Pharmacoeconomics* ***2006****; 24(4):355-371.*

(56) *Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMJ* ***2003;*** *326(7387):472.*

(57) *Robins JM, Finkelstein DM. Correcting for noncompliance and dependent censoring in an AIDS Clinical Trial with inverse probability of censoring weighted (IPCW) log-rank tests. Biometrics* ***2000****; 56(3):779-788.*

(58) *Caro JJ, Moller J, Getsios D. Discrete event simulation: the preferred technique for health economic evaluations? Value Health* ***2010****; 13(8):1056-1060.*

2

Chapter 2.2

The cloudy crystal ball of cost-effectiveness studies

Gerardus W.J. Frederix
Johan L. Severens
Anke M. Hövels
Jan A.M. Raaijmakers
Jan H.M. Schellens

Submitted for publication

Worldwide, healthcare costs are swiftly increasing and difficult to control. Of the various factors affecting the increase, i.e. technological advances, aging of the population and drug costs, drug expenditure appears to be the most tangible and therefore a logical target for cost containment. To ensure that healthcare professionals deliver care of the best possible quality and of the best value for money, a large number of health policy decision bodies over the world have incorporated cost-effectiveness evaluations in their drug reimbursement decision process, after witnessing a positive benefit-risk and added therapeutic value. In these evaluations, long-term effectiveness is predicted by mathematical modelling employing available short-term clinical efficacy data[1], for example of the HERA, FinHer (Trastuzumab) and ATAC (Anastrazole) trials. Because the outcome of cost-effectiveness studies can affect the availability of life-saving drugs to patients, it is essential that the methods for these evaluations are valid and the results robust. It is alarming, however, that this is often not guaranteed, as demonstrated by the case of the ATAC trial.

Results of the ATAC trial (Anastrazole, Tamoxifen, Alone or in Combination for the adjuvant treatment of postmenopausal women with localised hormone receptor-positive breast cancer) revealed a significant improvement in disease-free survival of anastrazole compared with tamoxifen[2]. Data from this large trial have since formed the basis for a considerable number of cost-effectiveness evaluations in various jurisdictions.

Trial efficacy data are used to populate mathematical models that aim to determine value for money. Value for money, as main outcome of cost-effectiveness evaluations, is expressed as the Incremental Cost Effectiveness Ratio (ICER). The ICER is the ratio of the difference in total costs of two interventions (incremental costs) and the difference in effects, where effects are commonly expressed as Life Year (LY) gained or Quality Adjusted Life Year (QALY) gained. ICERs are often used to determine whether a new intervention is considered cost-effective by comparing the ICER with a cost-effectiveness threshold that has been defined within a jurisdiction. A well-known threshold is the one implemented in the United Kingdom by the National Institute for Health and Clinical Excellence (NICE). Their formal threshold has been set at £30,000 pounds (~$47,000) per QALY gained, meaning that therapies having ICERs above this threshold are not considered to be cost-effective, and therefore are often not reimbursed by the National Health Service (NHS).

After the ATAC trial publication in 2002, eleven cost-effectiveness evaluations were published using clinical efficacy outcomes of the trial as primary input to the cost-effectiveness models. Analyses were performed in Belgium, the United Kingdom, Brazil, Germany, the United States, Canada and Spain. Using the same comparator and the same efficacy data, the eleven economic evaluations reported a wide variation in ICERs for anastrazole ranging from $4,868 per LY gained in Belgium to $92,657 per LY gained in

Spain, and from $4,546 per QALY gained to $147,926 per QALY gained in Belgium and Spain, respectively. In addition to the ICERs that were found to vary dramatically between countries, the reported QALYs gained also varied considerably (from 0·092 to 0·378) and, more remarkably, the incremental LY gained vary substantially, from 0·16 to 0·550[3].

It is well known that cost-effectiveness evaluations performed in different countries are subject to variation caused by country-specific populations, health care system characteristics, and country specific values for prizes and health related quality of life, so-called transferability factors[4]. In a recent review, a clear overview was given of the long list of factors affecting the transferability of cost-effectiveness evaluations between countries[5]. In our case, the differences found in the incremental costs of both therapies between countries could be ascribed to several of these transferability factors. For instance, differences in drug costs of anastrazole and tamoxifen, the costing factor with the highest impact on incremental costs, varied from $2.88 in Belgium to $5.94 per patient per day in Spain, thereby resulting in minimally a twofold difference in incremental costs. Furthermore, the differences in QALY estimates could be caused by differences in patient preferences for specific health-related outcomes (utilities) between countries. The strength for these preferences is measured on a scale, with zero reflecting death and one perfect health. For example, local recurrence, an essential health related outcome, was valued with a utility of 0.911 in the United Kingdom and 0.816 in Canada. Consequently, the ICERs reflecting costs per QALY can vary between countries.

In contrast, the estimated differences in LY gained, which are derived from the same efficacy data of the ATAC trial, are less simply explained by transferability characteristics, especially in situations where cost-effectiveness evaluations are performed in the same country and differences in transferability factors cannot play a role. Therefore, other explanations for differences between these evaluations must be present.

In a recent analysis we demonstrated that differences in modelling methods related to extrapolation of the original ATAC-data over time are the main cause of variability in outcome[3]. Investigator's own choices of time horizon, hazard rate for recurrence, incidence of recurrence and inclusion of a carry-over effect (i.e. an effect of treatment that persists after treatment was stopped) were the main cause for the wide variation in cost-effectiveness outcomes. Time horizon, the time-period over which costs and effects are taken into account, varied between studies from 10 years to lifetime, in the studies discussed here. In hormone receptor-positive breast cancer, relapse after ten years can develop in a relevant subset of patients, clearly indicating that a time horizon of 10 years is too short. Choice of hazard rate for recurrence varied between the use of the disease-free (primary ATAC trial endpoint) and recurrence-free (secondary endpoint) hazard ratio.

Important differences in the rate of recurrence were also applied, varying from constant and time-dependent rates to even Weibull functions. Finally, although a carry-over effect for anastrazole of approximately 5 years was confirmed in several clinical trials, some authors included no carry-over effect, a carry-over effect lasting for 5 years, or even a lifetime carry-over effect for anastrazole compared to tamoxifen. Sensitivity analyses in a Canadian study demonstrated that inclusion of the carry-over effect lasting for 5 years lead to a 46% reduction in cost per LY gained (i.e. $38,588 to $20,805), demonstrating the necessity of including a carry-over effect, if well established.

Author	Country	Life Years gained	QALYs gained	Incremental costs ($)	Cost per LY gained ($)	Cost per QALY gained ($)
Moeremans et al[6]	Belgium	0.353	0.378	1,718	4,868	4,546
Karnon et al[7] †	UK	0.350	0.360	3,793	10,836	10,536
Fonseca et al[8]	Brazil	0.550	NA	12,213	22,042	NA
Karnon et al[7] ‡	UK	0.250	0.260	4,348	17,374	16,965
Locker et al[9]	US	0.221	0.257	5,173	17,392	20,096
Rocchi and Verma[10] §	Canada	0.194	0.218	4,536	23,404	20,805
Skedgel et al[11]	Belgium	NA	0.231	5,306	NA	22,967
Skedgel et al[12] ‖	Canada	NA	0.227	5,055	NA	22,259
Rocchi and Verma[10] ¶	Canada	0.192	0.208	4,670	24,286	22,465
Lux et al[13]	Germany	0.290	0.320	7,753	26,730	23,952
Mansel et al[14]	UK	0.230	0.244	6,605	28,626	27,024
Skedgel et al[12] #	Canada	NA	0.092	4,970	NA	54,006
Hillner et al[15]	US	0.160	0.123	6,649	40,298	75,338
Gil et al[16] **	Spain	0.535	0.285	25,261	47,216	88,634
Gil et al[16] ††	Spain	0.182	0.114	16,863	92,657	147,926

**Karnon et al, Rocchi and Verma, Skedgel et al. and Gil et al. presented each two base case analyses with different modelling methods in their study. Therefore, each separate analysis was included in this table.*

† Carry-over effect of 5 years
‡ No carry-over effect
§ 3 year interim analysis
 # 10 year time horizon
‖ 20 year time horizon
¶ 5 year interim analysis
*** 20 year time horizon*
†† 10 year time horizon
NA = not analyzed

Although nowadays economic evaluations are extensively used to guide decision making about drug reimbursement and therefore drug availability to the community, our observations demonstrate that important challenges still exist in this area. Reported differences in ICERs and LY gained of the individual cost-effectiveness evaluations are largely determined by the modelling methods used by individual investigators, rather than by hard clinical efficacy data or well-defined and transparent transferability factors. Robustness and validity of the cost-effectiveness estimates, therefore, can seriously come into question, potentially undermining the added value of such evidence in

the decision making process. The widely divergent outcomes of the eleven cost-effectiveness evaluations based on one and the same ATAC-trial demonstrates the need for standardization and better guidance for disease-specific modelling in economic evaluations. This guidance is ideally provided through collaboration of international stakeholders, i.e. health economists, policy makers and physicians. Wide acceptance and implementation of crystal clear guidance should improve the standardisation of the methods and the robustness of the results of future cost-effectiveness evaluations.

References

(1) *Buxton MJ, Drummond MF, Van Hout BA, Prince RL, Sheldon TA, Szucs T et al. Modelling in economic evaluation: an unavoidable fact of life. Health Econ **1997**; 6(3):217-227.*

(2) *Baum M, Budzar AU, Cuzick J, Forbes J, Houghton JH, Klijn JG et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet **2002**; 359(9324):2131-2139.*

(3) *Frederix GW, Severens JL, Hovels AM, Raaijmakers JA, Schellens JH. Reviewing the cost-effectiveness of endocrine early breast cancer therapies: influence of differences in modeling methods on outcomes. Value Health **2012**; 15(1):94-105.*

(4) *Drummond M, Barbieri M, Cook J, Glick HA, Lis J, Malik F et al. Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report. Value Health **2009**; 12(4):409-418.*

(5) *Goeree R, He J, O'Reilly D, Tarride JE, Xie F, Lim M et al. Transferability of health technology assessments and economic evaluations: a systematic review of approaches for assessment and application. Clinicoecon Outcomes Res **2011**; 3:89-104.*

(6) *Moeremans K, Annemans L. Cost-effectiveness of anastrozole compared to tamoxifen in hormone receptor-positive early breast cancer. Analysis based on the ATAC trial. Int J Gynecol Cancer **2006**; 16 Suppl 2:576-578.*

(7) *Karnon J, Delea T, Barghout V. Cost utility analysis of early adjuvant letrozole or anastrozole versus tamoxifen in postmenopausal women with early invasive breast cancer: the UK perspective. Eur J Health Econ **2008**; 9(2):171-183.*

(8) *Fonseca M, Araujo GT, Saad ED. Cost-effectiveness of anastrozole, in comparison with tamoxifen, in the adjuvant treatment of early breast cancer in Brazil. Rev Assoc Med Bras **2009**; 55(4):410-415.*

(9) *Locker GY, Mansel R, Cella D, Dobrez D, Sorensen S, Gandhi SK. Cost-effectiveness analysis of anastrozole versus tamoxifen as primary adjuvant therapy for postmenopausal women with early breast cancer: a US healthcare system perspective. The 5-year completed treatment analysis of the ATAC ('Arimidex', Tamoxifen Alone or in Combination) trial. Breast Cancer Res Treat **2007**; 106(2):229-238.*

(10) *Rocchi A, Verma S. Anastrozole is cost-effective vs tamoxifen as initial adjuvant therapy in early breast cancer: Canadian perspectives on the ATAC completed-treatment analysis. Support Care Cancer **2006**; 14(9):917-927.*

(11) *Skedgel C, Rayson D, Dewar R, Younis T. Cost-utility of adjuvant hormone therapies with aromatase inhibitors in post-menopausal women with breast cancer: upfront anastrozole, sequential tamoxifen-exemestane and extended tamoxifen-letrozole. Breast **2007**; 16(3):252-261.*

(12) *Skedgel C, Rayson D, Dewar R, Younis T. Cost-utility of adjuvant hormone therapies for breast cancer in post-menopausal women: sequential tamoxifen-exemestane and upfront anastrozole. Breast Cancer Res Treat* ***2007****; 101(3):325-333.*

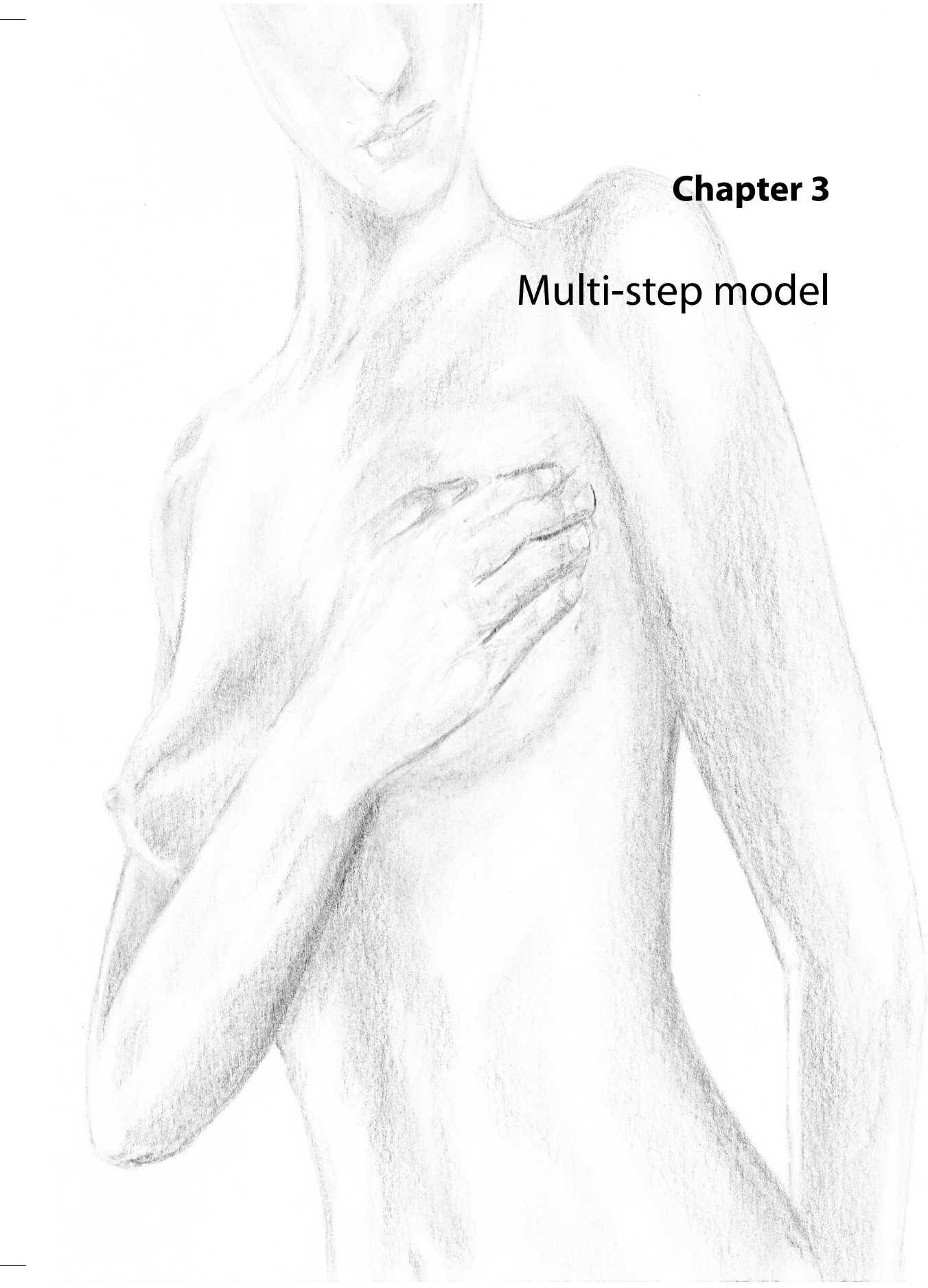
(13) *Lux MP, Wockel A, Benedict A, Buchholz S, Kreif N, Harbeck N et al. Cost-effectiveness analysis of anastrozole versus tamoxifen in adjuvant therapy for early-stage breast cancer - a health-economic analysis based on the 100-month analysis of the ATAC trial and the German health system. Onkologie* ***2010****; 33(4):155-166.*

(14) *Mansel R, Locker G, Fallowfield L, Benedict A, Jones D. Cost-effectiveness analysis of anastrozole vs tamoxifen in adjuvant therapy for early stage breast cancer in the United Kingdom: the 5-year completed treatment analysis of the ATAC ('Arimidex', Tamoxifen alone or in combination) trial. Br J Cancer* ***2007****; 97(2):152-161.*

(15) *Hillner BE. Benefit and projected cost-effectiveness of anastrozole versus tamoxifen as initial adjuvant therapy for patients with early-stage estrogen receptor-positive breast cancer. Cancer* ***2004****; 101(6):1311-1322.*

(16) *Gil JM, Rubio-Terres C, Del Castillo A, Gonzalez P, Canorea F. Pharmacoeconomic analysis of adjuvant therapy with exemestane, anastrozole, letrozole or tamoxifen in postmenopausal women with operable and estrogen receptor-positive breast cancer. Clin Transl Oncol* ***2006****; 8(5):339-348.*

2



Chapter 3

Multi-step model

Chapter 3

Development of a framework for cohort simulation in cost-effectiveness analyses using a multi-step ordinary differential equation solver algorithm in R

Gerardus W.J. Frederix[§]
Johan G.C. van Hasselt[§]
Johan L. Severens
Anke M. Hövels
Alwin D.R. Huitema
Jan A.M. Raaijmakers
Jan H.M. Schellens

[§]*Authors contributed equally to this manuscript*

Medical Decision Making. 2013 March; Epub ahead of print

Abstract

Introduction

Dynamic processes in cost-effectiveness analysis (CEA) are typically described using cohort simulations, which can be implemented as Markov models, or alternatively using systems of ordinary differential equations (ODEs). In the field of CEA, simple and potentially inaccurate single-step algorithms are commonly used for solving ODEs, which can potentially induce bias, especially if an incorrect step size is used. The aims of this project were i) to implement and demonstrate the use of a modern and well established hybrid linear multi-step ODE solver algorithm (LSODA) in the context of CEA using the statistical scripting language R, and ii) to quantify bias in outcome for a case example CEA as generated by a commonly used single-step ODE solver algorithm.

Methods

A previously published CEA comparing the adjuvant breast cancer therapies anastrazole and tamoxifen was used as a case example to implement the computational framework. A commonly used single-step algorithm was compared to the proposed multi-step algorithm, to quantify bias in the single-step method.

Results

A framework implementing the multi-step ODE solver LSODA was successfully developed. When using a single step ODE solver with step size of 1 year, incremental life-years gained was under-estimated by 0.016 years (5.6 % relative error, RE) and 158 GBP (6.8% RE), compared to the multi-step method.

Conclusion

The framework was found suitable for the conduct of CEAs. We demonstrated how the impact of the use of single step algorithms with insufficiently small step sizes causes unnecessary bias in outcomes measures of CEAs. Scripting languages such as R can further improve transparency, reproducibility and overall integrity in the field of health economics.

Introduction

Therapeutic benefit is the most important consideration for reimbursement of new drugs, although decisions to fund and use health care technologies are also increasingly informed by cost-effectiveness analysis (CEA). The purpose of economic evaluations is to aid decision makers in choosing between competing therapies within the constraint of resources[1]. This goal is achieved through measurement of the expected marginal costs and effects, associated with the displacement of a health technology by a new one[2]. A commonly used outcome measure of such analysis is the incremental cost-effectiveness ratio (ICER), which describes the cost of one additional unit of effect, such as life years (LY), or quality-adjusted life years (QALY)[3]. To make a decision regarding reimbursement of the new drug, the ICER for each therapy is compared to a threshold value which relates to the willingness to pay for one additional LY or QALY gained[4].

Dynamic models in cost-effectiveness analysis

Dynamic processes in cost-effectiveness models are frequently implemented as so-called cohort simulations[5] which describe the dynamics of patients moving between different health states. Cohort simulation models can be defined using Markov models, or alternatively using systems of ordinary differential equations (ODEs). For more complex models which are frequently used in CEA, e.g. with time-varying transition probabilities, deriving the analytical solution of a Markov model is usually not possible. In that case, Markov models are frequently approximated numerically by describing the dynamics of the system in terms of ODEs**.** However, where true Markov models account for the full stochastic nature of the process, ODE-based approaches only describe the typical (mean) change.

Single-step ODE solver methods

The numerical algorithm for solving ODEs which is used most commonly in the field of CEA is similar to the very first method proposed for numerical approximation of ODEs as described by Euler in 1768[6]. This method involves a single-step algorithm in which the dynamical change is only based on the previous state of the system, and the step size has a fixed length. This method is very easy to implement even in general purpose software as Excel, explaining their popularity in the health economics area. However, it is now well established that such single-step algorithms have poor accuracy if step size is not chosen small enough[7-9].

Another major drawback of the common use of general purpose software as Excel in the field of CEA is the lack of transparency, reproducibility and flexibility. Scripting languages like R are less user friendly but offer the possibility of full transparency by sharing the

employed scripts. By this, also results can be reproduced easily. Finally, scripts may easily be extended with more complex models, other numerical methods or probabilistic simulations.

Half-cycle corrections

One improvement to the single-step Euler method is the use of so-called half-cycle corrections[10], which are frequently applied in the field of CEA. Here, the term cycle is most commonly used in the context of Markov models, but it also used in the context of ODE-solvers, where it is equal to ODE-solver step size. By implementing a half cycle correction, it is assumed that, on average, people will transit to another state halfway through the cycle instead of at the end of each cycle, thereby decreasing bias in the outcome. Although commonly implemented and depicted as the "golden standard", some scepticism exists around the use of these corrections because this correction still causes biased results when for instance different unit costs per cycle, differing QALY weights per cycle and discounting are included[11;12].

Multi-step ODE-solver methods

Although in the field of CEA, the simple Euler-based method for numerical solving ODEs is still commonly used, substantial progress has been made in numerical methods for solving ODEs[13]. Currently used methods can be roughly subdivided into Runge-Kutta based methods[14;15], and linear multi-step (LMS) based methods. Well known LMS algorithms include the Adams algorithm[16] and the backwards differentiation formula (BDF) method[17]. The Runge-Kutta and Adams' methods are explicit methods which cannot adequately handle stiff problems, whereas the BDF-method is an implicit method which can handle stiff ODEs. Further advancements were made for instance in the development of the LSODA package[18] in which the algorithm dynamically switches between the Adams' method and the BDF method.

The aims of this project were i) to implement and demonstrate the use of a modern and well established hybrid linear multi-step ODE solver algorithm (LSODA) in the context of CEA using the statistical scripting language R, and ii) to quantify bias in outcome for a case example CEA as generated by a commonly used single-step ODE solver algorithm. The developed framework was demonstrated by implementation of a previously published case example CEA that compared adjuvant breast cancer therapies for tamoxifen and anastrazole.

Methods

Reference model

The adjuvant breast cancer model that was used as a case example was previously described by Mansel *et al*[19], who compared cost and effects of tamoxifen versus anastrazole based on the ATAC trial. We will refer to this published model, and their results reported, as the reference model.

Computational framework and ODE solver algorithms

We implemented the CEA in the scripting language R (version 2.10.0[20]). Different functional parts of the analysis such as, initial health state conditions, observation times and input parameters were implemented as separately defined subroutines, thereby simplifying the process of modification of the analysis.

Two ODE solver algorithms were included in the framework: i) a modern linear multiple-step ODE solver algorithm, and ii) the most commonly used single-step (fixed step size) algorithm, which was also used by Mansel et al[19], and we will refer to these two algorithms accordingly. The multi-step algorithm was implemented using the LSODA package[18] which is available in the R-package deSolve (version 1.10-2)[21].

The single-step fixed step size algorithm was implemented in the framework in order to assess the impact of different step sizes (e.g. cycle lengths) on bias in outcome measures. The transition rates used in the multi-step algorithm were scaled to different fixed step sizes that were considered.

Implementation of the reference model

The structure of the reference model as described by Mansel *et al*[19] is schematically depicted in **figure 1**. The following health states were present in the reference model: on treatment (On), switch treatment (ST), off treatment (Off), which are all three no relapse states, local recurrence (Loc), metastatic disease (Met), death due to breast cancer (DtCa), and death due to other causes (DtO). In the reference model, the cohort of patients enters the model in the 'on treatment' health state. After 5 years of treatment all women present in the on treatment health state go to the off treatment health state. All transitions were described using the transition rates provided in **table 1**, which originate from the reference model unless stated otherwise. Some input parameters and model assumptions were not available, or not clearly stated in the original publication. Below, we therefore further describe our implementation and necessary assumptions used during implementation of the reference model. It should be noted that any differences due to the lack of reproducibility of the analysis by Mansel et al, do not interfere with the

objectives of the current analysis.

Switch health state

In the reference model a switch health state was included to which patients transition who have an unplanned switch of adjuvant treatment due to adverse events. Unfortunately, no transition rates for entering or leaving this health state or the associated transition rates and costs after switching were stated in the reference model.

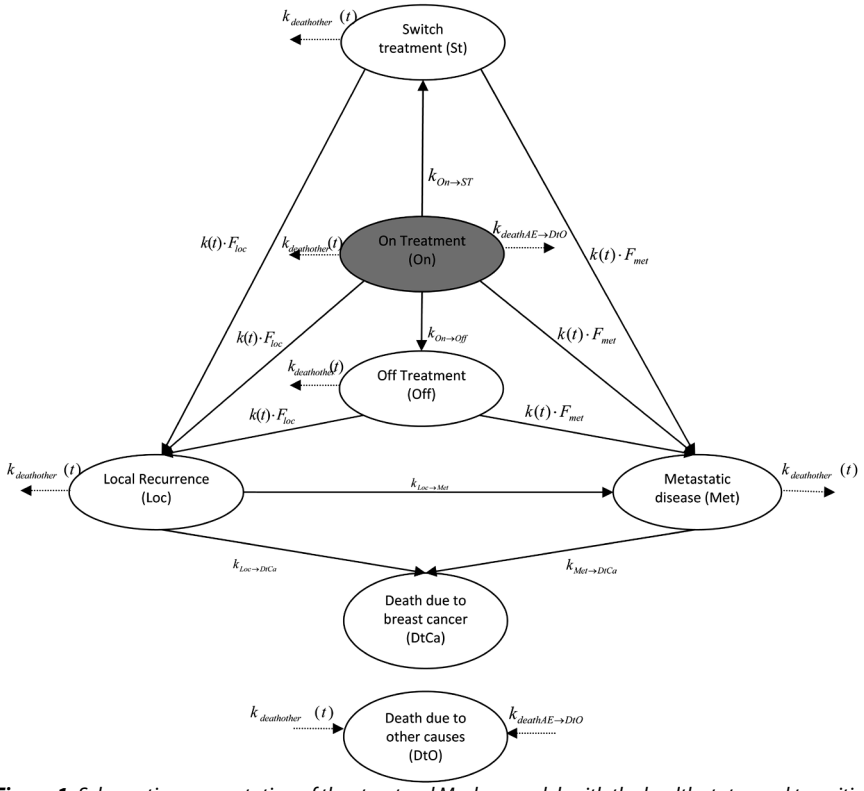


Figure 1. *Schematic representation of the structural Markov model, with the health states and transition rates depicted*

In the current analysis, the 5 year switch rate from the ATAC trial was used for patients to enter this state[22]. After entering this health state, patients were assumed to have a similar recurrence transition rate as patients present in the on treatment health state of the comparative treatment (**Table 1**). In addition to the transition rates, we also assigned costs of the comparative treatment to this health state. In agreement with the implementation by the reference model, patients in this health state could not experience any adverse event.

Adverse events

The reference model assumed summarized transition rates of adverse events into Life-Threatening (LT) and Non Life-Threatening (NLT) adverse events (**Table 2**). However, the origin of these composed transition rates was unclear and units were not clearly stated. Individual adverse event transition rates were not stated, although adverse event related costs were reported based on costs of individual adverse events. Therefore, in the current analysis, individual adverse event rates were determined based on the total number of LT and NLT adverse event, respectively. The fractional incidence for each of the fourteen adverse event was calculated based on the observed frequency[22] of the individual adverse event, divided by the sum of all observed frequencies of LT or NLT adverse events. All calculated individual fractions are presented in **table 2**.

Table 1. *Model input parameters as obtained from the reference model[19] unless undicated otherwise*

Description	Name	Value		Unit[a]
		Anastrazole	*Tamoxifen*	
Weibull function for incidence of recurrence on treatment (year 1-10)				
Intercept	I_1	9.17	9.42	
Scale parameter	S_1	0.83		
Weibull function for incidence of recurrence pooled across treatment arms (year 10-lifetime)				
Intercept	I_2	9.29		
Scale parameter	S_2	0.83		
Distant recurrences as a proportion of all recurrences during recurrence benefit				
Metastatic disease	F_{Met}	0.66	0.60	
Local recurrence	F_{Loc}	0.34	0.40	
Switch rate	$k_{On->ST}$	0.0222†	0.0286†	$year^{-1}$
Adverse events				
Life-threatening	k_{Life}	0.0094†	0.0132†	$year^{-1}$
Non life-threatening	$k_{nonLife}$	0.1396†	0.1314†	$year^{-1}$
Following local/regional recurrence				
Distant metastases-free at 5 years	$k_{Loc->Met}$	0.104†		$year^{-1}$
Distant metastases-free after 5 years	$k_{Loc->Met}$	0.077‡		$year^{-1}$
Death due to breast cancer	$k_{Loc->DtCa}$	0.222		$year^{-1}$
Following distant recurrence				
Overall survival at 2 years	$k_{Met->DtCa}$	0.250		$year^{-1}$
Mortality				
Background mortality	$k_{deathother}(t)$	[23§]		$year^{-1}$
Hip fractures	$k_{deathhip}$	0.040[24]		$year^{-1}$
Endometrial cancer	$k_{deathendo}$	0.035[24]		$year^{-1}$
Thromboembolic events	$k_{deaththrombo}$	0.200[24]		$year^{-1}$

*Values in reference model were originally reported in different units: * 2 $years^{-1}$, † 5 $year^{-1}$,‡10 $years^{-1}$.*

Death due to other causes

Mortality not related to breast cancer was divided into death due to adverse events and background mortality. The used mortality statistics for potentially fatal adverse events were not clearly reported in the reference model. Therefore, mortality statistics for potentially fatal adverse events as stated in two other CEAs were used[23;24]. The population at risk was defined as the population on treatment experiencing the LT adverse events.

For background mortality ($K_{deathother}(t)$), which includes time varying variables with values changing in five year[23] it was assumed that all patients alive independent of the health state were at risk.

Development of local recurrence or metastatic disease

In the reference model the transition rate to recurrence was defined using Weibull functions. Because of the inclusion of a carry over effect of 5 years, separate Weibull functions were used for both treatments during years 1-10 (I_1 and S_1). After 10 years a similar Weibull function was used for both treatments (I_2 and S_2). Associated intercept (I) and scale (S) parameters are stated in **table 2**. The associated hazard function was as follows (Eq. 1).

$$k(t) = \begin{cases} t < 10 \quad \exp(-\frac{S_1}{I_1}) \cdot \frac{1}{I_1} \cdot t^{\frac{1}{I_1}-1} \\ t \geq 10 \quad \exp(-\frac{S_2}{I_2}) \cdot \frac{1}{I_2} \cdot t^{\frac{1}{I_2}-1} \end{cases} \quad (1)$$

However, progressive disease can either be local recurrence or development of metastatic disease. Therefore, the transition rates were calculated using the fraction of patients who develop local recurrence (F_{Loc}) or metastatic disease (F_{Met}). These transition rates were then defined by (Eq. 2-3).

$$k_{loc}(t) = k(t) \cdot F_{loc} \quad (2)$$

$$k_{met}(t) = k(t) \cdot F_{met} \quad (3)$$

Local recurrence to metastatic disease and death due to breast cancer

Transition rates for local recurrence to metastatic disease and from both local recurrence and metastatic disease to death due to breast cancer were assumed to be both constant transition rates (**Table 2**)**.**

Other assumptions

In agreement with the reference model 5% of patients received biphosponates during anastrazole treatment and hysterectomy transition rates were 5.1% with tamoxifen and 1.3% with anastrazole. These percentages were obtained from expert opinion as stated in the reference model.

Table 2. *Fractional incidence of life-threatening and non-life-threatening adverse events for anastrazole and tamoxifen*

Description	Parameter	Fractional incidence	
Life threatening		*Anastrazole*	*Tamoxifen*
Endometrial cancer	F_{endo}	0.028	0.067
Hip fracture	F_{hip}	0.209	0.123
Thromboembolic events	$F_{thrombo}$	0.763	0.849
Non life-threatening			
Hot flushes	$F_{hotflus}$	0.254	0.271
Nausea and vomiting	F_{nausea}	0.090	0.082
Fatigue	$F_{fatigue}$	0.132	0.117
Mood disturbances	$F_{mooddis}$	0.137	0.119
Arthralgia (musculoskeletal dis)	$F_{musculo}$	0.253	0.195
Vaginal bleeding	$F_{vaginal}$	0.038	0.068
Vaginal discharge	$F_{dischar}$	0.025	0.087
Spine fracture	F_{spine}	0.010	0.006
Wrist fracture	F_{wrist}	0.017	0.014
Ischaemic cardiovascular	$F_{ischcero}$	0.029	0.022
Ischaemic cerebrovascular	$F_{ischcer}$	0.014	0.019

Costs

Two types of costs were present: health state related costs and event related costs. Health state related costs are dependent on the number of patients that are present in a particular health state over time. Event related costs, including adverse events, are determined by the number of patients transitioning from one health state to another, multiplied with the costs associated with the transition. Costs were presented in Great Britain Pounds (GBP) because the reference model was published from a UK perspective and UK costs were incorporated. All cost parameters are presented in **table 3** with an indication whether these are health state or event related.

Outcome measures

In agreement with the reference model, the gain in LY for anastrazole and tamoxifen, and the incremental cost per LY were the primary outcome of the analysis. Results were presented as means for costs and effects separately.

***Table 3**. Costs parameters associated that were reported for the reference model[*]*

Description	Parameter	Costs (GBP)	Event type
Drug (year^{-1})			
Anastrazole	C_{ana}	893.72	HS
Tamoxifen	C_{tam}	27.25	HS
Treatment/diagnosis			
Treatment initiation	C_{ini}	90	E
Diagnosis of recurrence	C_{diarec}	808	E
Treatment for loco/regional recurrence	$C_{loctreat}$	2606	E
Treatment for distant recurrence	$C_{mettreat}$	3563	E
Follow-up and monitoring (year^{-1})			
Local/regional recurrence	$C_{locfollow}$	572	HS
Distant recurrence	$C_{metfollow}$	796	HS
Routine follow-up (year^{-1})			
Years 1	$C_{followy1}$	280	HS
Years 1+	$C_{follow1+}$	172	HS
Follow-up off treatment due to remission	$C_{followrem}$	96	HS
Follow-up off treatment due to adverse events	$C_{followadverse}$	204	HS
Death (year^{-1})			
Death from breast cancer	$C_{deathbreast}$	3783	HS
Death from other causes	$C_{deathother}$	500	HS
Adverse event (year^{-1})			
Endometrial cancer	C_{endo}	2245	E
Hip fracture	C_{hip}	10682	E
Thromboembolic events	$C_{thrombo}$	2110	E
Hot flushes	$C_{hotflus}$	239	E
Nausea and vomiting	C_{nausea}	20	E
Fatigue	$C_{fatigue}$	20	E
Mood disturbances	$C_{mooddis}$	109	E
Arthralgia (musculoskeletal dis)	$C_{musculo}$	533	E
Vaginal bleeding	$C_{vaginal}$	1407	E
Vaginal discharge	$C_{dischar}$	240	E
Spine fracture	C_{spine}	2915	E
Wrist fracture	C_{wrist}	1463	E
Ischaemic cardiovascular	$C_{ischcero}$	3251	E
Ischaemic cerebrovascular	C_{ischer}	6299	E
Biphosphonate treatment	C_{biphos}	1432	E
Hysterectomy	C_{hyster}	1873	E

**All costs are subdivided in health state (HS) related costs or event (E) related costs*

Evaluation of the impact of step size in the single-step algorithm

For the reference model, we computed the outcome measures life years gained and incremental costs for both i) the multi-step algorithm, and ii) the single-step fixed step size algorithm. For the single-step algorithm, we used the following step sizes 1/ {1, 2, 4, 8, .., 128} years. These step sizes were chosen in order to achieve informative coverage of a range of step sizes. In addition, although the reference model did not include a half-cycle correction, we did also included half-cycle corrected values because it is seen as the "golden" standard in CEA as described by Briggs *et al*[5].

Subsequently, to determine the impact of the value of step size in the single-step fixed step size algorithm on bias in outcome measures, we determined the relative error compared to the "true" value as obtained by the multi-step approach by computation of the relative error (RE):

$$RE = \frac{(O_S - O_M)}{O_M} \cdot 100\% \qquad (4)$$

where O_S is the outcome parameter for the single-step algorithm, and O_M is the outcome parameter for the multi-step algorithm.

Results

Development of the framework for cohort simulation in R

A schematic representation of the developed framework is depicted in **figure 2**.

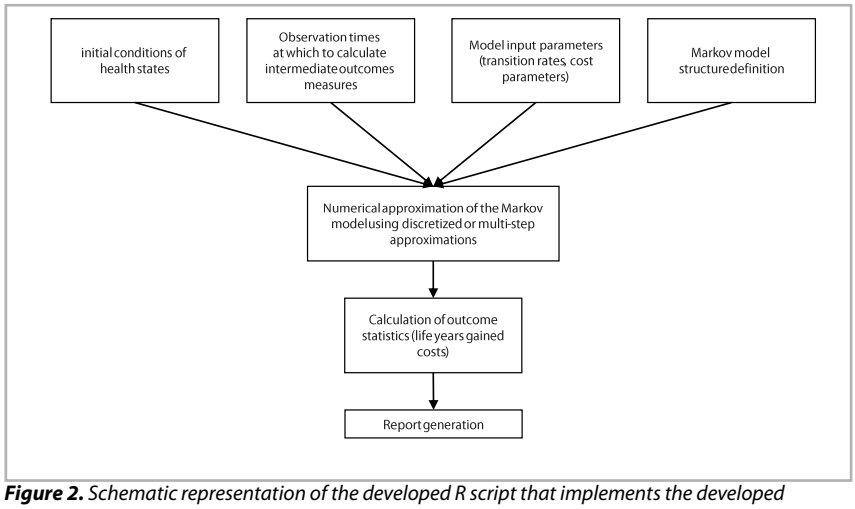


Figure 2. *Schematic representation of the developed R script that implements the developed multi-step and single-step algorithm*

Here, the initial health state condition represents the initialization vector for the system of ODEs, e.g. these are all set to 0, except for the On Treatment health state, were all patients enter the system. The observation times vector contains the time points for which the evaluation of the ODE system is requested. The dynamic model described by Mansel *et al*[19] was defined using the following system of ODEs (Eq. 5-11).

$$\frac{dOn}{dt} = -\left(k_{On \to ST} \cdot On\right) - \left(k(t) \cdot On \cdot F_{Loc}\right) - \left(k(t) \cdot On \cdot F_{Met}\right) - \left(k_{deathother}(t) \cdot On\right) - \left(k_{deathAE} \cdot On\right) \quad (5)$$

$$\frac{dST}{dt} = \left(k_{On \to ST} \cdot On\right) - \left(k(t) \cdot ST \cdot F_{Loc}\right) - \left(k(t) \cdot ST \cdot F_{Met}\right) - \left(k_{deathother}(t) \cdot ST\right) \quad (6)$$

$$\frac{dOff}{dt} = -\left(k(t) \cdot Off \cdot F_{Loc}\right) - \left(k(t) \cdot Off \cdot F_{Met}\right) - \left(k_{deathother}(t) \cdot Off\right) \quad (7)$$

$$\frac{dLoc}{dt} = \left(k(t) \cdot On \cdot F_{Loc}\right) + \left(k(t) \cdot ST \cdot F_{Loc}\right) + \left(k(t) \cdot Off \cdot F_{Loc}\right) - \left(k_{Loc \to Met} \cdot Loc\right) - \left(k_{Loc \to DtCa} \cdot Loc\right) - \left(k_{deathother}(t) \cdot Loc\right) \quad (8)$$

$$\frac{dMet}{dt} = \left(k(t) \cdot On \cdot F_{Met}\right) + \left(k(t) \cdot ST \cdot F_{Met}\right) + \left(k(t) \cdot Off \cdot F_{Met}\right) + \left(k_{Loc \to Met} \cdot Loc\right) - \left(k_{Met \to DtCa} \cdot Met\right) - \left(k_{deathother}(t) \cdot Met\right) \quad (9)$$

$$\frac{dDtCa}{dt} = \left(k_{Loc \to DtCa} \cdot Loc\right) + \left(k_{Met \to DtCa} \cdot Met\right) \quad (10)$$

$$\frac{dDtO}{dt} = \left(k_{deathother}(t) \cdot On\right) + \left(k_{deathother}(t) \cdot ST\right) + \left(k_{deathother}(t) \cdot Off\right) + \left(k_{deathother}(t) \cdot Loc\right) + \left(k_{deathother}(t) \cdot Met\right) + \left(k_{deathAE} \cdot On\right) \quad (11)$$

Differences between fixed step size single-step algorithm and the multi-step algorithm

Between both incremental outcomes, a step size of 1 year resulted in an underestimation of 0.016 absolute LY (5.6%), 0.260 LYs gained for a step size of 1 year vs. 0.276 LYs for the multi-step model **(Table 4)**. Furthermore, an underestimation of 158 GBP (6.8%) was identified, with incremental costs of respectively 2132 GBP for a step size of 1 year vs. 2290 GBP for the multi-step model. For a step size of 0.125 years or less, only small differences were observed between both models and both outcomes (**Table 4** and **Figure 3**).

As the step size is shortened, the discretized solution approaches the multi-step process solution for both incremental LYs gained and incremental costs, as expected.

Table 4. *Outcomes and costs as obtained from our discrete model with varying steps size and the multi-step model*

	Outcomes (25 year time horizon)					
Step size	**Life years gained (years)**				**Incremental life years gained (years)**	
	Anastrazole	*RE (%)*	*Tamoxifen*	*RE (%)*	*Difference*	*RE (%)*
Single-step algorithm						
1 year	10,217	-6,07	9,956	-6,09	0,261	-5,46
1 year + half cycle correction	10,511	-3,37	10,256	-3,27	0,256	-7,42
6 months	10,551	-3,00	10,283	-3,01	0,269	-2,60
6 months + half cycle correction	10,698	-1,66	10,432	-1,60	0,266	-3,63
3 months	10,716	-1,49	10,444	-1,49	0,273	-1,20
3 months + half cycle correction	10,790	-0,81	10,518	-0,79	0,271	-1,73
1.5 months	10,798	-0,73	10,524	-0,74	0,275	-0,51
1.5 months + half cycle correction	10,835	-0,40	10,561	-0,39	0,274	-0,78
Multi-step algorithm	**10,878**		**10,602**		**0,276**	
Step size	**Total costs (GBP)**				**Incremental costs (GBP)**	
	Anastrazole	*RE (%)*	*Tamoxifen*	*RE (%)*	*Difference*	*RE (%)*
1 year	8,510	-4,41	6,377	-3,54	2,133	-6,94
1 year + half cycle correction	8,658	-2,75	6,488	-1,86	2,169	-5,37
6 months	8,708	-2,19	6,494	-1,77	2,214	-3,40
6 months + half cycle correction	8,784	-1,34	6,550	-0,92	2,233	-2,57
3 months	8,806	-1,09	6,553	-0,88	2,253	-1,70
3 months + half cycle correction	8,844	-0,66	6,581	-0,45	2,263	-1,27
1.5 months	8,855	-0,54	6,582	-0,44	2,273	-0,83
1.5 months + half cycle correction	8,874	-0,33	6,596	-0,23	2,277	-0,65
Multi-step algorithm	**8,903**		**6,611**		**2,292**	

Differences in LYs gained for both anastrazole and tamoxifen decrease for all step sizes when a half cycle correction was implemented (**Table 4**). A step size of 1 year lead to an underestimation of 0.020 absolute LY (7.42%), which is larger, compared to the outcome without a half cycle correction.

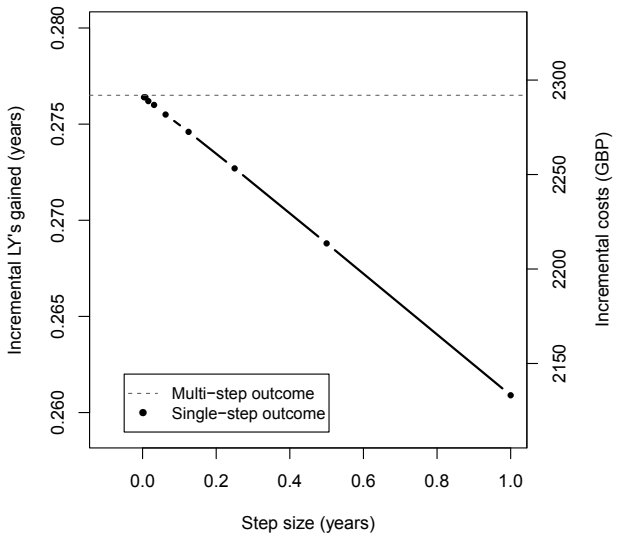


Figure 3. *Impact of step-size on incremental LYs gained and costs between anastrazole and tamoxifen*

Discussion

We demonstrated the development and implementation of a comprehensive computational framework for cost-effectiveness cohort simulation in the scripting language R using a modern multi-step ODE solver algorithm. In addition, for the case example CEA comparing anastrazole and tamoxifen, we quantified the impact of the use of fixed step sizes on outcome measures.

Impact of fixed step size in single-step ODE solver algorithms

For the evaluated case example, bias in incremental LYs and costs was calculated for different step sizes using the fixed step size single-step algorithm versus the multi-step algorithm. A step size of one year led to an underestimation of 0.016 LYs gained and 158 GBP.

Implementing a half cycle correction for the fixed step size single-step algorithm outcomes decreased bias in LYs gained for both anastrazole and tamoxifen, but bias increased in incremental LYs gained, possibly related to the larger differences in number of patients in death health states in subsequent cycles for tamoxifen. Although bias on LYs gained decreased when a half cycle correction was implemented, still not all bias is overcome. Furthermore, as stated in the introduction section, scepticism exists regarding

the elegance, efficiency and use of implementing a half cycle correction[11;12].
The observed magnitude of bias was limited for this case example. Nonetheless, if the step size is not carefully chosen with respect to the magnitude of change over time, there is a potential risk of larger bias in outcome measures. In many cases, when the step size is carefully chosen, this may not represent an issue. However, specifically for more complex health economic models, it may not be straightforward to rationally determine an appropriate value for step size. Additionally, when using software such as Excel, there are also practical limitations to the how small step size can be chosen, related to the maximum number of rows allowed.

All these difficulties can be overcome by used the described multi-step ODE solver algorithm, which does not suffer from such disadvantages, and will always use an adequate step size regardless of how complex the model may be.

Scripting language for health economic analysis

Dynamical CEA models are frequently implemented in i) software packages designed specifically for CEA, or ii) using general spreadsheet application software (e.g. Excel). Software packages developed for conduct of CEAs typically have user-friendly graphical user interfaces (GUIs), which is a potential benefit in terms of user-friendliness. Alternatively, CEA analyses can be implemented in scripting-based software packages such as, but not limited to, the scripting language R. Other examples of scripting languages which are frequently used in the field of quantitative data analysis are SAS and Matlab. A comparison of the scripting language R and the frequently used spreadsheet application Excel for different aspects of health economic analyses is provided in **table 5**. Scripting-languages do not use graphical user interfaces, but instead employ direct text-based programming to define an analysis, and are more complex to learn initially compared to GUI-based software or spreadsheet applications for CEA.

An important drawback of both many tailored GUIs for CEA, but also spreadsheet applications such as Excel, is their poor transparency and reproducibility, e.g. it may be unclear how different components of these often highly complex models are interlinked, or which input parameters are used. These characteristics complicate quality control, e.g. identifying potential errors, and generation of analysis reports that can be used for reproduction by external reviewers (e.g. the reproducibility problems we experienced when reproducing the publication by Mansel et al). In contrast, analyses conducted in R (or any other scripting language), can be easily appended in full to any report, as they are fully text-based.

Furthermore, the support of advanced mathematical-statistical functions in CEA tailored

GUIs but also spreadsheet packages, is usually limited. In contrast, statistical-mathematical scripting languages such as R, SAS and Matlab typically support advanced mathematical and statistical functions (e.g. global sensitivity analyses, modern ODE solver algorithms, Bayesian priors, less commonly used probability distribution functions).

Modification of health economic analysis is also very flexible when using scripting languages, due to the modular nature of most scripts (e.g. in subroutines). This allows easy adaptation, update or extension of earlier conducted analyses, for instance when modifying country specific characteristics or costs.

Although the learning-curve of R is potentially slightly steeper, a large user community exists, and a substantial collection of freely available documentation is available. R is available free of charge and open source. Overall, we consider the use of scripting languages to be highly relevant and useful for conduct of health economic analyses, that can potentially lead to increased integrity and reproducibility of analyses.

Limited reproducibility of the reference model

We meticulously attempted to reproduce the reference model by Mansel *et al*[19]. However, as discussed, the methodology section of the reference model was not fully complete and unclear in some aspects of model building. It was therefore not possible to accurately reproduce all of their results. Although total life years gained and incremental life years gained did not differ much between the fixed step size algorithm and the reference case, respectively (13% and 18%), substantial differences were observed in costs of adverse events -56%, follow up for tamoxifen 54% and the switch health state. These involve health states and rates which were not completely stated and for which additional assumptions were initially needed. Inclusion of a switch health state in economic evaluations is an incorrect assumption, because economic evaluations need cross over free data. The reference model does not state why this switch health state was included and how costs and effects were linked to this state. Furthermore, accumulation of costs for adverse events were observed in the reference model after 5 years. This accumulation is unexpected considering the assumptions made in the reference model regarding adverse events. In addition to this, differences in total costs for follow up were observed in the reference model, for which no explanation was given. Costs involved in health states for which all necessary rates were present (i.e drug and recurrence and palliative care costs) had an overall good resemblance.

Table 5. *Overview of essential characteristics R and Excel*

Characteristic	Example	R (and most other scripting languages)	Excel (and other spreadsheet applications)
Transparency	Is it clear how computations are being made, and which input parameter are being used?	Highly transparent. Scripts contain all computations and input parameters in an accessible fashion.	Less transparent as it is difficult to see how and in which sequence computations are made, and which parameters are used.
Reproducibility	Is it easy to extract all information necessary that will allow full reproducibility of the analysis performed?	Good. Scripts can be easily included in analysis reports and re-run by others.	Limited. Excel sheets can be re-run, but if not included it may be difficult to provide all necessary information and input parameters in a report, making reproducibility of an analysis challenging.
Quality control	How easy is it to detect potential errors in an analysis?	Straightforward. The script can be evaluated and checked step-by-step. Commenting of scripting allows quick understanding of different steps.	Difficult, as it is not clear how computations are linked in a spreadsheet, and which cells contain computations.
Practical limitations	Are there any practical limitations to the use of the software?	None. No relevant limitations in the context of cost-effectiveness analysis.	Limited number of rows, which is relevant for numerical solutions of dynamic CEA models.
Modularity	How easy can components of an analysis (e.g. model structure or other computational tasks) be exported or replaced?	Good. R scripts are usually composed out of number of different subroutines with clear input/output characteristics, hence allowing easy replacement, re-use or sharing of certain parts of an analysis.	Limited, as different parts of a spreadsheet are dependent on the overall implementation of the full sheet.
Graphics generation		Professional-looking advanced graphics can be easily (re-) generated	Limited.
Operating systems		Windows, Linux, Mac OS	Windows and Mac OS (open source alternatives also Linux)
Support		Large user community (mailing lists, forums)	User community support for these type of analysis is limited.
		Large body of literature and integrated help functions	Used frequently in health economic community
		Currently less used in health economic community	

Table 5. Continued. *Overview of essential characteristics R and Excel*

Characteristic	Example	R (and most other scripting languages)	Excel (and other spreadsheet applications)
Ease of learning		Less familiarity and initial learning steps can be challenging	Most people are already familiar with spreadsheet software.
Costs		Free (open source)	$100 - $150, but free open-source alternatives are available
CEA related functionality			
Ease of model building		Model components can be easily re-used, extended or shared.	Re-use or adaptation of previously developed models can be less straightforward.
Sensitivity analysis		Advanced local and global sensitivity analysis packages are available.	Limited to local sensitivity analysis.
Uncertainty analysis (Monte Carlo sampling		Sampling from a wide range of distributions and correlation structures is supported. Also more efficient Latin-Hypercube Sampling supported.	Sampling from a limited number of distributions without correlations is supported.
Bayesian analysis		Bayesian sampling methods (e.g Gibbs etc.) can be easily implemented using R2BUGS	Less straightforward although links to WinBUGS have been described.
Differential equation solver		A range of ODE solver algorithms is available.	No ODE solver is available, and needs to be manually implemented.

The observed differences in analysis outcome between the current analysis and the results published for the reference model have no consequences by itself, but merely demonstrate the difficulty to reproduce the CEA by Mansel *et al*[19] due to lacking model details. Especially due to the high complexity of CEAs, it is of pivotal importance to clearly report on input parameters, model structure and assumptions. The importance of reproducible health economic analyses has also recently been discussed by Smith-Spangler[25].

Conclusion

This work described the development and implementation of framework for cost effectiveness cohort simulation in the statistical scripting language R. We also illustrated the impact of fixed step sizes on bias in CEA outcome measures. Although the ultimate differences in costs for this example were limited, for other situations where costs differences are larger, the magnitude of bias may become of substantial relevance, and could potentially affect decision making. The developed framework which implements a modern multi-step ODE solver algorithm eliminates the need of specifying step size in the context of the more often used fixed step size single step methods. Moreover, we encourage the use of scripting languages such as R in the field of health economics, which can potentially substantially improve the transparency, reproducibility and overall integrity of conducted CEAs. Finally, the developed framework for cost effectiveness cohort simulations can be applied for all deterministic (e.g. Markov model approximation) cost effectiveness cohort simulations in general.

Acknowledgements

PhD student G.W.J. Frederix was funded by an unrestricted grant from GlaxoSmithKline (GSK). The authors declare no conflicts of interest.

References

(1) *Szucs TD, Dedes KJ. Balancing costs and benefits in cancer therapy and prevention. Ann Oncol* ***2008****; 19 Suppl 7:vii313-vii319.*

(2) *Garber AM, Phelps CE. Economic foundations of cost-effectiveness analysis. J Health Econ* ***1997****; 16(1):1-31.*

(3) *Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for the economic evaluation of health care programmes. 2nd ed.* ***1997****. New York: Oxford University Press.*

(4) *Johannesson M, Weinstein MC. On the decision rules of cost-effectiveness*

*analysis. J Health Econ **1993**; 12(4):459-467.*

(5) Briggs A, Sculpher M, Claxton K. Decision Modelling for Health Economic Evaluation, Oxford University Press.

(6) Euler L. Institutionum calculi integralis, Petropoli, Impensis Academiae Imperialis Scientiarum.

*(7) Gear C.W. Numerical Initial Value Problems in Ordinary Differential Equations, Prentice Hall, Englewood Cliffs. **1971**.*

*(8) Hairer E.Norsett S.P and Wanner G. Solving Ordinary Differential Equations I: Nonstiff Problems. Springer-Verlag. Berlin, second edition. **1993**.*

*(9) Bird J. Higher Engineering Mathematics, Elsevier Ltd. **2010**.*

*(10) Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making **1993**; 13(4):322-338.*

*(11) Barendregt JJ. The half-cycle correction: banish rather than explain it. Med Decis Making **2009**; 29(4):500-502.*

*(12) Naimark DM, Bott M, Krahn M. The half-cycle correction explained: two alternative pedagogical approaches. Med Decis Making **2008**; 28(5):706-712.*

*(13) Butcher JC. Numerical Methods for Ordinary Differential Equations, Wiley,**2003**.*

*(14) Kutta W. Beitrag zur naherungsweisen Integration von Differentialgleichungen, Zeit. Math. Physik, v. 46, **1901**, p. 435-453.*

*(15) Runge C. Uber die numerische Auflosung von Differential-gleichungen, Math. Ann., v. 46, **1895**, p. 167-178.*

*(16) Bashforth F, Adams JC. An attempt to test the theories of capillary action : by comparing the theoretical and measured forms of drops of fluid. With an explanation of the method of integration employed in constructing the tables which give the theoretical forms of such drops, Cambridge University Press, (**1883**).*

*(17) Ascher UM, Petzold LR. Computer Methods for Ordinary Differential Equations and Differential-Algebraic Equations, SIAM, Philadelphia, ISBN 0-89871-412-5 . (**1998**).*

*(18) Petzold LR. Automatic Selection of Methods for Solving Stiff and Nonstiff Systems of Ordinary Differentail Equations. Siam J. Sci.Stat. Comput., 4, 136-148. **1983**.*

*(19) Mansel R, Locker G, Fallowfield L, Benedict A, Jones D. Cost-effectiveness analysis of anastrozole vs tamoxifen in adjuvant therapy for early stage breast cancer in the United Kingdom: the 5-year completed treatment analysis of the ATAC (‚Arimidex', Tamoxifen alone or in combination) trial. Br J Cancer **2007**; 97(2):152-161.*

*(20) R Development Core Team (2011). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/. **2011**.*

*(21) Soetaert K, Petzold T, Setzer R. Solving Differential Equations in R: Package deSolve, Journal of Statistical Software, 33, 9, 1-25. **2010**.*

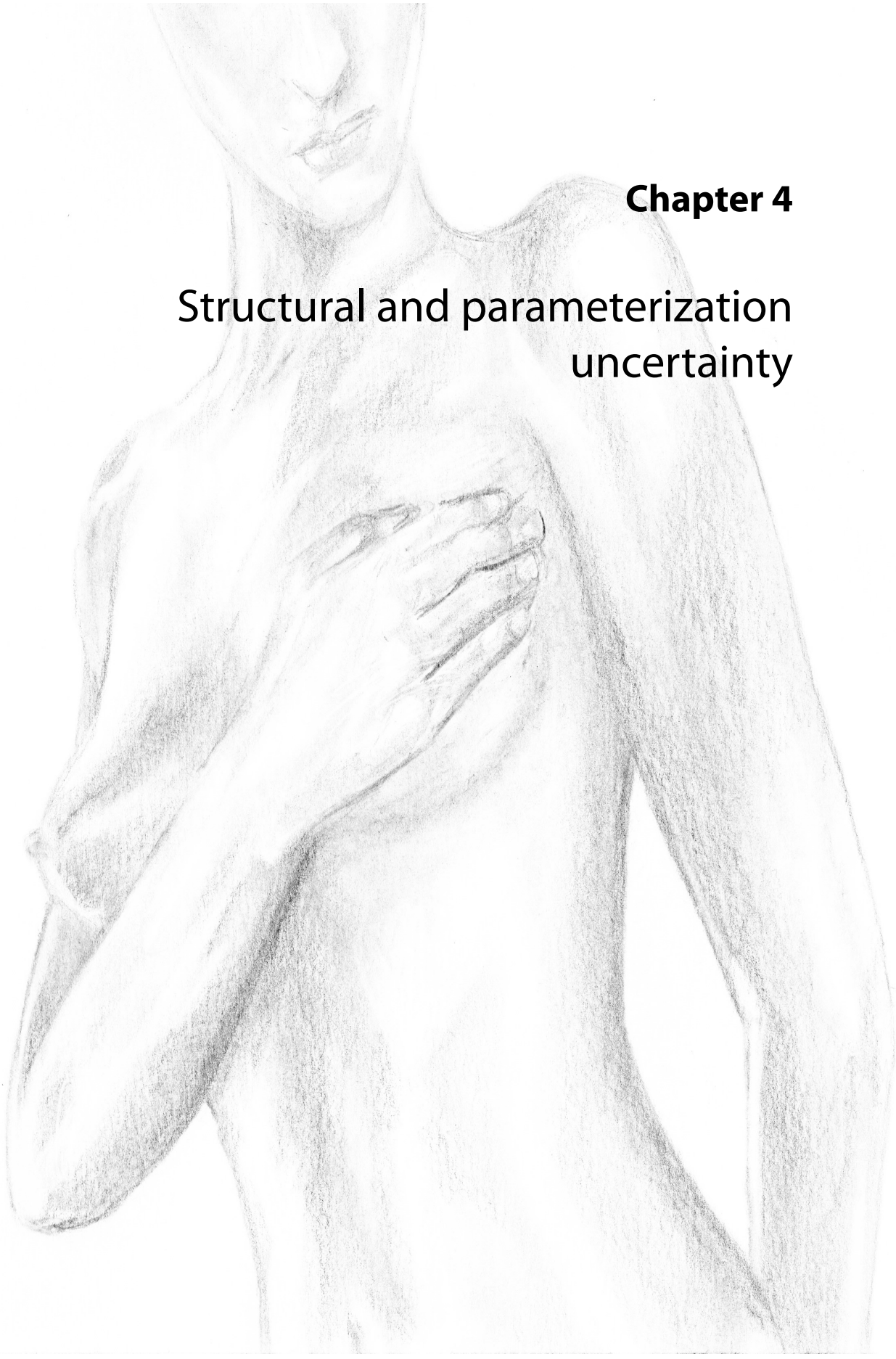
*(22) Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet **2005**; 365(9453):60-62.*

*(23) UK office of National Statistics (**2002**).*

*(24) Karnon J, Delea T, Barghout V. Cost utility analysis of early adjuvant letrozole or anastrozole versus tamoxifen in postmenopausal women with early invasive breast cancer: the UK perspective. Eur J Health Econ **2008**; 9(2):171-183.*

*(25) Smith-Spangler C M. Transparency and Reproducible Research in Modeling Why We Need It and How to Get There. Med Decis Making. Oct 2012 vol. 32 (5) 663-666. Med Decis Making. In press **2012**.*

3



Chapter 4

Structural and parameterization uncertainty

Chapter 4

Uncertainty of model structure and parameterization: the need for a standardized cost-effectiveness model for adjuvant breast cancer therapies

Gerardus W.J. Frederix
Johan G.C. van Hasselt
Jan H.M. Schellens
Anke M. Hövels
Jan A.M. Raaijmakers
Alwin D.R. Huitema
Johan L. Severens

Submitted for publication

Abstract

Introduction

Models for cost-effectiveness analysis (CEA) are usually based on a number of choices regarding model structure and parameterization. For many published health economic analyses in oncology, substantial differences in such choices exist, which can thereby lead to differences in modelling outcomes, and ultimately impact the associated decision making processes. The objective of this analysis was i) to identify differences in options regarding model structure and parameterization for CEAs comparing tamoxifen and anastrazole for adjuvant breast cancer (ABC) treatment, and ii) to quantify the impact of such options on analysis outcomes.

Methods

The analysis consisted of four steps: i) review of the literature for identification of eligible CEAs; ii) definition and implementation of a base model structure; iii) definition and implementation of changing options for model structure and parameters estimation; and iv) quantification of the impact of these changes to model structure and parameterization on the modelling outcomes (life years (LY) gained, incremental costs (IC) and incremental cost effectiveness ratio (ICER)).

Results

We identified 11 CEA analyses comparing anastrazole and tamoxifen as ABC treatment. The base model consisted of the following health states: on treatment, off treatment, local recurrence, metastatic disease, death due to breast cancer and death due to other causes. The base model estimates for LY, IC and ICER were 0.263 years, €3,647 and €13,868/LY gained for anastrazole respectively. Changes to this base model were related to model structure (adding health states and transition possibilities) and parameterization (incidence of recurrence, local recurrence to metastatic disease and metastatic disease to death) as were found in published models. The separate impact of changing options on LY gained ranged from 0.207 years to 0.356 years, incremental costs ranged from €3,490 to €3,714, and ICER ranged from €9,804/LY gained to €17,966/LY gained. For the comparison of combining changes, LY gained ranged from 0.207 years to 0.383 years, IC ranged from €3,556 to €3,731 and ICERs ranged from €9,683/LY gained to €17,570/LY gained.

Conclusion

Although the impact on the ICERs was modest in absolute values, this analysis demonstrated that changing model structure and parameterization can impact the relative estimation of patient life expectancy substantially. This analysis supports the need for standardized model structures in adjuvant breast cancer therapy.

Introduction

Decision making for reimbursement of new drugs is increasingly supported by health economic analyses. In order to derive informed decisions, it is important to quantify the uncertainty associated with model predictions. Sources of uncertainty include parameter uncertainty, methodological uncertainty and structural uncertainty[1]. Parameter and methodological uncertainties are frequently included in health economic analyses, and have been discussed in various guidelines[2,3]. Structural uncertainty, however, has been considered much less[4].

Models aim to represent reality, but simplifications or assumptions are unavoidable since knowledge may either be not available or may be irrelevant with respect to the objectives of an analysis. Structural uncertainty deals with the uncertainty associated with such assumptions or simplifications. Important components of structural uncertainty are the assumptions included in the model with respect to disease progression and treatment response. This includes for instance the health states that need to be considered, their relationships, and the mathematical description of transition rates. With respect to health economic analyses for breast cancer therapies, we have recently described some important differences in modeling methods and structures used[5]. These differences were related to both structural model components such as additional health states or additional transitions and differences in the mathematical description of transition rates, hereby outlined as parameterization.

The impact of structural uncertainty on analysis outcome can be substantial. Bojke *et al*[4] have shown a potentially large influence of the different possible ways health states or other model components have been implemented, demonstrating changes in outcome that could potentially change reimbursement decisions. Kim and Thompson[6] have shown that the impact of structural uncertainty on estimated incremental cost effectiveness ratios (ICERs) can be similar to the impact of parameter uncertainty. However, despite the large number of cost-effectiveness analyses of therapies in the oncology area, and the potential major impact of structural uncertainty, currently no studies have been reported regarding their impact.

The objectives of this analysis were: i) to identify differences in reported structural models and model parameterizations for cost-effectiveness analyses (CEAs) comparing tamoxifen and anastrazole for adjuvant breast cancer (ABC) treatment, and ii) to quantify the impact of the differences in these model components on analysis outcome measures.

Methods

The analysis was performed in four steps: i) identification of eligible CEAs; ii) definition and implementation of a base model structure; iii) definition and implementation of additional model components and iv) quantification of differences induced by inclusion of different structural model components that were identified. For steps ii) to iv) we used a previously developed scripting framework which was implemented using the statistical scripting language R (version 2.10.0)[7] together with the ordinary differential equation solver algorithm LSODA[8] (Frederix GWJ. *et al*, submitted for publication). With respect to nomenclature, we will refer to the base model as base model and to additional model components identified using higher numbers, e.g. M1, M2 etc.

I. Literature review

Eleven adjuvant breast cancer CEAs were identified earlier in a recently published systematic literature review[5]. These CEAs were eligible for this analysis when a Markov model or ordinary differential equation-based approach was used, and a comparison was made between anastrazole and tamoxifen for the treatment of early breast cancer. The structural model components were subsequently extracted and summarized. All identified model components were categorized in three groups: i) health states, ii) transition rates, and iii) parameterization of transition rates.

II. Definition and implementation of base model structure

Based on the identified model structures, a base model was defined by including the health states that were present in all different published models, i.e. representing the "core" model structure that was included in all published models.

Transition rate parameterization for the base model was selected by using the simplest implementation as published in the different CEAs. For instance, when a certain transition rate was included using either a time-varying or a constant rate constant, the constant rate constant was used in the base model. The parameter estimates used for the base model were obtained from the most complete report with respect to availability of parameter estimate values.

III. Identification and implementation of optional model components

For each identified CEA in step I, the full model structure was compared to the base model and all differences were identified as additional model components. Different model components were divided in 1) structural model components, such as additional health states and additional transitions between health states and 2) model components related to different mathematical descriptions of transition rates (parameterization).

IV. Quantification of differences induced by different model components identified

To assess the impact of different additional model components identified in step III, each of the model components were included in separate models and associated analysis outcome measures were computed (univariate analysis). Subsequently, the different additional model components were combined to reproduce the different CEAs as identified in step I (multivariate analysis). For each evaluated model implementation that was evaluated, life years (LY) gained for anastrazole, incremental costs (IC), and the incremental costs-effectiveness ratio (ICER) were computed.

Results

I: Literature review

All eleven publications assessing the cost-effectiveness of anastrazole versus tamoxifen[9-19] as identified previously in our review, were eligible for this analysis. In addition to our previous review, we identified differences between these analyses with respect to health states and adverse events which are depicted in **table 1**. Each of these publications used the ATAC clinical trial as basis for implementation of recurrence rates.

Table 1. *Overview of health states as defined in published cost-effectiveness models.*

Model properties	**Model implementations**											
	Base model	18	19	13	15	14	9	17	16	12	10	11
On treatment												
Disease free	x	x	x	x	x	x	x	x	x	x	x	x
Disease free with complications											x	
Switch treatment				x	x	x						
Off treatment, remission	x	x	x	x	x	x						
Local recurrence												
Loco-regional recurrence	x	x	x	x	x	x	x	x	x	x	x	x
Contralateral tumor/remission										x		
Metastatic disease												
Metastatic disease	x	x	x	x	x	x	x	x	x		x	x
Soft tissue metastasis										x		

Table 1. Continued. *Overview of health states as defined in published cost-effectiveness models.*

Model properties	Model implementations											
	Base model	18	19	13	15	14	9	17	16	12	10	11
Bone metastasis										x		
Visceral metastasis										x		
Treated relapse		x	x									
Adverse events												
Vaginal bleeding or venous thromboembolism												x
Hip fracture												x
Experience of adverse event due to adjuvant treatment							x					
Need to change treatment after an adverse event							x					
Fracture (any)		x	x									
Venous thromboembolic		x	x									
Local relapse		x	x									
Several adverse events											x	
Death												
Death (no differentiation between cause)		x	x						x	x	x	x
Death due to other causes	x			x	x	x	x	x				
Death due to breast cancer	x			x	x	x	x	x				

II. Definition and implementation of base model structure

Health states

An overview of health states identified across the different cost-effectiveness studies is depicted in **Table 1**.

Common health states across all analyses were on treatment, off treatment, local recurrence, metastatic disease, death due to breast cancer and death due to other causes. The resulting base model, which consisted of these six health states, is depicted in **figure 1**.

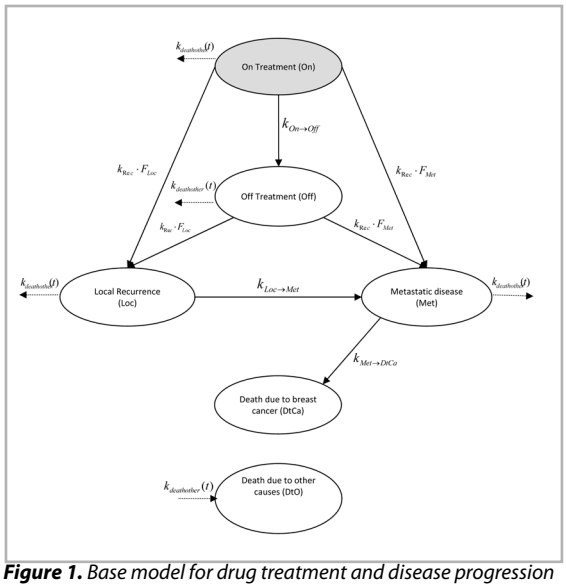


Figure 1. *Base model for drug treatment and disease progression of early breast cancer.*

Transition rates

The following transition rates were included in the base model: i) incidence of local recurrence from both on treatment and off treatment ($K_{rec} \cdot F_{loc}$) and incidence of metastatic disease from both on treatment and off treatment ($K_{rec} \cdot F_{met}$), ii) rate of metastasis following local recurrence ($K_{loc \rightarrow Met}$), iii) death after metastatic disease ($K_{met \rightarrow DtCa}$) and iv) a (time-varying) background mortality ($K_{deathother}(t)$) for patients in the health states on treatment, off treatment, local recurrence and metastatic disease. In addition, after five years of treatment, the proportion of women present in the on treatment health state switched to the off treatment health state.

Parameterization of transition rates

The most common implementation for all parameterizations was the use of a constant rate, which was therefore used for the base model implementation (**Table 2**). The only exception was the implementation of background mortality, which was a time-varying rate constant changing every five years[15].

The publication by Mansel *et al*[15] was found to be most transparently reported with respect to defined parameter values and costs, and was therefore used for both transition rate estimates and cost parameters estimates. The rates of adverse events were not clearly stated in each manuscript, and were therefore derived from the 5-year results of the ATAC trial[20].

Table 2. *Model input parameters for base model obtained from Mansel et al 15, unless indicated otherwise by other references.*

Description	Name	Unit	Estimate	
			Anastrazole	Tamoxifen
Incidence of recurrence [16]				
Year 1-10	k_{Rec}	$year^{-1}$	0.02276	0.02964
Year 10-lifetime	k_{Rec}	$year^{-1}$	0.02964	0.02964
Distant recurrences as a proportion of all recurrences during recurrence benefit				
Metastatic disease	F_{Met}		0.66	0.60
Local recurrence	F_{Loc}		0.34	0.40
Adverse events				
Life-threatening	k_{Life}	$year^{-1}$	0.0094	0.0132
Non life-threatening	$k_{NonLife}$	$year^{-1}$	0.1396	0.1314
Following local/regional recurrence				
Distant metastases [17]	$K_{Loc->Met}$	$year^{-1}$	0.193	
Death rate after metastatic disease				
Overall survival at 2 years	$K_{Met->DtCa}$	$year^{-1}$	0.250	
Mortality				
Background mortality	$K_{deathother}(t)$	$year^{-1}$	*	

** Background mortality rate includes time varying variables with values changing in five year intervals and was obtained from the UK office of National Statistics (2002). Included yearly rates were;*

Background mortality: 65-70 year[-1], 0.0140; 70-75, 0.0247; 75-80, 0.0415; 80-85, 0.0717; >85, 0.1615

III. Identification and implementation of optional model extensions

In **table 3** the choices regarding model structure and parameterization from the published models is shown.

Based on this overview we identified three choices that were related to model structure: addition of health states, and two additional transition possibilities between health states. Six differences between the existing models were related to choices regarding the method for parameterization. All different model components are referred to as (M1-M9).

Table 3. *Combinations of structural and parameterization differences in published articles and base model*

Model	Health states	Additional transitions	Parameterization		
			Rate for recurrence incidence	*Rate for death after metastatic disease*	*Rate for metastasis after local/regional recurrence*
Base model	Local and metastatic recurrence (Base model)		Constant (base model)	Constant (base model)	Constant (base model)
Skedgel[18]	Base model	**Mortality due to adverse events (M2)**	Base model	Base model	Base model
Skedgel[19]	Base model	**Mortality due to adverse events (M2)**	Base model	Base model	Base model
Locker[13]	Base model	**Mortality due to adverse events (M2)** **Mortality due to local recurrence (M3)**	**Weibull (M6)**	Base model	**Depending on time spent in recurrence state (M9)**
Mansel[15]	Base model	**Mortality due to adverse events (M2)** **Mortality due to local recurrence (M3)**	**Weibull (M6)**	Base model	**Depending on time spent in recurrence state (M9)**
Lux[14]	Base model	**Mortality due to adverse events (M2)** **Mortality due to local recurrence (M3)**	**Weibull (M6)**	Base model	**Depending on time spent in recurrence state (M9)**
Fonseca[9]	Base model	Base model	Base model	**Time dependent (M7)**	**Depending on time spent in recurrence state (M9)**
Rocchi [17]	Base model	Base model	**Partly time dependent (M4)**	**Time dependent (M7)**	Base model
Moeremans[16]	Base model	Base model	Base model	Base model	**Depending on time spent on therapy (M8)**
Karnon[12]	**Various metastatic health states (M1)**	**Mortality due to adverse events (M2)**	**Time dependent (M5)**	**Time dependent (M7)**	**Depending on time spent in recurrence state (M9)**
Gil[10]	Base model	-*	Base model	-*	-*
Hillner[11]	Base model	**Mortality due to adverse events (M2)**	Base model	Base model	Base model

** Implementation could not be derived from original manuscript and was therefore assumed to be unknown.*

Identified transition rates for the different components are depicted in **table 4**. Origin, explanation and implementation of these options are stated in the following sections

Table 4. *Structural and parameterization differences and implemented probabilities.*

Description	Parameter	Unit	Estimate	
			Tamoxifen	Anastrazole
Additional health states				
M1: Additional recurrence health states[12]				
Contralateral tumour	F_{Cont}		0.144	0.103
Locoregional recurrence	F_{Loc}		0.256	0.237
Soft tissue	F_{Soft}		0.048	0.053
Bone	F_{Bone}		0.256	0.282
Visceral	$F_{Visceral}$		0.296	0.326
Death rates				
Soft tissue				
1-5 years	$k_{Soft->DtCa1-5}$	$year^{-1}$	0.165	
6 years-lifetime	$k_{Soft->DtCa6-lt}$	$year^{-1}$	0.160	
Bone				
1-5 years	$k_{Bone->DtCa1-5}$	$year^{-1}$	0.245	
6 years-lifetime	$k_{Bone->DtCa6-lt}$	$year^{-1}$	0.192	
Visceral				
1-5 years	$k_{Visceral->DtCa1-5}$	$year^{-1}$	0.284	
6 years-lifetime	$k_{Visceral->DtCa6-lt}$	$year^{-1}$	0.262	
Additional transitions				
M2: Mortality due to life threatening adverse events[12]				
Death due to hip fracture	$k_{deathhip}$	$year^{-1}$	0.040	
Death due to endometrial cancer	$k_{deathendo}$	$year^{-1}$	0.035	
Death due to thrombosis	$k_{deaththrombo}$	$year^{-1}$	0.200	
M3: Mortality due to local recurrence[13-15]				
Years 1-lifetime	$k_{Loc->DtCa}$	$year^{-1}$	0.222	
Alternative parameterization				
Incidence of recurrence rates				
M4: Time dependent[17]				
1st year	k_{Rec1}	$year^{-1}$	0.0257	0.0190
2nd year	k_{Rec2}	$year^{-1}$	0.0384	0.0284
3rd year	k_{Rec3}	$year^{-1}$	0.0363	0.0269
4th your	k_{Rec4}	$year^{-1}$	0.0321	0.0238

Table 4. Continued. *Structural and parameterization differences and implemented probabilities.*

Description	Parameter	Unit	Estimate	
			Tamoxifen	Anastrazole
5th year	k_{Rec5}	$year^{-1}$	0.0276	0.0204
6th year	k_{Rec6}	$year^{-1}$	0.0238	0.0176
7th year	k_{Rec7}	$year^{-1}$	0.0221	0.0164
8th year	k_{Rec8}	$year^{-1}$	0.0273	0.0202
9th year	k_{Rec9}	$year^{-1}$	0.0203	0.0150
10th year	k_{Rec10}	$year^{-1}$	0.0138	0.0102
Year 11-Lifetime	k_{Rec11}	$year^{-1}$	0.0215	0.0215
M5: Partly time dependent[12]				
Year 1-5	k_{Rec1-5}	$year^{-1}$	0.0391	0.0289
Year 6-10	$k_{Rec6-10}$	$year^{-1}$	0.0288	0.0231
Year 10-lifetime	$k_{Rec10-lt}$	$year^{-1}$	0.0287	0.0287
M6: Weibull[13-15]				
Year 1-10				
Intercept	I_1		9.42	9.17
Scale parameters	S_1		0.83	
Year 10-lifetime				
Intercept	I_2		9.29	9.29
Scale parameters	S_2		0.83	0.83
M7: Death rate after metastatic disease [9]				
0-1 year	$k_{Met->DtCa1}$	$year^{-1}$	0.500	
1-2 year	$k_{Met->DtCa2}$	$year^{-1}$	0.410	
2-5 year	$k_{Met->DtCa5}$	$year^{-1}$	0.320	
5-lifetime	$k_{Met->DtCa5-lt}$	$year^{-1}$	0.220	
Rate of metastasis following local recurrence				
M8: Metastatic rate depending whether a patients is on therapy [16]				
On therapy	$k_{Loc->Meton}$	$year^{-1}$	0.142	
Off therapy	$k_{Loc->Metoff}$	$year^{-1}$	0.100	
M9: Time-varying metastatic rate [12]				
Years 1-5	$k_{Loc->Met1-5}$	$year^{-1}$	0.124	
Years 6-15	$k_{Loc->Met6-15}$	$year^{-1}$	0.0752	

Health states: Recurrence health states (M1)

Karnon *et al*[12] described a CEA in which three metastatic health states were included instead of only one. This was implemented by dividing the metastatic disease health state into: soft-tissue metastasis, bone metastasis and visceral metastasis. In addition to these health states, corresponding death rates were defined. Local recurrence was subdivided into two separate health states: contralateral breast cancer and local recurrence. To implement the time dependent death rates, six "tunnel" states for each metastatic health state were implemented[21]. Tunnel states were defined for each year from one year to five years, and from five years and onwards. An individual can only be present in a tunnel state for a pre-stated time and this state represents both the disease state the individual is in and the time previously spent in this state.

The fractions for recurrence used by Karnon et al were based on the BIG-trial. We implemented these alternative health states using the fractions derived from the ATAC trial because in all other analyses these fractions were used and otherwise differences in outcome would be related to differences in parameter choices.

Transitions: Mortality estimates (M2 and M3)

Various authors included death rate due to adverse events[11;13-15;18;19] in their model. For M2, mortality rates for three life threatening adverse events were included, respectively hip fractures, endometrial cancer and thrombosis[12]. The population at risk was defined as the population on treatment experiencing the life threatening adverse events.

For M3, an additional rate for breast cancer related death after having local recurrence was included, which was identified in three different articles[13-15].

Parameterization of transition rates: (M4-M9)

Three model components (M4, M5 and M6) were identified to describe recurrence rate. In M4, time varying parameters over the first 10 years were implemented instead of a constant recurrence rate[17]. For M5, partly time dependent parameters were included by varying recurrence rate after five and ten years from start of therapy[12]. In M6 a Weibull equation was used (Equation (1)) to calculate recurrence rate[13-15].

Time-dependent death rates following distant metastases were included in the three different publications[9;12;17]. In M7, these rates were implemented by using tunnel states. Metastatic disease and the time previously spent in this state were defined by using the following series of six tunnel states with corresponding death rates: 0-1 years, 1-2 years, 2-3 years, 3-4 years, 4-5 years and more than 5 years in metastatic disease[9].

Component M8 was a variation on the rate of having metastatic disease after local recurrence by time spent on therapy. A different rate was used for the first five years and after five years of therapy[16]. For component M9 time-dependent metastatic rates were included by using tunnel states for the first five years after having local recurrence and for years 6-15 after having a local recurrence[12].

IV. Quantification of differences induced by different model components identified

The base model showed average costs per patient of €3,647 and 0.263 LY gained, leading to an ICER of €13,868. The results of the analyses based on the different components are presented in **table 5**.

Table 5. *Incremental outcome of anastrazole vs. tamoxifen for different individual model components*

	LY gained		**Incremental costs**		**ICER**	
Model	Estimate (years)	Relative difference from base model (%)	Estimate (Euro)	Relative difference from base model (%)	Estimate (€/LY)	Relative difference from base model (%)
Base model	0.263	NA	3,647	NA	13,868	NA
Additional health states						
M1: Additional metastatic health states	0.289	9.00	3,714	1.82	12,854	-7.89
Additional transitions						
M2: Inclusion of mortality due to life threatening adverse events	0.263	0.04	3,647	0.00	13,868	0.00
M3: Inclusion of death due to breast cancer after local recurrence	0.320	17.81	3,694	1.28	11,545	-20.11
Alternative parameterization						
M4: Time dependent recurrence	0.324	18.83	3,545	-2.86	10,944	-26.72
M5: Partly time dependent recurrence	0.356	26.12	3,490	-4.49	9,804	-41.44
M6: Weibull equation for recurrence	0.295	10.85	3,641	-0.15	12,344	-12.34
M7: Time dependent death rate	0.281	6.41	3,655	0.22	13,008	-6.61
M8: Metastatic rate depending on time spent on therapy	0.207	-27.05	3,673	0.70	17,744	21.84
M9: Metastatic rate depending on time spent in local recurrence	0.206	-27.67	3,701	1.45	17,966	22.81

ICER = Incremental Cost Effectiveness Ratio, LY= Life Years, NA= Not Applicable

** Difference computed as: ((LY gained new model – LY gained base model) / LY gained new model) * 100%*

Health states

Inclusion of additional metastatic health states (M1) resulted in a 9.0% increase in LY gained and respectively a 7.9% decrease in ICER.

Transitions

Inclusion of mortality due to life threatening adverse events (M2) resulted in a very small decrease in LY gained (0.04%) and almost no change in ICER. Inclusion of death rates after local recurrence (M3) resulted in a change of 17.8% in LY gained and subsequently of -20.1% in ICER.

Parameterization of transition rates

Component M4, in which a time dependent rate for the first 10 years was implemented resulted in large differences in respectively LY gained (18.8%) and a decrease in ICER of 26.7%. Component M5 in which a partly time dependent rate of recurrence was implemented caused the largest difference in LY gained (26.1%) and subsequently the ICER (-41.4%). Analysis M6 (in which a Weibull method was implemented for rate of recurrence) demonstrated a large change in the ICER (-23.3%) which is due to the change in LY gained of 0.032 (10.9%). Inclusion of time dependent rates of metastatic disease following local recurrence resulted in large differences, respectively -27.0% for M8 and -27.7% for M9 in LY gained. Analyses with alternative component M7, resulted in small changes in LY gained (less then 9.0%) and ICERs (less then 7.9%).

Comparison between overall published analyses

The impact of the implementation of combinations of components as present in published model (**Table 3**), is presented in **table 6**.

Combining components M2, M3, M6 and M9 as observed in[13-15] resulted in a 25.3% change in LY gained ultimately leading to a decrease in ICER of 31.1%. A combination of M7 and M9[9] resulted in a -15.4% change in LY gained and subsequently in a 15.3% change in ICER. Only incorporating component M8[16] resulted in 0.207 incremental LY gained, corresponding to a decrease in LY of 27.1% and an increase in ICER of 21.1%. Including component M4 for incidence of recurrence and component M7 following distant recurrence resulted[17] in a 23.9% change in LY gained and subsequently in a decrease in ICER of 34.9% to €10,278. A combination of components M1, M2, M5, M7 and M9 as observed in Karnon *et al*.[12] resulted in an increase in LY gained of 31.3% to 0.383 and the largest decrease in ICER of 43.2% to €9,683. Overall incremental costs did not vary much between all analyses.

Table 6. *Incremental outcome of anastrazole vs. tamoxifen for different combinations of model components*

	LY gained		**Incremental costs**		**ICER**	
Model	Estimate (years)	Relative difference from base model (%)	Estimate (€)	Relative difference from base model (%)	Estimate (€/LY)	Relative difference from base model (%)
Base model	0.263	NA	3,647	NA	13,868	NA
Model according to Locker, Lux and Mansel[13-15]	0.352	25.28	3,723	2.05	10,578	-31.10
Model consisting of;						
-Inclusion of mortality due to life threatening adverse events (M2)						
-Inclusion of death due to breast cancer after local recurrence (M3)						
-Weibull equation for recurrence (M6)						
-Metastatic rate depending on time spent in local recurrence (M9)						
Model according to Hillner, Skedgel and Skedgel[11;18;19]	0.263	0.00	3,647	0.00	13,868	0.00
Model consisting of;						
Inclusion of mortality due to life threatening adverse events (M2)						
Model according to Fonseca[9]	0.228	-15.35	3,731	2.26	16,367	15.27
Model consisting of;						
-Time dependent death rate (M7)						
-Metastatic rate depending on time spent in local recurrence (M9)						
Model according to Moeremans[16]	0.207	-27.05	3,673	0.70	17,744	21.84
Model consisting of;						
-Metastatic rate depending on time spent on therapy (M8)						
Model according to Rocchi[17]	0.346	23.99	3,556	-2.56	10,278	-34.93
Model consisting of;						
-Time dependent recurrence (M4)						
-Time dependent death rate (M7)						

Table 6. Continued. *Incremental outcome of anastrazole vs. tamoxifen for different combinations of model components*

	LY gained		**Incremental costs**		**ICER**	
Model	Estimate (years)	Relative difference from base model (%)	Estimate (€)	Relative difference from base model (%)	Estimate (€/LY)	Relative difference from base model (%)
Model according to Karnon[12]	0.383	31.33	3,708	1.66	9,683	-43.21
Model consisting of;						
-Additional metastatic health states (M1)						
-Inclusion of mortality due to life threatening adverse events (M2)						
-Partly time dependent recurrence (M5)						
-Time dependent death rate (M7)						
-Metastatic rate depending on time spent in local recurrence (M9)						

ICER = Incremental Cost Effectiveness Ratio, LY= Life Years

Discussion

This work illustrated the impact of different choices of researchers in structural and parameterization components on the cost-effectiveness outcome of early hormonal breast cancer therapies. We demonstrated how components used in previously conducted CEAs for early breast cancer had an impact of substantial magnitude on differences in life expectancy of the patients and thus the incremental cost-effectiveness estimate.

Health states

Inclusion of multiple metastatic sites (M1) instead of a single one, and time varying death rates instead of constant rates resulted in an increase in incremental life years gained. This difference was caused by a varying death rate between included metastatic sites. Pooled data from various sources demonstrated that metastasis of breast cancer occurs in different parts of the body with varying and time dependent death rates[22-27]. Therefore, the use of various metastatic sites and time dependent death rates, most closely resembles disease progression.

Transitions

Inclusion of mortality due to adverse events (M2) did not have a large effect on the outcome. Small differences in serious adverse event rates between anastrazole and tamoxifen are the cause for this small difference in outcome. Although death due to serious adverse events is not commonly seen in practice, inclusion of this component resembles outcomes seen in clinical practice at best, regardless of the small rate of death after occurrence of an adverse event.

Including a death rate due to breast cancer after having local recurrence M3 resulted in a significant increase in LY and a decrease in ICER. Although this structure has an essential impact on the outcome, all other publications assumed patients could only die of breast cancer after having distant metastasis thereby resembling disease progression of early breast cancer. In addition no proof in literature could be found for including this component.

Parameterization of transition rates

Time dependent rates of recurrence were incorporated in three different ways, time dependent for the first 10 years (M4), partly time dependent (M5) and a Weibull function (M6). Both M4 and M5, demonstrated to have the largest influence on the outcome. Inclusion of a Weibull function (M6) for recurrence resulted in an increase in LY gained compared to the base model. Because various large clinical trials have demonstrated that the majority of relapses in early breast cancer occur in the first two years after

diagnosis[20;28;29] and for estrogen receptor positive (ER+) and progesterone receptor positive (PR+) tumors relapses can occur even after a period of ten years from the end of treatment[30;31] the approach which most closely reflects disease progression is the time dependent rate of recurrence. Constant (base model), Weibull and partly time dependent rates do not resemble this essential characteristic of breast cancer.

Inclusion of time dependent death rates after metastasis, component M7, resulted in a decrease in ICER. Although this component does not have a large impact, various published articles have demonstrated that patients have an increased risk of death in the first years after metastasis, thereby indicating the clinical relevance of this component[32;33]. Therefore, inclusion of a time dependent death rate after occurrence of metastasis most closely resembles disease progression. Inclusion of constant death rates could result in an under- or overestimation of the observed death rate.

Inclusion of components M8 and M9, which involve time dependency of having metastatic disease after local recurrence of the tumor, resulted in a reduction in LY gained. This reduction in incremental LY gained was caused by smaller rates involved in both M8 and M9, which demonstrates the existence of both structural and parameter uncertainty in both cases. Time dependent rates of having metastatic disease after experiencing a first local recurrence was demonstrated by several published articles[20;33-35]. Therefore, inclusion of a time dependent rate after having local recurrence resembles natural disease progression best.

Comparison between overall analyses

By combining components as were implemented in the identified analyses large differences were observed between outcome measures, with a LY gained ranging between 0.207 and 0.383 years. The largest difference from the base model was observed combining components used by Karnon *et al*, which resulted in a decrease in ICER of 43.2%.

In these analyses, the ICERs remained in a range for which no implications for reimbursement status are likely to occur when compared to for instance the formal threshold of £30,000 used by NICE in the United Kingdom[36]. These relatively low ICERS are due to the relatively low incremental costs between both therapies. Differences in LY gained of 31.3%, observed by combining components as published by Karnon *et al*. could, however, become very relevant when higher incremental costs are involved.

As many factors are contributing to the overall uncertainty in outcome measures[5], it is difficult to isolate its individual contribution. Our analysis allowed a relatively objective

comparison of the impact of structural differences, eliminating other potential sources of differences between the outcomes of cost-effectiveness models such as modelling methods and differences between countries. Undoubtedly, our attempt to reproduce the previously published analysis will give somewhat different results compared to the originally published values.

Conclusions

In this analysis, we demonstrated the individual and combined impact of structural and parameterization model components relevant to adjuvant hormonal breast cancer therapies on CEA outcome measures. The differences in reported model components lead to differences in outcome, regardless of the using the same clinical trial data. This demonstrates the impact of specific choices of individual researchers regarding the model structure or including other parameterizations.

Table 7. *Description of a standardised cost-effectiveness model for treatment of adjuvant breast cancer*

Structure	Options	Recommendations
Health states	Various (see table 1)	Inclusion of a disease free, local recurrence, soft tissue metastasis, visceral metastasis, bone metastasis, death due to breast cancer and death due to other causes adequately reflects disease progression
Incidence of recurrence	Constant **Time dependent** Partly time dependent Weibull method	To have an adequate reflection of disease progression A time dependent incidence of recurrence should be implemented (M1)
Following local regional recurrence	Constant Time spent on therapy **Time spent in metastatic health state**	Inclusion of time dependency of having metastatic disease after experiencing local recurrence has the best reflection of disease progression (M6)
Recurrence health states	Single metastatic health state **Multiple metastatic health states**	Inclusion of multiple metastatic health states most closely resembles disease progression (M7)
Death rate after metastatic disease	Constant **Time dependent**	Inclusion of time dependency of death after recurrence most closely represents disease progression (M4)

Bold text *= recommended*

In oncology, the differences between competing therapies with respect to efficacy/ patient outcome are small, whereas incremental costs may be very large. Therefore, it is important to not only account for, but also decrease uncertainty as much as possible.

In the current analysis we have shown the substantial impact of including other model components, which is created by differences in choices made by scientists across different analyses. Therefore, we suggest the development of standardized model structures and parameterizations that may reduce the magnitude of variation between analyses. In other disease areas such as rheumatology[37;38] and osteoporosis[39], standardized/reference models have are already been implemented.

We identified four key components related to structural and parameterization components in CEAs of adjuvant breast cancer analyses which are both scientifically well understood, and also significantly affect CEA outcome measures: i) time dependency of recurrence, ii) inclusion of time dependency of having metastatic disease after experiencing local recurrence, iii) inclusion of soft tissue, bone and visceral metastasis health states, and iv) inclusion of time dependency of death after recurrence (**Table 7**).

The use of mortality due to adverse events is scientifically well supported, but has demonstrated to have limited impact on analysis outcome. Nonetheless, this is also considered relevant for inclusion in future CEAs because in other oncology CEAs this could also have considerable effects due to varying transition rates. The importance of accepting and using a standardized model structure for analyzing the long term cost-effectiveness of adjuvant breast cancer therapies needs international collaboration between health economists and clinical researchers.

References

(1) *Briggs AH, Gray AM. Handling uncertainty in economic evaluations of healthcare interventions. BMJ **1999**; 319(7210):635-638.*

(2) *Claxton K, Sculpher M, Drummond M. A rational framework for decision making by the National Institute For Clinical Excellence (NICE). Lancet **2002**; 360(9334):711-715.*

(3) *Spiegelhalter DJ, Best NG. Bayesian approaches to multiple sources of evidence and uncertainty in complex cost-effectiveness modelling. Stat Med **2003**; 22(23):3687-3709.*

(4) *Bojke L,Claxton K, Sculpher M, Palmer S. Characterizing structural uncertainty in decision analytic models: a review and application of methods. Value Health **2009**; 12(5):739-749.*

(5) *Frederix GW, Severens JL, Hovels AM, Raaijmakers JA, Schellens JH. Reviewing the cost-effectiveness of endocrine early breast cancer therapies: influence of differences in modeling methods on outcomes. Value Health **2012**; 15(1):94-105.*

(6) *Kim LG, Thompson SG. Uncertainty and validation of health economic decision models. Health Econ **2010**; 19(1):43-55.*

(7) *R Development Core Team (2011). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL **http://www.R-project.org/**.*

(8) *Petzold LR. Automatic Selection of Methods for Solving Stiff and Nonstiff Systems of Ordinary Differentail Equations. Siam J. Sci.Stat. Comput., 4, 136-148. **1983**.*

(9) *Fonseca M, Araujo GT, Saad ED. Cost-effectiveness of anastrozole, in comparison*

*with tamoxifen, in the adjuvant treatment of early breast cancer in Brazil. Rev Assoc Med Bras **2009**; 55(4):410-415.*

*(10) Gil JM, Rubio-Terres C, Del Castillo A, Gonzalez P, Canorea F. Pharmacoeconomic analysis of adjuvant therapy with exemestane, anastrozole, letrozole or tamoxifen in postmenopausal women with operable and estrogen receptor-positive breast cancer. Clin Transl Oncol **2006**; 8(5):339-348.*

*(11) Hillner BE. Benefit and projected cost-effectiveness of anastrozole versus tamoxifen as initial adjuvant therapy for patients with early-stage estrogen receptor-positive breast cancer. Cancer **2004**; 101(6):1311-1322.*

*(12) Karnon J, Delea T, Barghout V. Cost utility analysis of early adjuvant letrozole or anastrozole versus tamoxifen in postmenopausal women with early invasive breast cancer: the UK perspective. Eur J Health Econ **2008**; 9(2):171-183.*

*(13) Locker GY, Mansel R, Cella D, Dobrez D, Sorensen S, Gandhi SK. Cost-effectiveness analysis of anastrozole versus tamoxifen as primary adjuvant therapy for postmenopausal women with early breast cancer: a US healthcare system perspective. The 5-year completed treatment analysis of the ATAC ('Arimidex', Tamoxifen Alone or in Combination) trial. Breast Cancer Res Treat **2007**; 106(2):229-238.*

*(14) Lux MP, Wockel A, Benedict A, Buchholz S, Kreif N, Harbeck N et al. Cost-effectiveness analysis of anastrozole versus tamoxifen in adjuvant therapy for early-stage breast cancer - a health-economic analysis based on the 100-month analysis of the ATAC trial and the German health system. Onkologie **2010**; 33(4):155-166.*

*(15) Mansel R, Locker G, Fallowfield L, Benedict A, Jones D. Cost-effectiveness analysis of anastrozole vs tamoxifen in adjuvant therapy for early stage breast cancer in the United Kingdom: the 5-year completed treatment analysis of the ATAC ('Arimidex', Tamoxifen alone or in combination) trial. Br J Cancer **2007**; 97(2):152-161.*

*(16) Moeremans K, Annemans L. Cost-effectiveness of anastrozole compared to tamoxifen in hormone receptor-positive early breast cancer. Analysis based on the ATAC trial. Int J Gynecol Cancer **2006**; 16 Suppl 2:576-578.*

*(17) Rocchi A, Verma S. Anastrozole is cost-effective vs tamoxifen as initial adjuvant therapy in early breast cancer: Canadian perspectives on the ATAC completed-treatment analysis. Support Care Cancer **2006**; 14(9):917-927.*

*(18) Skedgel C, Rayson D, Dewar R, Younis T. Cost-utility of adjuvant hormone therapies with aromatase inhibitors in post-menopausal women with breast cancer: upfront anastrozole, sequential tamoxifen-exemestane and extended tamoxifen-letrozole. Breast **2007**; 16(3):252-261.*

*(19) Skedgel C, Rayson D, Dewar R, Younis T. Cost-utility of adjuvant hormone therapies for breast cancer in post-menopausal women: sequential tamoxifen-exemestane and upfront anastrozole. Breast Cancer Res Treat **2007**; 101(3):325-333.*

*(20) Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet **2005**; 365(9453):60-62.*

*(21) Briggs A, Sculpher M. An introduction to Markov modelling for economicevaluation. Pharmacoeconomics **1998**; 13(4):397-409.*

*(22) Borner M, Bacchi M, Goldhirsch A, Greiner R, Harder F, Castiglione M et al. First isolated locoregional recurrence following mastectomy for breast cancer: results of a phase III multicenter study comparing systemic treatment with observation after excision and radiation. Swiss Group for Clinical Cancer Research. J Clin Oncol **1994**; 12(10):2071-2077.*

*(23) Haylock BJ, Coppin CM, Jackson J, Basco VE, Wilson KS. Locoregional first recurrence after mastectomy: prospective cohort studies with and without immediate chemotherapy. Int J Radiat Oncol Biol Phys **2000**; 46(2):355-362.*

*(24) Kamby C, Sengelov L. Pattern of dissemination and survival following isolated locoregional recurrence of breast cancer. A prospective study with more than 10 years of follow up. Breast Cancer Res Treat **1997**; 45(2):181-192.*

(25) Moran MS, Haffty BG. Local-regional breast cancer recurrence: prognostic groups

based on patterns of failure. Breast J **2002**; 8(2):81-87.

(26) Schmoor C, Sauerbrei W, Bastert G, Schumacher M. Role of isolated locoregional recurrence of breast cancer: results of four prospective studies. J Clin Oncol **2000**; 18(8):1696-1708.

(27) Toonkel LM, Fix I, Jacobson LH, Wallach CB. The significance of local recurrence of carcinoma of the breast. Int J Radiat Oncol Biol Phys **1983**; 9(1):33-39.

(28) Coates AS, Keshaviah A, Thurlimann B, Mouridsen H, Mauriac L, Forbes JF et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. J Clin Oncol **2007**; 25(5):486-492.

(29) Saphner T, Tormey DC, Gray R. Annual hazard rates of recurrence for breast cancer after primary therapy. J Clin Oncol **1996**; 14(10):2738-2746.

(30) Chen RC, Lin NU, Golshan M, Harris JR, Bellon JR. Internal mammary nodes in breast cancer: diagnosis and implications for patient management -- a systematic review. J Clin Oncol **2008**; 26(30):4981-4989.

(31) Fisher B, Jeong JH, Bryant J, Anderson S, Dignam J, Fisher ER et al. Treatment of lymph-node-negative, oestrogen-receptor-positive breast cancer: long-term findings from National Surgical Adjuvant Breast and Bowel Project randomised clinical trials. Lancet **2004**; 364(9437):858-868.

(32) Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer **2007**; 109(9):1721-1728.

(33) Hines SL, Vallow LA, Tan WW, McNeil RB, Perez EA, Jain A. Clinical outcomes after a diagnosis of brain metastases in patients with estrogen- and/or human epidermal growth factor receptor 2-positive versus triple-negative breast cancer. Ann Oncol **2008**; 19(9):1561-1565.

(34) Haffty BG, Yang Q, Reiss M, Kearney T, Higgins SA, Weidhaas J et al. Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. J Clin Oncol **2006**; 24(36):5652-5657.

(35) Cianfrocca M, Goldstein LJ. Prognostic and predictive factors in early-stage breast cancer. Oncologist **2004**; 9(6):606-616

(36) National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. London: NICE, **2008**. 2012.

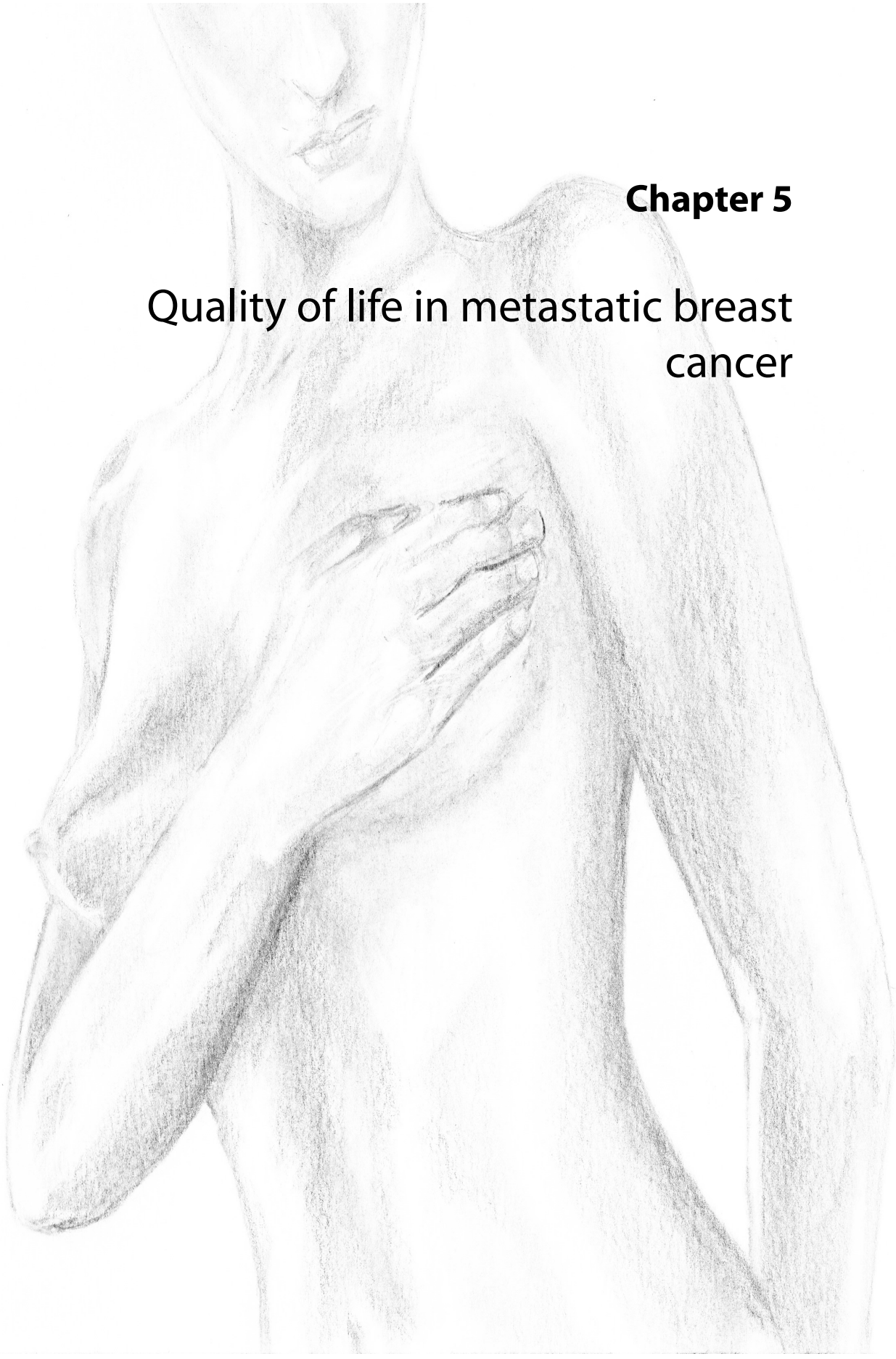
(37) Drummond M, Maetzel A, Gabriel S, March L. Towards a reference case for use in future economic evaluations of interventions in osteoarthritis. J Rheumatol Suppl **2003**; 68:26-30.

(38) Gabriel SE, Tugwell P, Drummond M. Progress towards an OMERACT-ILAR guideline for economic evaluations in rheumatology. Ann Rheum Dis **2002**; 61(4):370-373.

(39) Coyle D, Tosteson AN. Towards a reference case for economic evaluation of osteoporosis treatments. J Rheumatol Suppl **2003**; 68:31-36.

4

Part II
Metastatic breast cancer



Chapter 5

Quality of life in metastatic breast cancer

Chapter 5

Utility and work productivity data for economic evaluation of breast cancer therapies in the Netherlands and Sweden

Gerardus W.J. Frederix[§]
Nuz Quadri[§]
Anke M. Hövels
Fleur T. van de Wetering
Hans Tamminga
Jan H.M. Schellens
Andrew J. Lloyd

[§]*Authors contributed equally to this manuscript*

Clinical Therapeutics. 2013 April; 35(4):e1-e7

Abstract

Objective

This study aims to estimate utility values in laypeople and productivity loss for women with breast cancer in Sweden and the Netherlands.

Study Design

To capture utilities, validated health state vignettes were used, which were translated into Dutch and Swedish. They described progressive disease, stable disease, and seven grade 3/4 adverse events. 100 members of the general public in each country rated the states using the visual analogue scale (VAS) and Time Trade Off (TTO) method. To assess productivity, women who had recently completed or were currently receiving treatment for early or advanced breast cancer (The Netherlands =161 and Sweden =52) completed the Work Productivity and Activity Impairment- General Health (WPAI-GH) questionnaire. Data were analysed using means and standard deviations.

Results

The utility study showed that the Swedish sample rated progressive and stable disease (0.61 (95%CI= ±0.07), 0.81 (±0.05)) higher than the Dutch sample (0.49 (±0.06), 0.69 (±0.05)). The health states incorporating the toxicities in both countries produced similar mean scores. Results of the WPAI-GH showed those currently receiving treatment reported productivity reductions of 69% (The Netherlands) and 72% (Sweden); those who had recently completed therapy reported reductions of 41% (The Netherlands) and 40% (Sweden).

Conclusion

The differences in the utility scores between the countries underline the importance of capturing country specific values. The significant impact of adverse events on health related quality of life (HRQL) was also highlighted. The WPAI-GH results demonstrated how the negative impact of breast cancer on productivity persists after women have completed their treatment.

Introduction

Health care expenditures are growing faster than incomes of most developed countries, thereby jeopardizing the stability of health care systems in individual countries and globally. To increase value of health care services, evidence from Comparative Effectiveness Research (CER) is needed to inform health care decision makers.

A large number of health policy decision bodies over the world have incorporated the use of economic evaluations as part of CER in their reimbursement decision process, aiming to assess value for money. In economic evaluations, survival and health-related quality of life (HRQL) are often the main measure of treatment benefit, measured as utilities which range from 0 (dead) to 1 (full health)[1]. In a majority of countries this data is collected using a societal perspective, which means that preferences of the general public are taken into account, as well as all costs directly or indirectly related to the disease and treatment, including productivity losses.

The need for robust data for valid decision making in health care is evident, especially when it comes to costly targeted therapies in severe diseases. However, there are no reports of utility values in some severe diseases, such as in Human Epidermal Growth Factor Receptor 2 positive (HER2+) advanced breast cancer, despite the established need for this data[2,3]. In addition, there has been very little research published on productivity losses due to metastatic breast cancer in general[4]. Some research in the United States has examined the national impact of cancer mortality and productivity loss[5,6]. However, much less is known regarding the effects of breast cancer on individual level productivity loss[7].

To overcome the lack of utility and productivity data in certain countries, 'foreign' data from other countries has been used to apply to another jurisdiction, examples of which are present in literature. For example, the use of Swedish utility data for a Dutch cost-effectiveness analysis of Trastuzumab[8]. However, doubts have been expressed regarding the transferability of utility data from one jurisdiction to another[9], indicating that national decision makers should avoid accepting 'foreign' data without demonstrating pertinence for their own country. Although the results of clinical studies of pharmaceuticals can be generalised from one jurisdiction to another, the results of economic evaluations have been reported to be location dependent, due to factors such as demography and the epidemiology of disease, differences in clinical practice patterns, and differences in relative prices[10].

Differences in national guidelines regarding utility measurements may further limit the transferability of preference weights from one country to another,[9] as reimbursement

agencies in different countries may have specific criteria in terms of the demographics of the 'societal perspective'. An example of this is in the Netherlands and Sweden as both countries have different formal requirements for cost-effectiveness analyses from a societal perspective, thus the transferability of data between these countries could be questioned. The Dutch reimbursement agency advocates preferences to be representative of the general public[11]. In contrast, the Swedish reimbursement agency prefers to see utilities derived from members of the public with the same demography as people with the disease[12]. In the case of breast cancer, this would be the inclusion of only older female participants. With such differences outlined in how data should be collected, it could be beneficial for economic analyses to be performed in both countries to adequately collect robust and valid data, rather than transfer data between these countries.

This study had two aims: one to elicit utilities for HER2+ advanced breast cancer health states in Sweden and the Netherlands, in order to assess whether it is beneficial to capture country specific utility data. A second aim of this study was to understand the impact of early and advanced breast cancer on work productivity in both countries.

Methods

Health state description development

Health state descriptions of stages of HER2+ advanced breast cancer were developed and validated based on in depth qualitative interviews with women with advanced breast cancer and oncology experts. The health states included: progression free survival (stable disease), disease progression, and seven grade 3-4 adverse events of treatment for HER2+ advanced breast cancer: diarrhoea, fatigue, anaemia, leukopenia, anorexia, decreases in left ventricular ejection fraction, and skin rash. These health states were used in a valuation exercise to elicit utility values.

Health state valuation

During the study procedures, participants completed a background questionnaire and the EQ-5D, a generic HRQL measure[13], followed by a warm up task where they were asked to rate the health states from 0 to 100 using a VAS. The anchors for the VAS were 'full health' at 100 and 'dead' at 0. Participants proceeded onto completing the TTO exercise[14]. For the TTO exercise, the health states were presented in a random order and participants were asked to choose between remaining in the health state for 10 years or in full health for 10-x years. The time in full health was then varied until the participant became indifferent between the two prospects. A 'ping-pong' method which contrasted longer and shorter durations of time was used. The method did not assess states worse than dead.

Measurement of productivity loss

The WPAI-GH[15] was used to estimate the degree of productivity loss experienced by advanced breast cancer women in both countries. The WPAI-GH produced summary scores for: absenteeism (work time missed); presenteeism (impairment at work / reduced on-the-job effectiveness); work productivity loss (overall work impairment / absenteeism plus presenteeism); and activity impairment (impact on usual daily activities).

Participants health state valuation

For the utility study, a hundred members of the general public were recruited in the Netherlands and Sweden to participate in a valuation exercise. In Sweden, recruitment was aimed at females aged over 50 in order to try to match the socio-demographic profile of women suffering from HER2+ advanced breast cancer. In the Netherlands participants were from both genders, and of mixed age. The sampling strategy used was to recruit participants that represented the preferenced population as closely as possible in each country. Participants were recruited into the study by word of mouth and by placing newspaper adverts to generate interest. All interviews were conducted in the native language and all forms that were presented to participants were translated into the native language.

Participants productivity loss

For the work productivity survey, a hundred and sixty one participants with breast cancer in the Netherlands were recruited from an existing market research panel. In Sweden a similar commercial panel was used and 52 women with breast cancer completed the survey. Patients in both countries had actively sought participation in health research, and were listed on an existing patient database. Written informed consent was obtained from all participants and the study was conducted in accordance with the Helsinki Declaration 1975, as revised in 2008. Data collection was run according to the ESOMAR, the European Market Research Organisation which has an ethical code of conduct.

Results

Participant characteristics health state valuation

Comparing the characteristics of the two general public samples showed an obvious shift in gender and age ranges due to sampling strategies used (**Table 1**)

Table 1. *Participant characteristics of sample per country*

	Sweden (n=100)	The Netherlands (n=100)
Age		
18-29	0	48
30-49	0	34
50-59	51	13
60-69	37	5
70+	12	0
Gender		
Female	100%	50%
Employment Status		
Full time employed	42	53
Part time employed	21	19
Student	0	19
Retired	30	4
Sick leave/ unable to work	3	0
Other	30	5
Education		
Left school at 16 with qualifications /VBO	17	7
Left school at 18 with qualifications /MBO	27	22
Completed college/HBO	32	23
Completed university	24	48

**All participants are healthy members from the general public recruited both in the Netherlands and Sweden*

Utility study

The VAS ratings and utilities from both countries were quite consistent and revealed a very similar ranking of health states in terms of their impact on HRQL (**Table 2**). The relative ordering of states between the two countries is similar but the absolute values were somewhat different. The largest difference between the countries was for the two base states - stable disease and progressive disease. Grade III skin rash, diarrhoea and left ventricular ejection fraction were rated to have the greatest impact on HRQL (as rated by

Table 2. *Mean health state utilities and VAS ratings per country*

	Sweden		The Netherlands	
Health State[a]	**TTO[b] Utility Mean *(SD[c])***	**VAS[d] Mean *(SD[c])***	**TTO[b] Utility Mean *(SD[c])***	**VAS[d] Mean *(SD[c])***
Stable disease	0.81 *(0.23)*	66.8 *(22.37)*	0.69 *(0.25)*	59.2 *(17.73)*
Diarrhoea	0.52 *(0.31)*	36.8 *(19.90)*	0.50 *(0.25)*	45.9 *(14.93)*
Fatigue	0.64 *(0.30)*	45.1 *(20.91)*	0.56 *(0.27)*	47.9 *(16.24)*
Anaemia	0.69 *(0.29)*	52.0 *(20.39)*	0.59 *(0.26)*	49.2 *(17.91)*
Leukopenia	0.58 *(0.31)*	40.9 *(18.63)*	0.60 *(0.26)*	51.1 *(16.86)*
Anorexia	0.56 *(0.30)*	41.6 *(23.00)*	0.66 *(0.24)*	54.4 *(16.77)*
Skin rash	0.58 *(0.31)*	43.3 *(22.05)*	0.54 *(0.27)*	33.0 *(26.10)*
Decrease in LVEF	0.54 *(0.29)*	36.8 *(19.34)*	0.47 *(0.25)*	42.0 *(18.03)*
Progressive disease	0.61 *(0.34)*	39.5 *(24.06)*	0.49 *(0.31)*	44.5 *(22.14)*

[a] *All adverse events are grade III-IV*
[b] *TTO = Time Trade Off*
[c] *SD = Standard Deviation*
[d] *VAS = Visual Analogue Scale*

There were important differences between the profiles of the samples: the sample from Sweden reported overall worse HRQL on the EQ-5D compared with the Dutch sample. Nearly half of the Swedish sample reported some pain and a quarter reported some anxiety or depression. In the Dutch sample, the reported rates of anxiety or depression and pain were 2% and 9% respectively.

Work productivity survey

Fifty one percent of the patients in the sample were currently working in a job. Of the 213 respondents to the survey across both countries who reported breast cancer, 51 (24%) reported that it was metastatic. The data from the productivity survey indicates the impact of participants' health problems on their ability to work (**Table 3**). Women from both countries reported substantial limitations in their usual activities. Women who had recently completed treatment also reported on average that about 20-25% of their work time in the previous week they were absent due to ill health. In addition about 20-30% of their time at work was non-productive.

Table 3.*Work productivity results from the WPAI-GH per country*

	Percent work time missed due to ill health (absenteeism)	Percent impairment while working (presenteeism)	Overall work impairment due to health (work productivity)	Activity impairment
The Netherlands (n=161)				
Currently have breast cancer (n=38)	56%	34%	69%	62%
Had breast cancer in recent past (n=123)	21%	30%	41%	41%
Sweden (n=52)				
Currently have breast cancer (n=8)	61%	30%	72%	55%
Had breast cancer in recent past (n=44)	25%	21%	40%	35%

**All participants are currently having or had breast cancer in recent past*

Discussion

This study was designed to estimate utility weights for HER2+ advanced breast cancer health states in Sweden and the Netherlands, and to capture data regarding the impact of breast cancer on productivity. Some interesting differences emerged in the utility scores between the countries which underlines the importance of capturing country specific values. These differences in scores are most likely due to the difference in demography in both countries, as the Netherlands data used an approach where the general population was included, and the Swedish data used an approach where the sample was representative of breast cancer demography.

The Swedish participants rated both stable disease and progressive disease higher than the Dutch sample. This finding could be explained by highlighting this difference in demography.

Data from both countries also underlines the significant impact of some of the adverse events on HRQL. All of the adverse events were described in the health states to reflect grade 3-4 toxicity which was confirmed with the physicians. The general public recognised the severity of these adverse events. When making treatment decisions at national level or individual level we believe that oncologists and policy makers should consider the importance of adverse events alongside other factors such as efficacy. The degree to which toxicities can affect HRQL and the fact that these patients have a much reduced life

expectancy should be considered in decision making.
These are important sources of variation and will have an effect on the resulting cost effectiveness of a treatment. By capturing weights in Sweden and the Netherlands, rather than relying on published weights from other countries, the present study should support more accurate estimates of cost effectiveness in these countries, thereby increasing the efficient allocation of scarce health care resources in both countries.

Because both countries demand different preferences for utility valuations, the Swedish participants were older than the Dutch sample and only included female participants. As the Swedish participants were generally older than the Dutch sample they may have a different perspective when they are asked to consider trading years of life in the TTO task compared to younger people from the Dutch sample resulting in higher ratings for both stable and progressive disease. In addition, some of the differences may be explained by the fact that the Swedish sample reported worse health status on the EQ-5D than the Dutch sample. The experience of health problems may make participants less concerned about the prospect of poor health states which would effectively give such states a higher preference weight. Again, the worse health status on the EQ-5D could also be caused by the differences in age because older people are likely to value their current health lower compared to younger people. These examples indicate that the differences observed between countries in utility valuation are likely to be caused by the large differences in age, which in turn is related to the difference in preference requirements by reimbursement agencies between both countries.

The productivity data also provide important information regarding the extent to which women are able to continue working while they receive treatment and after they have completed treatment. As expected women receiving treatment (for either primary or advanced disease) reported that their ability to work was greatly reduced, although some persevered. Women who were currently receiving treatment and those who had finished reported greatly reduced levels of work and non-work related activity. The women and oncologists who took part in our interviews commented that as far as possible women are encouraged to return to work in Sweden and the Netherlands. These results indicate a significant impact on costs outside health care due to breast cancer, underlining the relevance of a societal perspective in decision making in these countries.

There are some limitations to the study which should be considered. To develop the health states we undertook some interviews with women with advanced breast cancer in each country. These interviews were designed to review and confirm or edit the contents of the states, however there was quite substantial idiosyncratic variation between the women, and their responses provided different information to what was identified from the

literature. Due to these differences, the health states may not be entirely representative of advanced breast cancer as experienced by women in each country. Also the adverse events were only reviewed by clinicians because it was not possible to identify women who had experienced these adverse events.

The two samples recruited for the utility study were selected to match the requirements of the respective agencies in each country. For the Netherlands the sample included men and women, of different ages. As participation in this study was completely voluntary, with an incentive to reimburse participants for their time, the sampling strategy became somewhat opportunistic as older participants were less likely to want to participate in such research. Although, the age characteristic is therefore not accurately represented in the age groups according to official statistics for the Netherlands, the sample was distributed reasonably over different age categories and gender.

The women in the productivity survey were a convenience sample and so may not be representative of women with advanced breast cancer generally. While the WPAI-GH has been reported to be valid and has been very widely used, no independent verification of the productivity data was obtained. Unfortunately, a small number of patients currently having breast cancer in Sweden was included. Due to this small number, conclusions are difficult to make for this individual example. More patients would be needed in this group to come to more reliable outcomes, and therefore no explicit conclusions are made between both countries regarding work productivity of patients currently experiencing breast cancer.

It could be questioned as to whether it is appropriate for both men and women to judge the value or HRQL of a state of health which is gender specific (such as breast cancer). In the present study the health states were deliberately designed to be gender neutral in their description of the disease and its impact on HRQL. In addition the impact of the disease is described in terms of different domains of HRQL such as physical functioning and mental health. On this basis, we believe that it is quite possible and appropriate for men to provide valid ratings for health states for diseases that they will not experience.

Furthermore, direct quantification and interpretation of differences in utilities found in this study and published utilities is unfortunately not possible due to the differences in valuation methods and in who conducted the valuation[16].

In conclusion this study has captured country specific utilities for health states related to HER2+ advanced breast cancer. Important differences emerged in the utility scores between the countries which underlines the importance of capturing country specific

values to improve the validity of the resulting cost effectiveness analysis. Differences in the requirements of reimbursement agencies in Sweden and the Netherlands in terms of the participant samples that are appropriate has led to various differences in the resulting utilities. In addition, our data show that breast cancer has a significant impact on productivity loss of patients in both countries.

Acknowledgements

The authors would like to acknowledge the following people who assisted with data collection: E. Roddick, E. Stolk, J. Groot, J. Gutteling, and U. Talenti.

References

(1) *Drummond MF, Sculpher MJ, Torrance. GW, O'Brien B, Stoddart GL, Methods for the economic evaluation of health care programmes. Oxford university Press;**2005**.*

(2) *Lloyd A, Nafees B, Narewska J, DeWilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer. **2006**; 95:683-690*

(3) *Perez D, Williams S, Christensen E, McGee R. A longitudinal study of health related quality of life and utility measures in patients with advanced breast cancer.Qual Life Res. 2001;10:587-593 **2001**.*

(4) *Foster TS, Miller JD, Boye ME, Blieden MB, Gidwani R, Russell MW. The economic burden of metastatic breast cancer: a systematic review of literature from developed countries. Cancer Treat Rev **2011**; 37 (6):405-415.*

(5) *Bradley CJ, Yabroff KR, Dahman B, Feuer EJ, Mariotto A, Brown ML. . Productivity costs of cancer mortality in the United States: 2000-2020.J Natl Cancer Inst **2008**; 100: 1763-70*

(6) *Ekwueme DU, Chesson HW, Zhang KB, Balamurugan A. Years of potential life lost and productivity costs because of cancer mortality and for specific cancer sites where human papillomavirus may be a risk factor for carcinogenesis-United States, 2003.Cancer. **2008**;113 (10 Suppl):2936-45*

(7) *Lavigne JE, Griggs JJ, Tu XM, Lerner DJ. Hot flashes, fatigue, treatment exposures and work productivity in breast cancer survivors. J Cancer Surviv. **2008**;2:296-302*

(8) *Essers BA, Seferina SC, Tjan-Heijnen VC, Severens JL, Novak A, Pompen M, Oron UH, Joore MA. Transferability of model-based economic evaluations: the case of trastuzumab for the adjuvant treatment of HER2-positive early breast cancer in the Netherlands. Value Health, **2010**; 4: 375-380*

(9) *Knies S, Evers SM, Candel MJ, Severens JL, Ament AJ. Utilities of the EQ-5D: Transferable or Not? Pharmacoeconomics. **2009**;27:767-79*

(10) *Drummond,M.F.; Bloom,B.S.; Carrin,G.; Hill man,A.L.;Hutchings,H.C.;Knill-Jones,R.P.; de Pouvourville,G.; Torfs,K.Issues in the cross-national assessment of health technology. nt J Technol Assess Health Care 8, 671- 682 (**1992**).*

(11) *College voor Zorgverzekeringen (CVZ). Guidelines for pharmacoeconomic research. Actualized version. [In Dutch: Richtlijnen voor farmaco-economisch onderzoek, geactualiseerde versie], College voor Zorgverzekeringen,Diemen **2006**.*

(12) *Läkemedelsförmånsnämnden. General guidelines for economic evaluations from the Pharmaceutical Benefits Board (LFNAR*

2003:2) http://www.tlv.se/in-english/

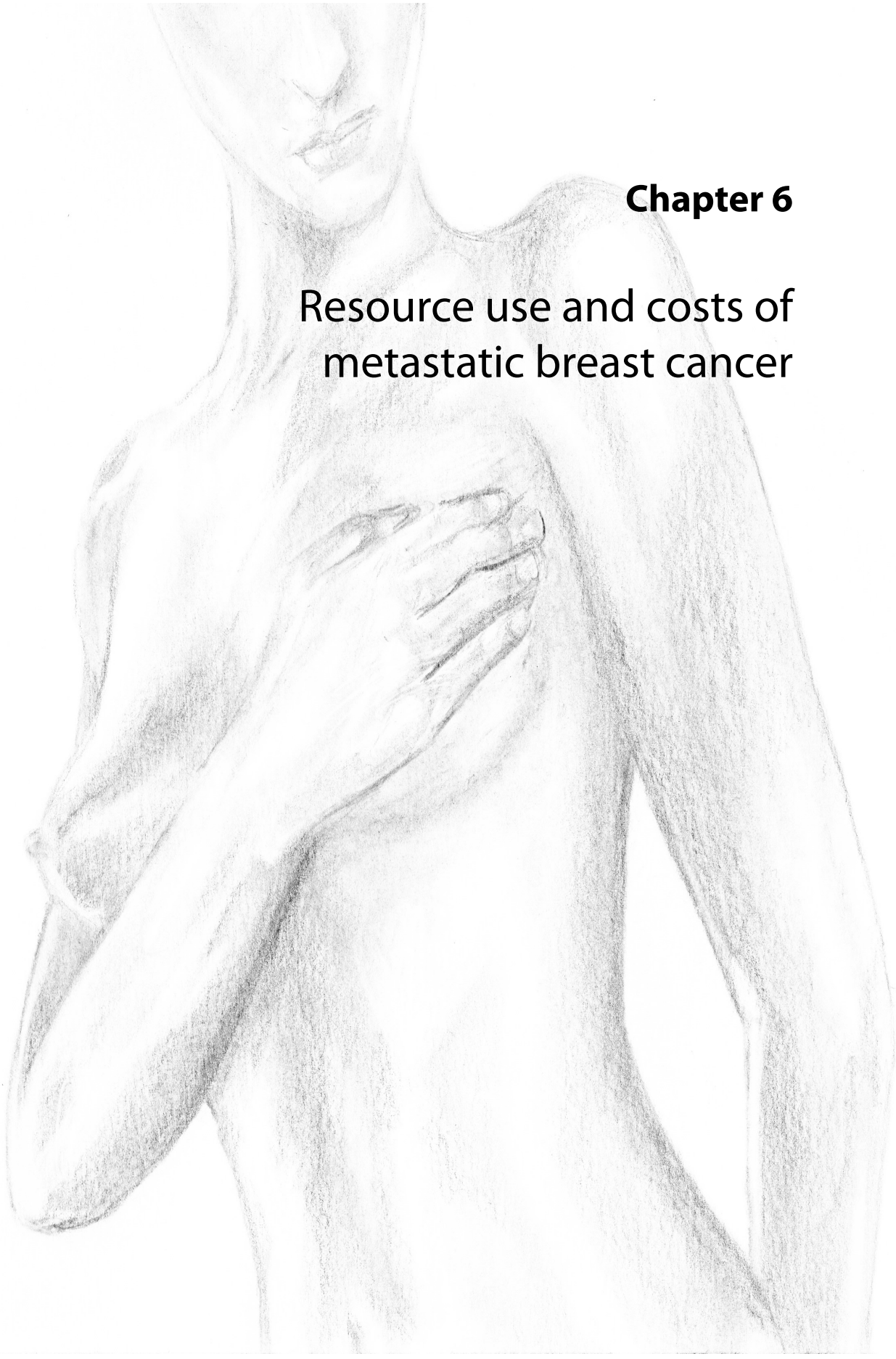
(13) Brooks R. EuroQol: the current state of play. Health Policy ***1996***;37:53

(14) Bennett KJ, Torrance GW. Measuring health state preferences and utilities: rating scale, time trade-off, and standard gamble techniques. In Spilker B, (ed). Quality of Life and Pharmacoeconomics in Clinical Trials. Philadelphia, PA: Lippincott-Raven Publishers; ***1996***: p.253-265

(15) Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics ***1993***; 4: 353-65

(16) Peasgood T, Ward SE, Brazier J. Health-state utility values in breast cancer. Expert Rev Pharmacoecon Outcomes Res ***2010***; 10(5):553-566.

5



Chapter 6

Resource use and costs of metastatic breast cancer

Chapter 6.1

Real world cost of HER-2 positive metastatic breast cancer patients:

a longitudinal incidence based observational costing study in the Netherlands and Belgium

Gerardus W.J. Frederix
Johan L. Severens
Anke M. Hövels
Johan G.C. van Hasselt
Michel J.J. Hooiveld
Patrick Neven
Jan A.M. Raaijmakers
Jan H.M. Schellens

Submitted for publication

Abstract

Introduction

Currently no country specific metastatic breast cancer (MBC) observational costing data is available for the Netherlands and Belgium. The objective of this research is to describe country specific resource use and costs of human epidermal receptor 2 (HER-2) positive MBC in the Netherlands and Belgium making use of real world patient data.

Methods

The eligibility period for patient selection was from April 2004 to April 2010. Inclusion and retrospective data collection begins at the time of first diagnosis of HER-2 positive MBC during the eligibility period and ends 24 months post index diagnosis of MBC or at patient death. Resource use was analyzed from a health care payer perspective and all volumes and costs were expressed in mean, median and range.

Results

We identified 88 eligible patients in the Netherlands and 44 patients in Belgium. Total costs of medical treatment and other resource use utilization amounted to a mean per patient of €48,301 (median: €40,953; range: €122 – €178,314) in the Netherlands and €37,431 per patient (median: €32,632; range; €1,349 – €105,124) in Belgium. Majority of costs was related to use of trastuzumab in both countries, which was 50% of total costs in the Netherlands and 56% in Belgium, respectively.

Conclusion

Our study provides estimates of resource use and costs for (HER-2) positive MBC in the Netherlands and Belgium. We noticed essential differences in resource use between both countries demonstrating the need for country specific resource use data instead of transferring cost estimates, or even resource volume data from other countries.

Introduction

In recent decades several treatment improvements have been achieved that prolong life and maintain quality of life of patients diagnosed with metastatic breast cancer (MBC)[1;2]. However, questions are often being raised about the value of such improvements as they also put a large burden on health care system resources[3;4].

To enable an effective use of these limited health care resources, cost-effectiveness analyses (CEAs) are used, aimed at comparing costs and health-related consequences of at least two alternative treatments[5]. One of the essential components of these CEAs are costing studies, providing an overview of resource use and costs of specific diseases.

Costing studies can be set up using specifically developed costing instruments for prospective data collection, retrospective use of primary data from patient files or analyzing secondary datasets originating from insurance databases or interviews with physicians[6]. In a recent review[7] it was identified that only five studies investigated the costs of MBC using primary patient data[7-12] and a majority made use of secondary data. A disadvantage of the secondary data sets, as compared to the data originating from a patient level, is that they are likely to generate incomplete overviews[6]. In addition, none of these published MBC costing studies has primarily focussed on patient having an overexpression of human epidermal growth factor receptor 2 (HER-2) on tumour tissue, a clinical and economic relevant subgroup.

Up to approximately 25% of patients diagnosed with MBC have such a HER-2 over expression, which is usually associated with a more aggressive tumour phenotype, and a poor overall prognosis[13]. Optimal first-line treatment for these patients is the expensive monoclonal antibody trastuzumab, which interferes with the HER-2 receptor[13]. Despite the high costs of treatment, and therefore the established need for reliable data, currently no HER-2 positive MBC costing data, obtained from observational data, is available in the literature.

The **objective** of this study was to describe the country specific resource use and costs of HER-2 positive MBC in the Netherlands and Belgium making use of primary, real world, patient data.

Methods

Design

Resource use and costs were analyzed using longitudinal patient data derived from patient medical records. For this reason, a health care perspective was used for the analysis.

Patient selection

In the Netherlands, MBC patients were identified in three different hospitals. In Belgium eligible patients were identified in one single hospital. The inclusion period for selection was from April 2004 to April 2010.

Inclusion criteria were: women with HER-2 positive MBC (either de novo or recurrent) during the eligibility period (i.e. an index diagnosis), 18 years of age or older at time of index diagnosis, known hormonal status of the tumour and known sites of metastases.

Patients were not eligible when they participated in Phase I and II clinical trials during the study period, i.e. the period from MBC diagnosis up to 24 months, and patients who were in the treatment arm of Phase III clinical trials during the study period. Patients in a phase III trial control arm were eligible as these patients underwent normal daily practice.

Study period

For eligible HER-2 positive MBC patients, inclusion and collection of resource use begins at the time of first diagnosis of MBC. Data collection proceeds during the eligibility period and ends 24 months post index diagnosis of MBC or at patient death, or at loss to follow-up, if either of these events occur earlier. Duration of study period was set at 24 months as in recent trials median overall survival of HER-2 positive MBC patients was estimated at 17.3 months[14].

Data collection

We incorporated five categories of data: patient demographics, MBC clinical history, medical treatment, other MBC related resource utilizations and clinical outcomes (date of progression and death). The following demographic outcomes were collected at time of index diagnosis: sex, height and weight.

MBC clinical history data were collected consisting of date of initial breast cancer diagnosis, date of MBC diagnosis, physician type who confirmed the index diagnosis, type of breast cancer, classification: de novo metastatic disease or recurrent metastatic disease, stage of breast cancer at diagnosis (IIB, IIC, III and IV), sites and total number of metastases, menopausal status at time of index diagnosis and co morbidities.

Medical treatment data consisted of pharmacotherapeutic treatment during the study

period, start date, end date, dose, number of cycles (IV therapies), cycle duration, treatment days per cycle, unit route of administration and modifications of the prescribed treatment regimen.

The following additional MBC related resource utilization was collected: in-patient hospital stays (including unit and/or type of ward, admission date, discharge date and ward transfers), health care professional visits/consultations, accident and emergency visits, surgical and non-surgical procedures, laboratory tests, radiotherapy and imaging and transfusions.

Clinical outcomes consisted of patient's vital status at the end of study period, date of death, primary cause of death and date of first determination of disease progression following index diagnosis of MBC.

Unit costs

Dutch costing-guideline prices were used for therapy costs[15], other resource use unit costs were derived from Dutch reference prices[16;17], unless specified otherwise. Therapy costs for Belgium were mainly derived from Belgium prices[18;19] and other resource unit costs from Belgium costing-guideline prices[20], unless specified otherwise. All costs were expressed in Euros using the 2012 price level. When costs in one country were not available, identical costs as in the other country were taken.

Data analysis

Volumes obtained from the data collection were multiplied with unit costs and were expressed in mean, median and range averaged over all patients included in our study. In addition to the average per patient outcomes, we also analyzed the percentage of patients being treated/indicated with each therapy and the percentage which have used other resources. All assessed costs were categorized in pharmacotherapeutic treatment and other MBC related costs, which were further categorized in respectively sort of therapy and sort of other MBC related costs. Total costs per patient per category were calculated with mean, median, range and 2.5 and 97.5 percentiles.

The mean total costs per patient corrected for censoring were calculated using a partitioned inverse probability weighting (IPW)-based estimator, as described by Bang and Tsiatis[21]. Briefly, the observation period was divided into 24 one-month intervals. The intervals costs in each patient uncensored at the end of a partition were weighted by a Kaplan-Meier based estimator describing the probability of not being censored. Subsequently the IPW-corrected costs were summed by interval and individual and divided by the number of patients to obtain the IPW-corrected mean population cost.

Results

The Netherlands

Study population and clinical outcomes

We identified 88 patients in three different hospitals in the Netherlands. The mean age of patients at diagnosis was 55 years (range 32-89). The majority of patients was diagnosed with ductal carcinoma, most common sites of metastatic disease were visceral tissue and bone, respectively diagnosed in 49 and 48 patients **(Table 1)**. Of these patients, 31 died within the two years of follow up with a mean overall survival of 286 days (range, 20 – 690).

Table 1. Characteristics of the study population

	Netherlands		Belgium	
Patients (n)	88		44	
Age (range)	55 (32-83)		56 (32-84)	
	(n)	(%)	(n)	(%)
Type of breast cancer				
lobular	7	7.95%	2	4.55%
ductal	81	92.05%	34	77.27%
Luminal type A and B	0	0.00%	2	4.55%
Unknown	0	0.00%	6	13.64%
Classification				
De novo	47	53.41%	40	90.91%
recurrent	24	27.27%	4	9.09%
Unknown	17	19.32%	0	0.00%
Hormonal status				
ER positive	34	38.64%	13	29.55%
ER negative	54	61.36%	31	70.45%
Sites of metastatic disease*				
Visceral tissue	49	41.18%	26	41.94%
Soft tissue	3	2.52%	1	1.61%
Bone	48	40.34%	21	33.87%
Brain	6	5.04%	2	3.23%
Other	13	10.92%	12	19.35%
Menopausal status				
pre	17	19.32%	7	15.91%
Peri	4	4.55%	1	2.27%
Post	58	65.91%	25	56.82%
Unknown	9	10.23%	11	25.00%

** More then one site is possible per patient*

Pharmacotherapeutic treatment

For each individual patient a complete medication overview was generated including modifications to dose, cycle length and cycle duration. In **table 2** an overview is given of the unit price, mean volume, number of doses, median, range and mean cost per patient. In the Netherlands, total cost of pharmacotherapeutic treatment was €29,273 per patient of which chemotherapeutic and biological treatments were the main cost drivers. In addition, the percentage of patients treated with each sort of therapy is presented with mean, median and range.Based on an average of 30 doses, chemotherapy amounted to a mean cost of €4,266 (median; €2,721) per patient (**Table 6**). Docetaxel and paclitaxel accounted both for 33.1% of these costs with respectively 1.5 and 3.0 doses per patient. In total, 13.6% of the patients was treated with docetaxel and 38.6% with paclitaxel (**Table 2**).

Treatment with biologicals amounted to a total cost of €24,960 (median; €24,960) per patient of which 96.8% was related to trastuzumab with on average 56.9 doses per patient (median; 35.7). In total 69.3% of the patients was treated with trastuzumab with on average 82.1 doses and a cost per user of €34.859 (**Table 2**).

Other MBC related resource utilization

Total costs of other resource utilization was €19,025 per patient (**Table 3**). Categories with highest costs were health care professional visits, hospital stays and imaging. Patients visited on average 79 times a health care professional with total costs of €7,734 (median; €6,329), corresponding to 40.6% of total other resource utilization costs. Day care visits, which occurred in 95.4% percentage of patients, were the main cost driver with respectively 35.3 mean (median; 33.0) visits per patient over all patients, thereby representing a total of 83% of the costs for health care professional visits. Patients were hospitalized on average for 13.67 days, with a total cost of €6,675 (median; €3,096), thereby corresponding to 34.0% of total costs of other MBC related resource utilization. Stays in the oncology department (8.0 days on average) accounted for 56.8% of these costs and in total 45.5% of the patients was hospitalized on the oncology department for a certain moment during the 24 months of follow up. Imaging costs had a total of €2,369 (median; €2,108), thereby representing 12.5% of total other resource utilization cost. Surgical procedures, laboratory tests, radiotherapy, accident and emergency visits and transfusions respectively accounted for €118, €711, €666, €719 and €36 per patient.

Total MBC costs per patient

Total MBC costs per patient in the Netherlands was €48,301 (median; €40,953), of which 60.6% was related to costs of pharmacotherapeutic treatment and 39.4% to other MBC related resource utilization. IPW-corrected mean total costs were € 48,996 per patient.

Table 2. *Medical treatment costs per patient in the Netherlands*

	Average over all patients					Treated patients				
Medical treatment	**Price per dose (€)**	**Mean # of doses**	**Median # of doses**	**Range of doses**	**Mean cost per patient (€)**	**% treated**	**Mean # of doses**	**Median # of doses**	**Range of doses**	**Mean cost per treated patient (€)**
Hormonal therapy										
Anastrazole (1 mg)	0.05[15]	4.4	0.0	0-328	0	2.3	204.0	204.0	80-328	9
Exemestane (25 mg)	0.25[15]	4.4	0.0	0-327	1	2.3	195.0	195.0	63-327	48
Letrozole (2,5 mg)	0.06[15]	29.5	0.0	0-725	2	6.8	433.1	424.0	26-725	25
Tamoxifen (20 mg)	0.09[15]	7.7	0.0	0-188	1	5.7	135.8	153.0	28-188	12
Chemotherapy										
Capecitabine (4500 mg)	27.28[15]	16.0	0.0	0-258	437	21.6	74.3	50.4	9-258	2,026
Carboplatin (150 mg)	116.16[15]	1.0	0.0	0-52	114	3.4	28.8	24.7	10-52	3,343
Cyclophosphamide (1080 mg)	44.82[15]	0.6	0.0	0-17	25	13.6	4.1	3.1	1-17	183
Docetaxel (108 mg)	951.80[22]	1.5	0.0	0-63	1,436	13.6	11.1	6.8	1-63	10,528
Doxorubicin (90 mg)	204.00[15]	0.8	0.0	0-30	171	14.8	5.7	4.4	1-30	1,158
Fluorouracil (1800 mg)	174.43[15]	0.0	0.0	0-1	2	6.8	0.1	0.1	1-1	25
Methotrexate (5 mg)	0.36[15]	0.2	0.0	0-156	0	1.1	156.0	156.0	156-156	56
Paclitaxel (315 mg)	476.18[18]	3.0	0.0	0-21	1,429	38.6	7.8	7.4	1-21	3,698
Vinorelbine (36 mg)	90.00[23]	7.2	0.0	0-89	652	20.5	35.4	26.9	1-89	3,185
Biologicals										
Bevacizumab (500 mg)	1,976.91[24]	0.1	0.0	0-7	152	1.1	6.8	6.8	7-7	13,365
Lapatinib (1000 mg)	69.65[15]	9.2	0.0	0-525	644	3.4	271.2	183.8	105-525	18,893
Trastuzumab (284 mg)	424.74[25]	56.9	35.7	0-215	24,164	69.3	82.1	82.4	1-215	34,859

Table 2. Continued. *Medical treatment costs per patient in the Netherlands*

	Average over all patients					Treated patients				
Medical treatment	**Price per dose (€)**	**Mean # of doses**	**Median # of doses**	**Range of doses**	**Mean cost per patient (€)**	**% treated**	**Mean # of doses**	**Median # of doses**	**Range of doses**	**Mean cost per treated patient (€)**
Anti-emetics										
Dexamethasone (oral) (10 mg)	0.64[15]	9.2	0.0	0-301	6	21.6	42.8	13.2	2-301	28
Dexamethasone (intravenous) (5 mg)	3.41[15]	8.9	0.0	0-54	30	42.0	21.1	14.4	5-54	72
Granisetron (oral) (2 mg)	0.47[15]	4.3	0.0	0-27	2	33.0	13.2	12.0	3-27	6
Granisetron (intravenous) (1 mg)	4.41[15]	0.7	0.0	0-24	3	6.8	10.0	7.5	3-24	44
Metocloperamide (oral) (10 mg)	0.02[15]	8.7	0.0	0-384	0	5.7	152.4	48.0	36-384	3
Ondansetron (oral) (8 mg)	6.01[15]	0.4	0.0	0-18	3	4.5	9.7	9.0	3-18	59
Ondansetron (intravenous) (8 mg)	0.13[15]	0.4	0.0	0-34	0	1.1	34.0	34.0	34-34	4
Other										
Ranitidine (oral) (50 mg)	1.04[15]	0.3	0.0	0-18	0	2.3	12.0	12.0	6-18	12
Ranitidine (intravenous) (75 mg)	0.21[15]	3.1	0.0	0-18	1	30.7	10.2	12.0	3-18	2
Biphosphonates (10 mg)	0.01[15]	4.5	0.0	0-384	0	34.1	132.0	138.0	18-384	2
Total (€)					**29,273**					

Table 3. *Other treatment costs per patient in the Netherlands*

	Average over all patients					Treated patients				
Other MBC related costs	**Price per unit (€)**	**Mean # of units**	**Median # of units**	**Range of units**	**Mean cost per patient (€)**	**% treated**	**Mean # of units**	**Median # of units**	**Range of units**	**Mean cost per treated patient (€)**
Overnight stay (nights)										
Intensive care	2,275[16]	0.1	0.0	0-5	129	1.1	5.0	5.0	5-5	11,377
Intensive care respiratory	2,275[16]	0.0	0.0	0-3	78	1.1	3.0	3.0	3-3	6,826
Internal medicine	476[16]	1.4	0.0	0-70	687	8.0	18.1	11.0	2-70	8,642
Oncology	476[16]	8.0	0.0	0-100	3,794	45.5	17.5	12.0	1-100	8,348
Lung department	476[16]	0.1	0.0	0-5	27	1.1	5.0	5.0	5-5	2,382
Surgical ward	476[16]	2.5	0.0	0-43	1,185	21.6	11.5	8.0	2-43	5,491
Palliative care	476[16]	0.7	0.0	0-37	352	2.3	32.5	32.5	28-37	15,481
Unknown[a]	476	0.9	0.0	0-18	422	9.1	9.8	8.5	2-18	4,644
Health care professional visits										
Day care	183[16]	35.3	33.0	0-103	6,474	86.4	40.9	41.0	1-103	7,497
Nurse[b]	28[16]	3.4	2.0	0-14	24	55.7	6.1	6.0	1-10	42
Medical specialist[b]	108[16]	30.3	30.5	0-80	820	97.7	31.0	31.0	2-80	839
Dietician[c]	28[16]	0.3	0.0	0-6	8	14.8	2.0	2.0	1-6	56
Physiotherapist[c]	38[16]	0.1	0.0	0-3	4	5.7	2.0	2.0	1-3	75
Home visit	90[16]	0.0	0.0	0-3	3	1.1	3.0	3.0	3-3	269
Ambulatory visit consultation	157[16]	8.1	0.0	0-38	317	36.4	5.5	5.6	1-10	872
Other[d]	53	1.5	0.0	0-19	83	37.5	4.1	3.0	1-19	220
Accident and emergency visits	157[16]	0.8	0.0	0-7	118	36.4	2.1	1.5	1-7	325

Table 3. Continued. *Other treatment costs per patient in the Netherlands*

	Average over all patients					Treated patients				
Other MBC related costs	**Price per unit (€)**	**Mean # of units**	**Median # of units**	**Range of units**	**Mean cost per patient (€)**	**% treated**	**Mean # of units**	**Median # of units**	**Range of units**	**Mean cost per treated patient (€)**
Surgical and non surgical procedures										
Venous acces port implamantation	550[17]	0.3	0.0	0-1	181	33.0	1.1	1.1	1-1	595
Excisional biopsy	136[17]	0.0	0.0	0-2	6	3.4	1.3	1.0	1-2	181
Incisional biopsy	136[17]	0.1	0.0	0-3	8	3.4	1.7	1.0	1-3	227
Metastectomy	1,358[20]	0.0	0.0	0-1	31	2.3	1.0	1.0	1-1	1,358
Venous acces port removal	168[17]	0.0	0.0	0-1	2	1.1	1.0	1.0	1-1	168
Plastic surgery	1,693[26]	0.1	0.0	0-7	135	1.1	7.0	7.0	7-7	11,850
Surgical removal tumour	1,358[20]	0.1	0.0	0-2	108	5.7	1.4	1.0	1-2	1,901
Cathether	28[16]	0.0	0.0	0-1	1	2.3	1.0	1.0	1-1	28
Laparatomy	228[17]	0.0	0.0	0-1	3	1.1	1.0	1.0	1-1	228
Axillary lymph node dissection	367[26]	0.0	0.0	0-1	13	3.4	1.0	1.0	1-1	367
Fine needle bipsy	100[17]	0.1	0.0	0-2	7	5.7	1.2	1.0	1-2	120
Breast conserving surgery	342[26]	0.0	0.0	0-1	4	1.1	1.0	1.0	1-1	342
Radical mastectomy	479[26]	0.0	0.0	0-1	16	3.4	1.0	1.0	1-1	479
Needle biopsy	100[17]	0.1	0.0	0-2	9	8.0	1.1	1.0	1-2	115
Core needle biopsy	100[17]	0.0	0.0	0-1	2	2.3	1.0	1.0	1-1	100
Extensive radical mastectomy	562[26]	0.0	0.0	0-1	6	1.1	1.0	1.0	1-1	562
Removal ovary	882[20]	0.0	0.0	0-1	10	1.1	1.0	1.0	1-1	882
Ablation	136[17]	0.0	0.0	0-1	5	3.4	1.0	1.0	1-1	136
Stereotactic biopsy	136[17]	0.0	0.0	0-2	5	2.3	1.5	1.5	1-2	204
Modified radical mastectomy	479[26]	0.0	0.0	0-1	5	1.1	1.0	1.0	1-1	479

Table 3. Continued. *Other treatment costs per patient in the Netherlands*

	Average over all patients					Treated patients				
Other MBC related costs	**Price per unit (€)**	**Mean # of units**	**Median # of units**	**Range of units**	**Mean cost per patient (€)**	**% treated**	**Mean # of units**	**Median # of units**	**Range of units**	**Mean cost per treated patient (€)**
Other	171	0.9	0.0	0-31	153	22.7	4.0	1.0	1-31	675
Unknown	171	0.0	0.0	0-1	2	1.1	1.0	1.0	1-1	171
Laboratory tests										
Tumor marker (CA15.3)	10[17]	10.9	9.0	0-31	112	93.2	11.6	10.0	1-31	121
Tumor marker (CEA125)	10[17]	0.9	0.0	0-14	9	23.9	3.8	2.0	1-14	39
Tumor marker (CEA)	10[17]	3.6	1.0	0-32	37	60.2	5.9	3.0	1-32	62
Hematology[f]	9[17]	25.0	19.5	0-88	219	97.7	25.4	20.5	1-88	224
Liver function[g]	7[17]	17.6	14.0	0-57	123	97.7	17.9	14.0	1-57	126
Clinical chemistry[h]	11[17]	12.9	11.0	0-57	136	97.7	13.2	11.0	1-57	139
White blood cell differential count	2[17]	6.1	2.0	0-60	11	84.1	7.2	3.5	1-60	13
FISH test	125[17]	0.1	0.0	0-1	16	12.5	1.0	1.0	1-1	125
Radiotherapy (fractions)	111[27]	6.5	2.0	0-63	719	53.4	12.1	7.0	1-63	1,347
Imaging										
CT scan	160[17]	4.0	3.0	0-24	647	83.0	4.9	4.0	1-24	780
X-ray	50[17]	5.2	4.0	0-29	261	84.1	6.2	5.0	1-29	311
PET CT scan	994[17]	0.1	0.0	0-2	68	5.7	1.2	1.0	1-2	1,193
Ultrasound	39[17]	2.0	2.0	0-13	79	68.2	2.9	2.0	1-13	116
MRI	196[17]	1.6	1.0	0-13	323	59.1	2.8	2.0	1-13	546
LVEF function	199[17]	2.3	1.0	0-10	465	63.6	3.7	3.0	1-10	730
ECG	39[17]	0.1	0.0	0-4	5	8.0	1.7	1.0	1-4	68
Ductal lavage	236[17]	0.0	0.0	0-1	3	1.1	1.0	1.0	1-1	236

Table 3. Continued. *Other treatment costs per patient in the Netherlands*

	Average over all patients					Treated patients				
Other MBC related costs	**Price per unit (€)**	**Mean # of units**	**Median # of units**	**Range of units**	**Mean cost per patient (€)**	**% treated**	**Mean # of units**	**Median # of units**	**Range of units**	**Mean cost per treated patient (€)**
DEXA	88[17]	0.0	0.0	0-1	1	1.1	1.0	1.0	1-1	88
Whole body scintigraphy	265[17]	1.5	1.0	0-6	389	73.9	2.0	2.0	1-6	526
Other[i]	141	0.9	0.0	0-15	125	29.5	3.0	2.0	1-15	424
Unknown[i]	141	0.0	0.0	0-1	3	2.3	1.0	1.0	1-1	141
Transfusions	210[16]	0.2	0.0	0-6	36	3.4	5.0	3.0	1-11	1,048
Total (€)					**19,025**					

[a]*Similar costs as oncology department*
[b]*15 minutes consultation*
[c]*1 hour consultation*
[d]*Average costs of specialist, nurse, home visit, general practitioner,dietician and physiotherapist*
[e]*Average over other surgery costs*
[f]*On average consisting of five laboratory investigations*
[g]*On average consisting of four laboratory investigations*
[h]*On average consisting of four laboratory investigations*
[i]*Average over other imaging costs*

Belgium

Study population and clinical outcomes

We identified 44 patients in one hospital fulfilling the selection criteria. The mean age of patients at diagnosis was 56 years (range 32-84) (**Table 1**). Majority of patients were diagnosed with ductal carcinoma and a de novo tumour. Visceral tissue and bone metastases were the most common sites of metastatic disease at diagnosis and a majority of patients was post menopausal.

Of these 44 patients, 8 died within the eligibility period with a mean overall survival of 419 days (range: 176 – 658 days).

Pharmacotherapeutic treatment

Costs of pharmacotherapeutic treatment amounted to a total of €26,103 (**Table 6**). Costs for chemotherapy and biologicals were the main cost drivers making up a total of respectively 13.5% and 85.9% of medical treatment costs.

On average 28.6 doses of chemotherapy were given per patient, corresponding to a mean cost of €3,527 (median; €1,711). Docetaxel accounted for 40.7% of these costs and paclitaxel for 35.7% (**Table 4**), respectively with 3.6 and 2.6 doses per patient. In total, 31.8% of the patients was treated with docetaxel and 29.5% with paclitaxel (**Table 4**).

Biologicals had a mean total cost of €22,431 (median; €11,438) per patient of which trastuzumab accounted for 93.4% of the costs (50.2 doses). In total 63.6% of the patients was treated with trastuzumab with on average 78.9 doses and an average cost per user of €32,919.

Other MBC related resource utilization

Total costs of other resource utilization was €11,240 (**Table 5**). Categories with highest costs were hospital stays, health care professional visits and imaging. On average, patients had 4.6 overnight stays, thereby accounting for €1,953 (median: €0), corresponding to 17.4% of other MBC related resource utilization costs. Stays in the oncology department, 3.3 on average, accounted for 62.0% of these costs and 27.3% of the patients was hospitalized on the oncology department at a certain moment in time. Total costs of health care professional visits were €4,068 (median: €3,359). A patient visited on average 46.7 times a health care professional, with day care visits as mean cost driver with a total of 31 mean visits per patient, thereby representing a total of 86.2% of the costs for health professional visits. Almost all patients (95.5%) visited the day care facility. Imaging costs accounted for a total of €3,006 (median: €2,974), representing 26.7% of total other resource utilization costs. Almost all patients underwent CT-scans and X-rays, respectively 93.2% and 79.5%.

Table 4 . *Medical treatment costs per patient in Belgium*

	Average over all patients					Treated patients				
Medical treatment	**Price per dose (€)**	**Mean # of doses**	**Median # of doses**	**Range of doses**	**Mean cost per patient (€)**	**% treated**	**Mean # of doses**	**Median # of doses**	**Range of doses**	**Mean cost per treated patient (€)**
Hormonal therapy										
Anastrazole (1 mg)	-	-	-	-	-	-	-	-	-	-
Exemestane (25 mg)	2.03[18]	4.2	0.0	0-152	9	6.8	62.0	17.0	17-152	126
Letrozole (2,5 mg)	1.81[18]	67.6	0.0	0-608	122	18.2	371.7	396.0	6-608	672
Tamoxifen (20 mg)	0.36[18]	40.8	0.0	0-683	15	18.2	224.2	111.5	30-683	80
Chemotherapy										
Capecitabine (4500 mg)	31.32[18]	12.0	0.0	0-171	377	20.5	58.8	39.8	1-171	1,843
Carboplatin (150 mg)	66.81[18]	0.1	0.0	0-4	5	2.3	3.6	3.6	4-4	242
Cyclophosphamide (1080 mg)	15.95[18]	1.2	0.0	0-11	19	25.0	4.7	4.7	1-11	76
Docetaxel (108 mg)	391.72[19]	3.6	0.0	0-68	1,426	31.8	11.4	8.0	2-68	4,482
Doxorubicin (90 mg)	50.31[19]	8.4	0.0	0-313	420	13.6	61.3	10.4	6-313	3,082
Fluorouracil (1800 mg)	23.18[18]	0.6	0.0	0-6	14	20.5	2.8	2.8	1-6	66
Methotrexate (5 mg)	-	-	-	-	-	-	-	-	-	-
Paclitaxel (315 mg)	476.18[18]	2.6	0.0	0-36	1,259	29.5	9.0	5.2	1-36	4,263
Vinorelbine (36 mg)	200.34[19]	0.0	0.0	0-1	6	15.9	0.2	0.2	1-1	39
Biologicals										
Bevacizumab (500 mg)	-	-	-	-	-	-	-	-	-	-
Lapatinib (1000 mg)	75.25[19]	19.7	0.0	0-302	1,482	11.4	173.4	175.0	53-302	13,044
Trastuzumab (284 mg)	417.16[19]	50.2	21.9	0-213	20,948	63.6	78.9	73.2	1-213	32,919

Table 4. Continued. *Medical treatment costs per patient in Belgium*

	Average over all patients					Treated patients				
Medical treatment	**Price per dose (€)**	**Mean # of doses**	**Median # of doses**	**Range of doses**	**Mean cost per patient (€)**	**% treated**	**Mean # of doses**	**Median # of doses**	**Range of doses**	**Mean cost per treated patient (€)**
Anti-emetics										
Dexamethasone (oral) (10 mg)	-	-	-	-	-	-	-	-	-	-
Dexamethasone (intravenous) (5 mg)	-	-	-	-	-	-	-	-	-	-
Granisetron (oral) (2 mg)	-	-	-	-	-	-	-	-	-	-
Granisetron (intravenous) (1 mg)	-	-	-	-	-	-	-	-	-	-
Metocloperamide (oral) (10 mg)	-	-	-	-	-	-	-	-	-	-
Ondansetron (oral) (8 mg)	-	-	-	-	-	-	-	-	-	-
Ondansetron (intravenous) (8 mg)	-	-	-	-	-	-	-	-	-	-
Other										
Ranitidine (oral) (50 mg)	-	-	-	-	-	-	-	-	-	-
Ranitidine (intravenous) (75 mg)	-	-	-	-	-	-	-	-	-	-
Biphosphonates (10 mg)	0.49[18]	1.4	0.0	0-15	1	20.5	7.0	6.8	1-15	3
Total (€)					**26,103**					

Table 5. *Other treatment costs per patient in Belgium*

	Average over all patients					Treated patients				
Other MBC related costs	**Price per unit (€)**	**Mean # of units**	**Median # of units**	**Range of units**	**Mean cost per patient (€)**	**% treated**	**Mean # of units**	**Median # of units**	**Range of units**	**Mean cost per treated patient (€)**
Overnight stay (nights)										
Intensive care	1,511[28]	0.2	0.0	0-8	275	2.3	8.0	8.0	8-8	12,086
Intensive care respiratory	1,511[28]	0.0	0.0	0-1	34	2.3	1.0	1.0	1-1	1,511
Internal medicine	375[28]	0.6	0.0	0-23	239	9.1	7.0	2.0	1-23	2,624
Oncology	375[28]	3.3	0.0	0-41	1,218	27.3	11.9	7.0	1-41	4,467
Lung department	375[28]	0.0	0.0	0-2	17	2.3	2.0	2.0	2-2	750
Surgical ward	375[28]	0.1	0.0	0-5	43	2.3	5.0	5.0	5-5	1,874
Palliative care	-	-	-	-	-	-	-	-	-	-
Unknown[a]	375	0.3	0.0	0-9	128	6.8	5.0	4.0	2-9	1,874
Health care professional visits										
Day care	113[29]	31.0	35.0	0-116	3,508	95.5	32.5	36.0	1-116	3,675
Nurse[b]	36[29]	1.1	0.0	0-39	10	11.4	9.4	34.0	1-39	85
Medical specialist[b]	115[29]	11.2	9.0	0-41	321	95.5	11.7	97.9	1-41	336
Dietician[c]	-	-	-	-	-	-	-	-	-	-
Physiotherapist[c]	34[29]	0.5	0.0	0-20	18	11.4	4.8	1.0	1-20	163
Home visit	-	-	-	-	-	-	-	-	-	-
Ambulatory visit consultation	83[29]	2.3	0.0	0-30	184	15.9	14.0	13.4	2-29	1,160
Other[d]	46	0.6	0.0	0-16	26	22.7	2.5	1.0	1-16	114

Table 5. Continued. *Other treatment costs per patient Belgium*

	Average over all patients					Treated patients				
Other MBC related costs	**Price per unit (€)**	**Mean # of units**	**Median # of units**	**Range of units**	**Mean cost per patient (€)**	**% treated**	**Mean # of units**	**Median # of units**	**Range of units**	**Mean cost per treated patient (€)**
Accident and emergency visits	82	0.8	0.0	0-4	60	45.5	1.6	1.0	1-4	133
Surgical and non surgical procedures										
Venous acces port implamantation	70[20]	0.3	0.0	0-1	19	27.3	1.0	1.0	1-1	70
Excisional biopsy	-	-	-	-	-	-	-	-	-	-
Incisional biopsy	102[20]	0.0	0.0	0-1	2	2.3	1.0	1.0	1-1	102
Metastectomy	1,358[20]	0.0	0.0	0-1	31	2.3	1.0	1.0	1-1	1,358
Venous acces port removal	-	-	-	-	-	-	-	-	-	-
Plastic surgery	-	-	-	-	-	-	-	-	-	-
Surgical removal tumour	-	-	-	-	-	-	-	-	-	-
Cathether	6[20]	0.1	0.0	0-1	0	6.8	1.0	1.0	1-1	6
Laparatomy	228[20]	0.0	0.0	0-1	5	2.3	1.0	1.0	1-1	228
Axillary lymph node dissection	-	-	-	-	-	-	-	-	-	-
Fine needle bipsy	-	-	-	-	-	-	-	-	-	-
Breast conserving surgery	-	-	-	-	-	-	-	-	-	-
Radical mastectomy	479[26]	0.0	0.0	0-1	11	2.3	1.0	1.0	1-1	479
Needle biopsy	68[20]	0.0	0.0	0-1	2	2.3	1.0	1.0	1-1	68
Core needle biopsy	-	-	-	-	-	-	-	-	-	-
Extensive radical mastectomy	-	-	-	-	-	-	-	-	-	-
Removal ovary	882[20]	0.0	0.0	0-1	20	2.3	1.0	1.0	1-1	882
Ablation	-	-	-	-	-	-	-	-	-	-
Stereotactic biopsy	-	-	-	-	-	-	-	-	-	-
Modified radical mastectomy	-	-	-	-	-	-	-	-	-	-

Table 5. Continued. *Other treatment costs per patient Belgium*

	Average over all patients					Treated patients				
Other MBC related costs	**Price per unit (€)**	**Mean # of units**	**Median # of units**	**Range of units**	**Mean cost per patient (€)**	**% treated**	**Mean # of units**	**Median # of units**	**Range of units**	**Mean cost per treated patient (€)**
Other	171	0.2	0.0	0-2	31	15.9	1.1	1.0	1-2	195
Unknown	-	-	-	-	-	-	-	-	-	-
Laboratory tests										
Tumor marker (CA15.3)	11[20]	20.6	22.0	0-49	229	86.4	23.8	25.5	1-49	266
Tumor marker (CEA125)	-	-	-	-	-	-	-	-	-	-
Tumor marker (CEA)	-	-	-	-	-	-	-	-	-	-
Hematology[f]	10[20]	31.1	31.0	0-128	297	86.4	36.1	36.0	3-128	344
Liver function[g]	8[20]	30.0	28.0	0-122	229	86.4	34.7	35.0	3-122	265
Clinical chemistry[h]	19[20]	32.2	31.0	0-126	614	90.9	35.4	36.0	1-126	675
White blood cell differential count	6[20]	30.6	29.0	0-122	171	86.4	35.5	37.0	3-122	198
FISH test	125[17]	0.23	0.00	0-1	28	22.73	1.00	1.00	1-1	125
Radiotherapy (fractions)	111[27]	5.0	0.0	0-59	591	38.6	12.0	5.0	2-55	1,428
Imaging										
CT scan	130[20]	11.8	12.0	0-30	1,528	93.2	12.7	13.0	1-30	1,640
X-ray	23[20]	5.7	4.0	0-37	132	79.5	7.2	5.0	1-37	166
PET CT scan	994[16]	0.3	0.0	0-4	339	20.5	1.7	1.0	1-4	1,657
Ultrasound	26[20]	1.8	1.0	0-10	46	72.7	2.5	2.0	1-10	63
MRI	131[20]	0.6	0.0	0-7	83	31.8	2.0	1.5	1-7	262
LVEF function	204[20]	2.5	1.0	0-9	510	50.0	5.0	5.0	1-9	1,020
ECG	44[20]	1.4	0.0	0-21	62	34.1	4.2	2.0	1-21	183
Ductal lavage	-	-	-	-	-	-	-	-	-	-

Table 5. Continued. *Other treatment costs per patient Belgium*

	Average over all patients					Treated patients				
Other MBC related costs	**Price per unit (€)**	**Mean # of units**	**Median # of units**	**Range of units**	**Mean cost per patient (€)**	**% treat-ed**	**Mean # of units**	**Median # of units**	**Range of units**	**Mean cost per treated patient (€)**
DEXA	-	-	-	-	-	-	-	-	-	-
Whole body scintigraphy	173[20]	1.1	1.0	0-5	197	52.3	2.2	2.0	1-5	377
Other[i]	106	1.0	0.0	0-7	106	34.1	2.9	2.0	1-7	310
Unknown[i]	106	0.0	0.0	0-1	2	2.3	1.0	1.0	1-1	106
Transfusions	-	-			-					
Total (€)					**11,328**					

[a]*Similar costs as oncology department*
[b]*15 minutes consultation*
[c]*1 hour consultation*
[d]*Average costs of specialist, nurse, home visit, general practitioner,dietician and physiotherapist*
[e]*Average over other surgery costs*
[f]*On average consisting of five laboratory investigations*
[g]*On average consisting of four laboratory investigations*
[h]*On average consisting of four laboratory investigations*
[i]*Average over other imaging costs*

Table 6. *Mean per patient category costs*

	The Netherlands				Belgium			
	Mean	**Median**	**Range**	**2.5 – 97.5 percentiles**	**Mean**	**Median**	**Range**	**2.5 – 97.5 percentiles**
Pharmacotherapeutic treatment								
Hormonal therapy (€)	4	0	0-81	[1 - 7]	145	0	0-1,353	[29 - 262]
Chemotherapy (€)	4,266	2,721	0-59,928	[2,549 – 5,983]	3,527	1,711	0-26,637	[1,530 – 5,524]
Biologicals (€)	24,960	15,143	0-91,528	[18,703 – 31,217]	22,431	11,438	0-88,697	[13,142 – 31,720]
Anti-emetics (€)	44	7	0-291	[29 - 60]	NA	NA	NA	NA
Other (€)	2	1	0-19	[1 - 2]	1	0	0-7	[0 - 1]
Other MBC related costs								
Hospital stays (€)	6,675	3,096	0-53,827	[4,287 – 9,064]	1,953	0	0-19,207	[438 – 3,468]
Health care professional visits (€)	7,734	8,329	0-19,842	[6,470 – 8,998]	4,068	4,359	0-13,597	[3,017 – 5,118]
Accident and emergency visits (€)	118	0	0-1,102	[67 - 169]	60	0	0-248	[32 - 89]
Surgical and non surgical procedures (€)	711	550	0-11,850	[349 – 1,074]	121	3	0-1,528	[22 - 221]
Laboratory tests (€)	663	573	0-2,063	[553 - 772]	1,568	1,571	0-5.662	[1,151 – 1,958]
Radiotherapy (fractions) (€)	719	223	0-7,009	[422 – 1,017]	552	0	0-6,547	[128 - 976]
Imaging (€)	2,369	2,108	0-7,514	[1,992 – 2,746]	3,006	2,974	0-7,664	[2,415 – 3,597]
Transfusions (€)	36	0	0-2,305	[-26 - 98]	NA	NA	NA	NA
Total (€)	**48,301**	**40,953**	**122-178,314**	**[40,037 – 56,564]**	**37,431**	**32,632**	**1,349 - 105,124**	**[27,539 – 49,638]**

Surgical procedures, accident and emergency visits, laboratory tests and radiotherapy accounted respectively for €3, €60, €1,568 and €552. Patients in Belgium underwent no transfusions.

Total MBC costs per patient
Total mean MBC costs per patient amounted to €37,431 (median; €32,632). Of this total, 70% was related to pharmacotherapeutic treatment and 30% to other MBC related resource utilization.

Discussion

This analysis describes the distribution of costs across different categories and total costs per patient diagnosed with HER-2 positive MBC in representative populations in the Netherlands and Belgium. Although the economic burden of MBC has been the subject of several other analyses, only a limited number used primary patient data, and none of these has primarily focused on HER-2 positive patients. To the authors' knowledge, this is the first study examining costs in HER-2 positive MBC patients, using real world patient level data.

Currently, decision makers are expressing a much bigger interest in real life data to have better indications of uncertainty when making reimbursement decisions[30]. Randomized controlled trials, although recognized as the "gold standard", operate in an idealized environment and can only measure outcomes in limited populations. A major advantage of the current collection of real world patient data in The Netherlands and Belgium, instead of resource use collection linked to clinical trials, is the generalisability of outcomes to the Dutch and Belgian populations. As we included the percentage of patients treated, in addition to average outcomes over the entire patient population, outcomes of this real world observational analysis could be directly used in MBC CEAs. However, in trials specific prospective cost data can be obtained, while our approach relies on retrospective use of data from patient medical dossiers. For our purpose, this seemed to be sufficient since detailed micro costing information such as number and time of patient contact with professionals could not be obtained by using medical records.

A slight increase in mean per patient costs was observed (€695) when correcting for censoring by the IPW method for the Dutch population. Unfortunately, we were not able to correct for censoring in the Belgium population as not all costs were collected over time in this population. In both countries treatment with trastuzumab incurred the majority of costs and other resource utilization costs were mainly related to health care professional

visits and hospital stays. As all of the published MBC costing studies focused on the entire MBC population it is not relevant to compare our outcomes with those published in literature due to the large influence of patient selection on the outcome[7]. Although no HER-2 related costing studies are published, two studies have primarily focused on the cost of trastuzumab in the treatment of MBC. Their outcomes, respectively €21,569[31] per patient in Canada and €25,734[32] in France are comparable to the per patient treatment costs of trastuzumab in the Netherlands and Belgium of respectively €24,164 and €20,948 per patient, thereby demonstrating the consistency of our data.

Assessment of cost differences between NL and BE was not an objective of this study. Both groups had similar in- and exclusion criteria, and patient characteristics and MBC clinical history (**Table 1**), although the MBC classification was missing in a relatively large proportion of the Dutch sample. However, a linear regression analysis did not identify a clear relationship between MBC classification and outcome, potentially supporting a comparison between costs in NL versus BE.

Average cost per patient was €10,870 higher in the Netherlands, with a difference in pharmacotherapeutic treatment costs of €3,172 and difference in other resource use utilization of €7,698. Although a similar balance of overall costs between therapy and other resource use utilization was seen between countries, several important volumes and unit costs differed which have caused the difference in outcome. The differences in medical treatment costs were mainly related to a higher number of mean gifts trastuzumab per patient in the Netherlands. This higher mean number of gifts trastuzumab per patient in the Netherlands is possibly related to the subjective multidimensional decision process in MBC treatment selection[33], resulting in a longer exposure to trastuzumab for patients in the Netherlands.

Differences in other resource use utilization were mainly related to differences in total overnight stays and health care professional visits. More mean per patient stays in the oncology department were observed in the Netherlands 8.0 vs. 3.3 in Belgium which resulted in a €2,576 difference between both countries. In addition, also more stays on the surgical ward were observed in the Netherlands resulting in a €1,143 difference. Total day care visits were similar, 35.3 vs. 31.0 but due to a large difference in unit costs between both countries, this resulted in a €2,967 difference in total costs.

Remarkable differences in volumes were observed in total number of laboratory tests and CT-scans. In Belgium more laboratory tests were performed and more CT-scans which both could again be related to subjective decisions of physicians or hospital policy. Anti-emetic use was not collected in Belgium, but as described in the Netherlands no high

costs were involved for this therapy group.

Some limitations of our work deserve mentioning. First of all, although collection of retrospective patient data is preferred over the use of secondary insurance based datasets, these patient files could still be not fully complete. As mentioned earlier, micro costing methods imply following patients and collecting resources prospectively. However, this is not common in real world patient populations and only in performance based risk sharing schemes such data are collected[34]. Second, we only followed patients for a maximum of 24 months post index diagnosis. Thereby several patients were censored and we did not cover a complete view of costs for each patient from diagnosis to death. To overcome this, we corrected total estimates with the IPW method. Third, we did not take spillage of medication into account. Thereby it is possible that we underestimated total costs of medical treatment with approximately 5% accounting for additional costs of approximately €1,473 in the Netherlands and €1,305 in Belgium. Fourth, we only included one Belgium hospital, which might decreases the generalisability of outcomes to the overall Belgian situation.

As identified in this manuscript, current pharmacotherapeutic treatments encompass a majority of total MBC costs. Due to marginal gains in health care and high pharmacotherapeutic treatment costs, such treatments will always remain a topic of discussion with respect to cost lowering. It is uncertain whether costs for treating MBC will gradually decrease in both countries after 2015. Although the patent of trastuzumab will expire on 28 August 2015 in Europe novel drugs such as pertuzumab and combinations of HER-2-inhibiting therapies will be registered shortly in Europe for Her2 positive breast cancer, undoubtedly increasing costs of treatment.

Conclusion

In conclusion, this study has provided an estimate of resource use and health care cost of treating HER-2 positive MBC in the Netherlands and Belgium. Detailed overviews are given of treatment and other health care utilization factors contributing to the total costs. By adding percentage of treated/indicated patients and presenting descriptive statistics for the subsets of patients, this allows improvements in future CEAs. In addition, we would feel that it is essential that future costing studies provide more detailed information and publish these outcomes in addition to averaged patient outcomes too.

In both countries costs for pharmacotherapeutic treatment encompassed over half of total costs which further indicate the necessity of demonstrating cost-effectiveness of new

therapies. We furthermore identified essential differences in resource use between both countries, which underpin the collection of country specific resource use data instead of transferring volume data from one country to the other

Acknowledgements

The authors would like to thank Illona van Rooij, Janneke Coopmans, Sylvia Sprangers-van Campen and Joke Vanderhaegen for collection of the data.

Financial disclosure

PhD student (G.W.J. Frederix) was funded by an unrestricted grant from GlaxoSmithKline the Netherlands.

References

(1) *Colozza M, de Azambuja E, Personeni N, Lebrun F, Piccart MJ, Cardoso F. Achievements in systemic therapies in the pregenomic era in metastatic breast cancer. Oncologist **2007**; 12(3):253-270.*

(2) *Dodwell D, Wardley A, Johnston S. Postmenopausal advanced breast cancer: options for therapy after tamoxifen and aromatase inhibitors. Breast **2006**; 15(5):584-594.*

(3) *Foster TS, Miller JD, Boye ME, Blieden MB, Gidwani R, Russell MW. The economic burden of metastatic breast cancer: a systematic review of literature from developed countries. Cancer Treat Rev **2011**; 37(6):405-415.*

(4) *Uyl-de Groot CA, de Groot S, Steenhoek A. The economics of improved cancer survival rates: better outcomes, higher costs. Expert Rev Pharmacoecon Outcomes Res **2010**; 10(3):283-292.*

(5) *Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for the economic evaluation of health care programmes. 2nd ed. **1997**. New York: Oxford University Press.*

(6) *Larg A, Moss JR. Cost-of-illness studies: a guide to critical evaluation. Pharmaco economics **2011**; 29(8):653-671.*

(7) *Bonastre J, Jan P, Barthe Y, Koscielny S. Metastatic breast cancer: we do need primary cost data. Breast **2012**; 21(3):384-388.*

(8) *Bercez C, Lebrun T, Bonneterre ME, Selke B, Lenne X, Bonneterre J. [Advanced breast cancer: an evaluation of the cost of recurrence]. Bull Cancer **1999**; 86(6):585-590.*

(9) *Dahlberg L, Lundkvist J, Lindman H. Health care costs for treatment of disseminated breast cancer. Eur J Cancer **2009**; 45(11):1987-1991.*

(10) *Hurley SF, Huggins RM, Snyder RD, Bishop JF. The cost of breast cancer recurrences. Br J Cancer **1992**; 65(3):449-455.*

(11) *Stokes ME, Thompson D, Montoya EL, Weinstein MC, Winer EP, Earle CC. Ten-year survival and cost following breast cancer recurrence: estimates from SEER-medicare data. Value Health **2008**; 11(2):213-220.*

(12) *Thomas RJ, Williams M, Marshall C, Glen J, Callam M. The total hospital and*

community UK costs of managing patients with relapsed breast cancer. Br J Cancer 2009; 100(4):598-600.

(13) *Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med* ***2001****; 344(11):783-792.*

(14) *Cameron D, Casey M, Press M, Lindquist D, Pienkowski T, Romieu CG et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat* ***2008****; 112(3):533-543.*

(15) www.medicijnkosten.nl.

(16) *Hakkaart- van Roijen L, Tan SS, Bouwmans CAM. Manual for cost research. Methods and unit-prices for economic evaluations in health care (in Dutch). College voor zorgverzekeringen. Geactualiseerde versie* ***2010****.*

(17) http://www.nza.nl/regelgeving/beleidsregels/ziekenhuiszorg/BR-CU-2065.

(18) http://www.bcfi.be/.

(19) http://www.riziv.fgov.be/homenl.htm.

(20) http://www.riziv.be/insurer/nl/rate/index.htm.

(21) *Bang H TA. Estimating medical costs with censored data. Biometrika.* ***2000****;87:329-343.*

(22) http://www.cvz.nl/binaries/live/cvzinternet/hst_content/nl/documenten/cfh-rapporten/2011/cfh1109-cabazitaxel-jevtana.pdf.

(23) http://www.cvz.nl/binaries/live/cvzinternet/hst_content/nl/documenten/cfh-rapporten/2009/cfh0901+lapatinib+tyverb.pdf.

(24) http://www.cvz.nl/binaries/content/documents/cvzinternet/nl/documenten/cfh-rapporten/2007/cfh0710+bevacizumab+avastin.pdf.

(25) http://www.cvz.nl/binaries/live/cvzinternet/hst_content/nl/documenten/cfh-rapporten/2010/cfh1012-trastuzumab-herceptin.pdf.

(26) https://hiva.kuleuven.be/resources/pdf/publicaties/R1407.pdf.

(27) *van den Hout WB, van der Linden YM, Steenland E, Wiggenraad RG, Kievit J, de Haes H et al. Single- versus multiple-fraction radiotherapy in patients with painful bone metastases: cost-utility analysis based on a randomized trial. J Natl Cancer Inst* ***2003****; 95(3):222-229.*

(28) http://www.feb.ugent.be/nl/Ondz/wp/Papers/wp_03_180.pdf.

(29) *Cocquyt V, Moeremans K, Annemans L, Clarys P, Van Belle S. Long-term medical costs of postmenopausal breast cancer therapy. Ann Oncol* ***2003****; 14(7):1057-1063.*

(30) *Garrison LP, Jr., Neumann PJ, Erickson P, Marshall D, Mullins CD. Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. Value Health* ***2007****; 10(5):326-335.*

(31) *Drucker A, Skedgel C, Virik K, Rayson D, Sellon M, Younis T. The cost burden of trastuzum ab and bevacizumab therapy for solid tumours in Canada. Curr Oncol* ***2008****; 15(3):136-142.*

(32) *Poncet B, Colin C, Bachelot T, Jaisson-Hot I, Derain L, Magaud L et al. Treatment of metastatic breast cancer: a large observational study on adherence to French pre scribing guidelines and financial cost of the anti-HER2 antibody trastuzumab. Am J Clin Oncol* ***2009****; 32(4):369-374.*

(33) *Chung CT, Carlson RW. Goals and objectives in the management of metastatic breast cancer. Oncologist* ***2003****; 8(6):514-520.*

(34) http://www.ispor.org/taskforces/documents/ISPOR-Performance-Based-Risk-Sharing-Arrangements-TF-Final-Draft-Report.pdf.

6

Chapter 6.2

Time dependent resource use and costs associated with different states of disease in patients diagnosed with HER-2 positive metastatic breast cancer

Gerardus W.J. Frederix
Johan L. Severens
Anke M. Hövels
Johan G.C. van Hasselt
Jan A.M. Raaijmakers
Jan H.M. Schellens

Breast Cancer Research and Treatment: In Press

Abstract

Introduction

Adequate reflection of disease progression and costs over time is essential in cost-effectiveness analyses (CEAs) based on health state transition models. However costing studies normally investigate the burden of metastatic breast cancer (MBC) without explicitly examining impact of specific disease states on health care costs over time. The objective of this study was to assess time-dependent costs of different health states of human epidermal receptor 2 (HER-2) positive MBC and the factors contributing to these costs.

Methods

In the Netherlands, HER-2 positive MBC patients were identified in three different hospitals. Five categories of observational data were collected: demographics, MBC clinical history, medical treatment, other MBC related resource utilizations and clinical outcomes during 24 months. These data were linked to unit costs and related to time with respect to date of MBC diagnosis, disease progression and death for each individual patient. Subsequently, monthly costs for different health states were calculated. Finally, a nonlinear mixed effect modelling approach was used to provide a quantitative description of the time course of cumulative progression costs.

Results

Costs during stable disease were constant over time with a mean of €3,236 (median €2,929, range €83 – €17,585). In contrast, monthly costs for progressive disease demonstrated a change over time with the largest costs in the first two months after diagnosis, on average €4,339 (median €3,538, range €27 – €16,185) in the first and €4,366 (median €3,626, range €8 – €15,488) in the second month ($p<0.005$). The developed mixed effect model adequately described the cumulative cost time course and associated variability. During the last months of life, cost and distribution of costs varied over time, with the last month of life as the most expensive one with a mean of €4,522 per patient per month (median €4,154, range €0 – €14,552).

Conclusion

To reflect costs of HER-2 positive MBC accurately in Markov models, costs stable disease can be defined time-independent, however, costs of progressive disease should be defined time dependent, and costs related to the final months of life should be modeled as such. The mixed effect model we have developed could now be considered for adequate description of the time-dependent cost of progressive disease.

Introduction

Policy makers around the world face budget constraints that compel them to make decisions about how to invest funds for population and patient health. An essential aid in this decision making is the use of cost-effectiveness analysis (CEA) allowing policy makers to compare health gains that various interventions can achieve with a given level of input[1].

To estimate cost-effectiveness, mathematical models are used to connect both costs and effects[2]. Frequently, Markov models are used in this context, in which the disease in question is reflected by distinct health states with associated transitions probabilities[1-3]. By attaching estimates of health state values and resource use to the states and transitions in the model, it is possible to estimate long term costs and outcomes associated with a disease and a particular treatment.

In order for these cost-effectiveness models to be helpful to decision-makers they need to be credible and reliable, by adequately representing disease progression, health outcome and costs. Recently, a wide variety of modelling and structural characteristics in CEAs of early breast cancer was identified not having an adequate reflection of disease progression, thereby leading to biased outcomes[4]. In addition to the varying implementation of disease progression, also resource use estimates in breast cancer are subject to less accurate methods of data gathering which thereby could lead to incorrect costing estimates over time[5].

A majority of costing studies in metastatic breast cancer (MBC) have investigated the total burden of disease without specific consideration of the time-course and clinical status of the patient[5]. Recently, we identified the total resource use and costs of HER-2 positive MBC in primary patient level data in a retrospective study in both the Netherlands and Belgium (work submitted).

As costing studies often did not take time course and clinical status into account, several CEAs involving MBC treatments have implemented constant costs for health states over time[6;7], which is a doubtful assumption as it is likely that for instance progression costs fluctuate over time depending on an increased rate of hospitalization and change in therapy. When different therapies result in differences in progression free survival, inaccurate costing outcomes will thereby result in bias on the incremental cost-effectiveness ratio.
In order to provide a realistic description of health care related costs in health economical models for MBC, it is of importance to evaluate the potential time-dependency of health care related costs in this indication.

Therefore, the **objective** of this study was to quantitatively assess and explore the monthly real world costs of different states of HER-2 positive MBC, whether these are time-dependent, and the explanatory factors contributing to these costs.

Methods

Patient selection

MBC patients were identified in three different hospitals in the Netherlands. The eligibility period for selection was from June 2004 to June 2010. We selected all women having an index diagnosis of MBC and a primary tumor of confirmed HER-2 status during this eligibility period, were 18 years of age or older at time of index diagnosis, and had known hormonal status and known sites of metastases.
For subjects having HER-2 positive MBC as identified by the selection criteria, the study period begins at the time of first diagnosis of MBC (either de novo or recurrent) during the eligibility period and ends 24 months post index diagnosis of MBC or at patient death, or at loss to follow-up, if either of these events occur earlier.

We excluded all patients who participated in phase I, II and III clinical trials who were either i) receiving experimental agents, or, ii) patients for whom the treatment, i.e. experimental or standard or care, was blinded at the time of patient inclusion for the current analysis.

Data collection

Five categories of data were distinguished: patient demographics, MBC clinical history, medical treatment, MBC related resource utilizations and clinical outcomes (disease progression and survival). Using this format we obtained a complete descriptive overview of all resources used by these patients and their disease status over time.

Unit costs

Unit costs were derived from Dutch reference prices[8-10]. All costs were expressed in Euros using the 2012 price level. Volumes obtained from the data collection were multiplied with unit costs resulting in mean costs per patient. All monthly costs were expressed in mean, median, range and 2.5 and 97.5 percentiles.

Disease status

MBC disease state was determined by collecting date of disease progression and death for each individual patient. Patients were divided into two mutually exclusive groups (health states) based on their disease state. The states were defined to be relevant and useful both in clinical practice and economic modeling and it was expected that the states would

differ in resource use and costs. The defined states were stable disease and progressive disease. Resource use for patients having stable disease was collected from time of MBC diagnosis to progression or death, patients in the progressive state from time of progressive disease to end of follow up or death. In addition to both health states, the last three months of life were distinguished and resources and costs in these last three months of life were assessed separately.

Quantitative model for cumulative cost time course

Individual-level cumulative cost-time courses were described with a nonlinear mixed effect model approach[11], allowing description of both the mean typical change in (cumulative) costs over time, but also quantify variability in a hierarchical fashion, i.e. distinguishing inter-patient variability and residual variability. To account for the large spread in values, cumulative costs were natural log-transformed prior to analysis. Different nonlinear functions and variance-covariance structures were evaluated. Inter-patient variability random effects were either normally or log-normally distributed. Finally, model selection was performed based on visual fit and the likelihood ratio test.

Results

Patient characteristics and clinical history

We identified 88 eligible patients. A complete description of patient and tumour characteristics is shown in **table 1**. Mean age of patients at diagnosis was 55 years (range 32-83). The majority of patients was diagnosed with ductal carcinoma (92%), 38% had a hormone positive tumour and 61% of patients was hormone negative. Furthermore, the sites of metastatic disease varied between visceral tissue, soft tissue, bone, brain and other sites.

***Table 1**. MBC clinical history*

Patients (n)	88	
Age (range)	55 (32-83)	
	Number of patients	**% of total**
Type of breast cancer		
Lobular	6	6,82%
Ductal	81	92,05%
Inflammatory breast cancer	1	1,14%
Classification		
De novo	47	53,41%
Recurrent	24	27,27%
Unknown	17	19,32%

Table 1. Continued. *MBC clinical history*

	Number of patients	% of total
Hormonal status		
ER positive	34	38,64%
ER negative	54	61,36%
Sites of metastatic disease		
Visceral tissue	49	41,18%
Soft tissue	3	2,52%
Bone	48	40,34%
Brain	6	5,04%
Other	13	10,92%
Menopausal status		
Pre	17	19,32%
Peri	4	4,55%
Post	58	65,91%
Unknown	9	10,23%

Impact disease state

On average, patients had stable disease for 13.0 months (median 13.0) and progressive disease for 8.0 months (median 7.9 and range; 0.1 – 21.6 months).

Stable disease

Costs for stable disease were constant over time with an average monthly cost of €3,236 (median €2,929) per patient (**Table 2**). Main drivers of these monthly costs were cost of therapy, comprising 66.0% of total costs, visits to nurses or specialists at the hospital (16.9%), hospital stays (7.5%) and diagnostics (4.7%).

Table 2*. Costs per patient per month*

	Mean (€)	Median (€)	Range (€)	Percentiles (2,5% - 97.5%)	Number of patients
Stable disease					
Mean	3,236	2,929	83 – 17,585	(2,333 – 3,750)	NA
Progressive disease					
month 1	4,339	3,538	27 – 16,185	(3,197 – 5,481)	54
month 2	4,366	3,626	8 – 15,488	(2,984 – 5,747)	47
month 3	2,807	2,511	200 – 12,101	(1,942 – 3,672)	43
month 4	2,765	2,226	223 – 10,340	(1,880 – 3,651)	35

Table 2. Continued. *Costs per patient per month*

	Mean (€)	Median (€)	Range (€)	Percentiles (2,5% - 97.5%)	Number of patients
month 5	2,553	1,710	65 – 7,147	(1,638 – 3,467)	34
month 6	2,172	1,613	27 – 6,993	(1,293 – 3,051)	30
month 7	2,498	2,162	143 – 10,073	(1,495 – 3,500)	29
month 8	2,583	2,183	183 – 9,907	(1,371 – 3,796)	28
Last months of life					
Third last month	2,644	1,593	0-9,544	(1,423 – 3,865)	25
Second last month	2,750	1,061	0-10,072	(1,243 – 4,256)	27
Last month	4,522	4,154	0-14,552	(2,432 – 6,612)	29

**Number of patients for stable disease varies over time, therefore depicted with NA*

Progressive disease

Splitting up costs for progressive disease in the first until eight month after onset resulted in differences in monthly costs (**Table 2**) and relative and absolute distribution of these costs (**Figure 1A and 1B**).

Figure 1A

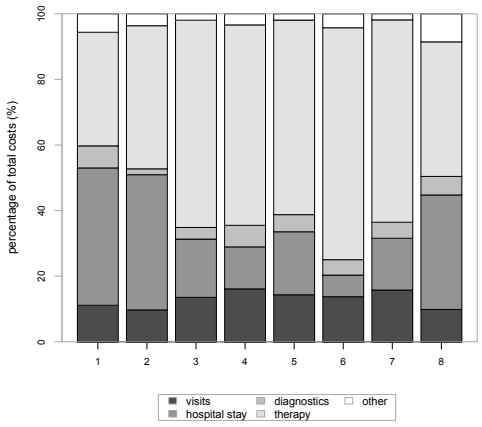


Figure 1B

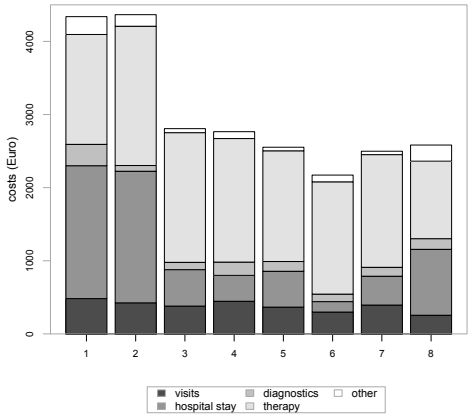


Figure 1. *Relative (A) and absolute (B) distributions of costs versus time (months) during progressive metastatic breast cancer (MBC), stratifiedby origin of costs. Only hospital stays, visits, therapy and diagnostics were depicted in this figure as these had the largest impact on theoutcome.*

Highest costs were incurred in the first two months of progressive disease, respectively a mean of €4,339 (median €3,538) for the first month and a mean of €4,366 (median €3,626) for the second month. A large percentage of costs in both months was related to hospital stays, respectively 41.9% in the first month and 41.2% in the second month. Percentage

of costs related to therapy was 34.6% in the first month and 43.6% in the second month. Finally, the percentage of costs related to therapy increased to 63.2% in month three of progression and the impact of costs related to hospital stays decreased during the first three months to 16.0%.

From month three to month eight mean costs ranged from €2,024 to €2,583 per month. In the distribution of costs from month four to month six a light increase in the contribution of therapy costs and a further decrease in contribution of hospital stays to 6.6% to total costs was observed. From month seven after progression, an increase in hospital stays was observed, which decreased afterwards. In addition, contribution of therapy costs decreased in month seven and increases afterwards.

Comparing the first two months of progression with the other months in a Wilcoxon signed-rank test demonstrated a significant difference ($p<0.005$) indicating the first two months have significant higher costs compared to the other months.

Subsequently, we described the typical change in cumulative progression costs using a nonlinear mixed effect model. The typical increase in costs was best described using the following equation (Eq 1):

$$C(t) = C_0 + \frac{C_{MAX} \cdot t^{y}}{C_{50} + t^{y}} \quad (1)$$

where C(t) represents the log-transformed cumulative costs as a function of time (months) with time starting at one month post-diagnosis, C_0 represents initial costs in the first month after diagnosis, C_{MAX} represents the maximum cost, C_{50} represents the time of reaching half-maximum costs, and γ was a Hill coefficient accounting for the slope of the curve. All parameter estimates could be estimated with adequate precision (RSE<42%). Addition of the Hill coefficient to the equation was statistically significant ($p<0.001$, likelihood ratio test). The final parameter estimates are depicted in **table 3**.

Table 3. *Parameter estimates of the nonlinear mixed effect model for cumulative costs after 1 month post-diagnosis. Both the original logtransformed estimated and posthoc back-transformed estimates are provided.*

Description	Parameter	Estimate (RSE%)	Back-transformed estimate
Fixed effects			
Baseline costs (log(€) or back-transformed €)	C_0	7.89 (2.2%)	2,670.44
Maximum cost effect (log(€) or back-transformed €)	C_{MAX}	3.6 (18.4%)	97,733 [b]

Table 3. Continued. *Parameter estimates of the nonlinear mixed effect model for cumulative costs after 1 month post-diagnosis. Both the original logtransformed estimated and posthoc back-transformed estimates are provided.*

Description	Parameter	Estimate (RSE%)	Back-transformed estimate	
Time of half-maximum costs (months)	C_{50}	6.76 (42.3%)	-	
Hill coefficient (-)	γ	0.861 (11.2%)	-	
Residual error (additive)	ε_a	0.0062(26.9%)		
Inter-patient random effect estimates (RSE)[a]				
	C_0	C_{MAX}	C_{50}	**γ**
Baseline costs*	126.9%(14.5%)			
Maximum costs	-16.9%	54.2% (24.3%)		
Half-maximum costs	23.8%	81.1%	140.4%(29.7%)	
Hill coefficient	-17.1%	-35.5%	-32.3%	61.3%(12.6%)

RSE=Relative standard error.
** At initial month post-diagnosis progressive disease.*
[a] Reported as relative standard deviations.
[b] The typical back-transformed maximum cost is exp(C0 + CMAX)= exp (7.89 + 3.6)=€97,733.

A full variance-covariance matrix for inter-patient random effects could be estimated for all fixed effect parameters. Inter-patient random effects were either modeled using a normal distribution for C_0, or using a log-normal distribution for C_{MAX}, C_{50} and γ. Subsequently, internal model evaluation was performed by performing stochastic simulations (n=1000) using the final model. Simulated time-courses were graphically depicted together with observed values, and indicated adequate description of the observed data (**Figure 2**).

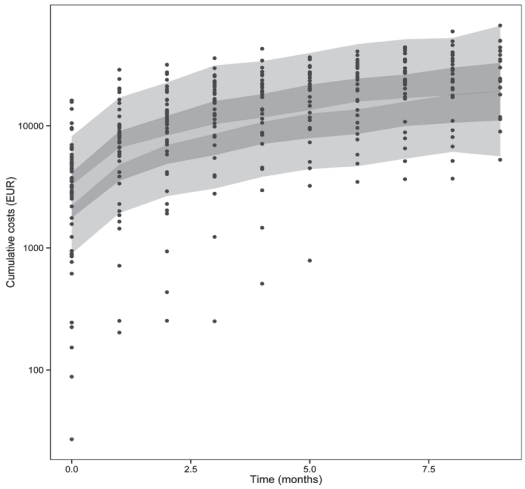


Figure 2. *Evaluation of the nonlinear mixed effect model for the time course of cumulative progression costs. Cumulative costs (EUR) versus time after diagnosis of progression (months) for observed costs (solid circles) and model simulated percentiles (5th, 30th and 70th). The areas represent 95% parametric confidence intervals around the simulated percentiles.*

Impact last months of life

Differences were observed in costs and distribution of costs in the last three months of life of a patient. Costs differed over these three months from a mean of €2,644 (median €1,593) for the third last month before death to a mean of €4,522 (median €4,154) for the last month of a patient's life (**Table 2**). During these last three months, an increase in contribution of hospital stays to total costs was observed, 44.0% in the third last month to 69.5% in the last month (**Figure 3A**). Furthermore, a decrease in contribution of therapy costs from 27.6% to 13.1% and visits to health care professionals from 14.6% to 4.7% in the last month were observed. At last, there was an increase in contribution of radiotherapy costs from 2.7% in the third last month to 6.5% in the last month of life.

Figure 3A

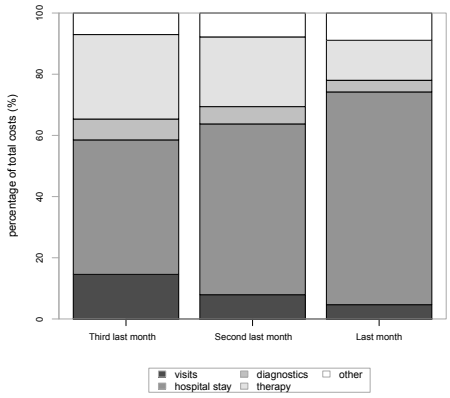


Figure 3B

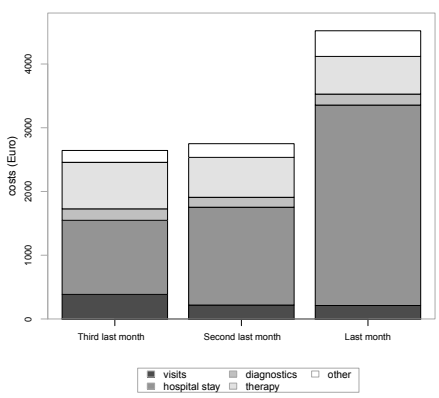


***Figure 3**. Relative (A) and absolute (B) distributions of costs versus time (months) during the last three months of life, stratified by origin of costs.*

Discussion

This study presents the monthly health care costs related to different health states in Dutch HER-2 positive MBC patients. This is the first study examining health state related costs in HER-2 positive MBC patients over time. As costs are expressed in monthly outcomes, these results could be directly used in economic evaluations of MBC therapies.

Stable disease

Patients having stable disease had constant cost and distribution of cost over time because no changes in therapy or additional visits to specialists had to be made during these months. These outcomes correlate with clinical experience as patients with stable disease are only seen by physicians during routine visits.

Progressive disease

Both costs as the distribution of costs for progressive disease over time demonstrated a change over time (**Table 2**). The first two months of progression were most expensive, which can be directly related to an increased rate of overnight stays in the hospital (**Figure 1**). Lower contribution of therapy costs during the first three months of progression is related to stopping expensive medication or reduction in doses, as expensive therapies such as trastuzumab and capecitabine are often stopped after onset of progression. Such time dependent estimations are of major relevance for Markov modelling especially when differences are apparent between therapies regarding total time spent in disease states.

The decrease in hospital stays and increase in the contribution of therapy to total costs from month two to month three is due to the dismissal of patients from hospital as progressive disease is under control and different therapies are again started or doses are increased.

The distribution of the costs from month three to month six is comparable with the distribution during stable disease, which is possibly related to the fact that a patient returns to stable disease again for sometime after having progressive disease for two months. The decrease in the contribution of therapy costs to total costs and the increase of the contribution of hospital stays from month six onwards is possibly related to recurrent progressive disease as distributions of costs are comparable to the distribution of costs in the first two months after documentation of disease progression. Patients were again hospitalized and the therapies were often stopped during these months.

The developed nonlinear mixed effect model allowed quantitative description of the costs time course across a cohort of patients in the progressive disease health state. The typical change over time can be described using the parameter estimates from **table 3** in Equation 1. In addition, as a full inter-patient random effect variance-covariance matrix for al fixed effect parameters could be estimated, realistic cost-time courses can be simulated on an individual level using the developed model. The variance-covariance matrix describes the observed correlation between individual parameter estimates, i.e. a correlation of -16.9% was found between individual estimates for C0 and CMAX (**Table 3**).

This model can be implemented in health economical models for metastatic breast cancer, to provide a realistic description of the demonstrated time-dependency in costs for patients with progressive disease. Moreover, as the model also describes inter-individual variation in cost-time profiles, it is also allows to describe such variation, which is of specific relevance for health economical simulations conducted at patient level (e.g. discrete event simulation or Markov models) and for probabilistic sensitivity analyses.

Last months of life

Although in published MBC CEAs death is another health state, we did not include this as a separate health state in this analysis, as only transition related costs are linked to death and no health state specific costs. Although no death health state was formed, it was observed that the costs in the last month of life are higher compared to month two and three before death. In the last months of life, therapy is often stopped or as it has no further rationale and advantage for a patient, which is demonstrated by the decreasing contribution of therapy costs to total costs from the third last month to the last month of life. In addition, there is an increased contribution of hospital stays to total costs observed in our analysis, which is related to increased hospitalization of patients in the last month of life. Furthermore, an increase in costs of radiotherapy in the last month of life was seen, related to palliative radiotherapy intended to decrease pain of for instance bone metastases[12]. Costs and distribution of costs in the second and third last month before death are comparable to the costs for progressive disease, compatible with knowledge that a patient is still having progressive disease during both months before death. The higher costs in the last month confirm the addition of transition costs when a patient dies. The exact height of these transition costs was not determined as it was no primary objective of the analysis, and therefore no detailed data regarding start of palliative care was available.

Some limitations of our work deserve mentioning. At first, only first disease progression was collected for each patient. Thereby new disease progression after a period of stable disease was not detected. Although not detected, we see a progressive costing pattern for patients after seven months of disease progression corresponding to an increase in rate of hospitalization and a decrease in the contribution of therapy costs. Second, although we demonstrated higher costs in the last month of life, we were not able to distinguish between progressive disease and palliative care as no clear onset data for palliative care were available. Clinical experience learns that this is a gradual process moving from active anti-cancer therapy towards palliative care.

Conclusion

In this analysis we outlined the monthly costs for different HER-2 positive MBC health states. The observed wide variety in costs and factors associated with the costs for progressive disease over time demonstrated the necessity of including time dependent costs for HER-2 positive MBC in economic evaluations to have an adequate and correct reflection of costs in the real world. The developed mixed effect model for the cumulative progressive cost time course can be implemented for specifically for this purpose, i.e. to account for time-dependent costs for patients with progressive disease. In addition, higher costs

in the last month of life indicate the need for adding additional transition related costs linked to the death of a patient. Future costing studies should keep in mind the additional costs of death and data regarding palliative care should be collected over time in addition.

Outcomes demonstrate the necessity of collecting patient related costing data, in which clinical progression could be linked to costing outcomes. Including such approaches in future costing studies will result in a better reflection of costs and factors associated with these costs over time, which thereby should result in more credible and reliable CEAs. Furthermore, such real world costing studies give more insight in the height and distribution of costs of a specific disease over time, which could serve very well as input for research into cost reductions during the entire management of a disease.

References

(1) *Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for the economic evaluation of health care programmes. 2nd ed.* ***1997****. New York: Oxford University Press.*

(2) *Briggs A, Sculpher M. An introduction to Markov modelling for economic evaluation. Pharmacoeconomics* ***1998****; 13(4):397-409.*

(3) *Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making* ***1993****; 13(4):322-338.*

(4) *Frederix GW, Severens JL, Hovels AM, Raaijmakers JA, Schellens JH. Reviewing the cost-effectiveness of endocrine early breast cancer therapies: influence of differences in modeling methods on outcomes. Value Health* ***2012****; 15(1):94-105.*

(5) *Bonastre J, Jan P, Barthe Y, Koscielny S. Metastatic breast cancer: we do need primary cost data. Breast* ***2012****; 21(3):384-388.*

(6) *Le QA, Hay JW. Cost-effectiveness analysis of lapatinib in HER-2-positive advanced breast cancer. Cancer* ***2009****; 115(3):489-498.*

(7) *Dedes KJ, Matter-Walstra K, Schwenkglenks M, Pestalozzi BC, Fink D, Brauchli P et al. Bevacizumab in combination with paclitaxel for HER-2 negative metastatic breast cancer: an economic evaluation. Eur J Cancer* ***2009****; 45(8):1397-1406.*

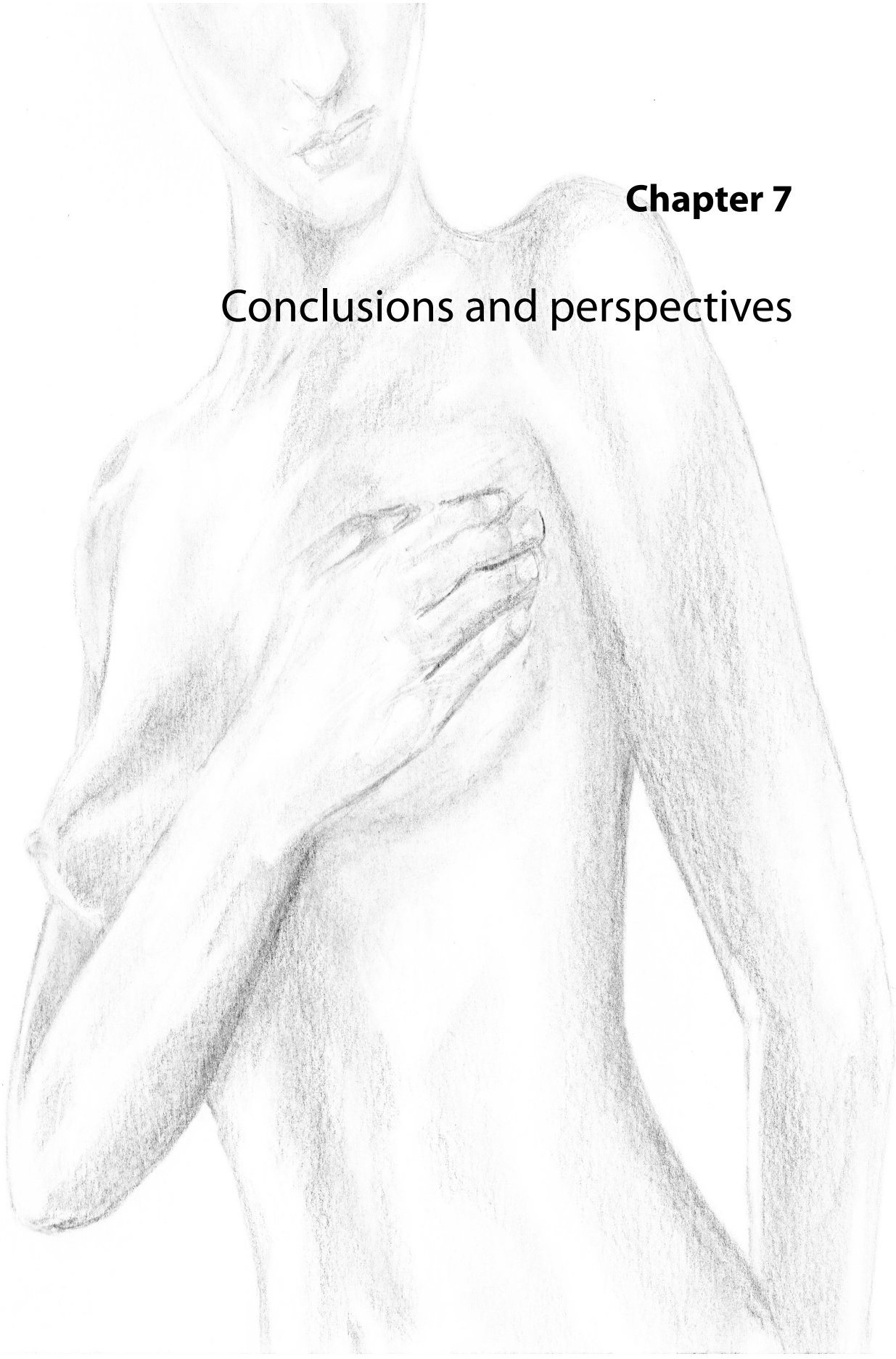
(8) *http://www.nza.nl/regelgeving/beleidsregels/ziekenhuiszorg/BR-CU-2065.*

(9) *Hakkaart- van Roijen L, Tan SS, Bouwmans CAM. Manual for cost research. Methods and unit-prices for economic evaluations in health care (in Dutch). College voor zorgverzekeringen. Geactualiseerde versie* ***2010****.*

(10) *www.medicijnkosten.nl.*

(11) *Beal SL, Boeckman AJ, Sheiner LB. NONMEM user guides.* ***1988****. 2013.*

(12) *Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol* ***2007****; 25(11):1423-1436.*



Chapter 7

Conclusions and perspectives

Conclusions

Cost-effectiveness analyses (CEAs) are widely considered as helpful tools to make informative decisions in a resource constrained environment. Since the introduction of economic evaluations in reimbursement submissions in Australia as a formal requirement in 1993, economic evaluations have become widespread with approximately half the countries in the European Union requesting economic data to varying degrees in their reimbursement decision process[1]. In order for CEAs to be helpful to decision-makers, analyses need to be reliable, relevant and credible. Studies in this thesis are focused on the quality of early breast cancer CEAs and collection of utility and costing data in metastatic breast cancer (MBC) patients. The most important conclusions of the thesis are presented here, and future perspectives are offered.

Early breast cancer

From the year 2000 several authors have developed and published CEAs of early breast cancer therapies. In **chapter 2.1** we have shown that these CEAs had widely diverging outcomes caused by differences in modelling methods for extrapolation of data. Although all analyses adhered well to current economic guidelines, several methods did not correctly reflect real world disease progression thereby demonstrating the lack of quality of these analyses. Furthermore, as methods differed so widely, outcomes between analyses were totally incomparable. Results from this analysis show that current quality guidelines are not sufficient as disease specific guidance is lacking and authors thereby have too much freedom of choice regarding the method for extrapolating data. To improve quality, comparability and reflection of real world disease progression in future early breast cancer CEAs, standardization and disease specific guidance is needed regarding the most important modelling characteristics. This issue was also already addressed by Annemans[2], but afterwards no steps towards disease specific guidance were made. Furthermore, such limitations could be prevalent not only in breast cancer, but also in a range of other oncological conditions thereby indicating the need for more research in other disease areas too.

To increase awareness to the problem described in the previous chapter, a short perspective is provided in **chapter 2.2.** In this perspective we outline the need for more collaboration between international stakeholders to increase credibility and accuracy of future CEAs. Physicians and economists should work more closely together to increase reflections of real world disease progression, thereby overcoming the problem described in chapter 2.1 in an earlier stage.

Furthermore, published early breast cancer CEAs also differed in the choice of cycle length and use of software programmes for model development. In **chapter 3** we have implemented a multi-step cost-effectiveness framework in the statistical scripting language R. In this chapter we showed that an incorrectly chosen cycle length leads to biased outcomes in life expectancy and incremental cost effectiveness ratio's (ICERs). As choice of cycle length impacted outcome, these results demonstrate that cycle lengths should be chosen carefully and adapted to the magnitude of change over time. This framework automatically adapts cycle length to this magnitude of change and thereby eliminates cycle length induced bias on the outcome. This analysis furthermore showed that the statistical scripting language R has marked advantages over non-scripting based languages regarding transparency, reproducibility and practical limitations and should therefore be the preferred software programme for the implementation of CEAs. A major advantage of this multi-step framework is that it is not only restricted to oncology therapies, but applicable for CEAs of all sorts of therapies.

In addition to the wide variety in modelling methods for extrapolation of data (chapter 2.1), several differences were observed in published model structure and parameterization for early breast cancer CEAs comparing tamoxifen and anastrazole. In **chapter 4** we showed that these differences have a substantial impact on the relative estimation of patient life expectancy. Differences in CEA outcomes, as identified in chapter 2.1, are therefore, in addition to differences in modelling methods, also partly related to the differences in model structure and parameterization. Several of the implemented structures and parameterizations did not adequately reflect breast cancer disease progression, thereby again reflecting incomparability and the lack of quality of these analyses. To improve quality, comparability and credibility of future early breast cancer CEAs also more guidance is needed regarding structures and parameterization in addition to guidance on modelling methods. Based on the results of this chapter we suggest the inclusion of various metastatic health states, time-dependent incidence of recurrence and inclusion of death due to adverse events.

Metastatic breast cancer

One of the aims of MBC therapy is to improve quality of life of a patient, which therefore is an essential parameter in CEAs. In **chapter 5,** we collected utility values for health states related to human epidermal growth factor receptor 2 (HER-2) positive MBC in laypeople in Sweden and the Netherlands and productivity loss in patients with breast cancer in both countries. In addition to capturing utility values, data showed that, regardless of similar perspectives in both countries, different preferences for utility valuations lead to differences in utility valuations between countries. Differences found in utility valuation

could ultimately lead to large differences in CEA outcomes and this data therefore demonstrate that it is necessary to capture country specific utility values instead of transferring values between countries.

In order to estimate health state related costs reliably resource use data are needed, which is therefore another essential input parameter for CEAs in addition to utilities. In **chapter 6**, resource use for patients diagnosed with HER-2 MBC was collected over time. In this respect, **chapter 6.1** focussed on resource use and costs of MBC in both the Netherlands and Belgium. In this analysis it was shown that a majority of costs in both countries was related to the use of trastuzumab, respectively 50% of total costs in the Netherlands and 56% in Belgium thereby visualizing the impact of biologicals on total costs and confirming the need for reliable CEAs. Moreover, essential differences in resource use were identified between both countries, such as length of hospital stays and number of physician visits, confirming the need for collecting country specific resource use data instead of transferring volume data between countries.

In **chapter 6.2** we focused on health state related costing over time in the Dutch HER-2 MBC population as described in chapter 6.1. Although health state related costs in MBC are often modelled as constant costs over time, data from this analysis have shown that the first two months of progression are most expensive due to an increase in number and length of hospitalizations. In addition, costs in the last month of life are higher compared to average progression costs, indicating the relevance of death related transition costs. Both outcomes demonstrate the need for incorporating time dependent costs in MBC CEAs. Outcomes in this analysis have therefore shown that costing data should be analyzed over time and linked to disease progression to obtain adequate costing estimates. Such analyses could ultimately lead to more insights in costing patterns of different diseases over time.

In conclusion, the current thesis presents the existence of a wide variety in modelling methods, structures and parameterization in early breast cancer CEAs thereby making outcomes of economic evaluations incomparable and widely diverging. Several recommendations are made to enhance reflection of "real world" breast cancer disease progression in CEAs which should ultimately lead to more credible, reliable and comparable outcomes (**Table 1**).

Table 1. *Disease specific recommendations*

	Chapter 2.1
1	Inclusion of a life long time horizon
2	Inclusion of a carry over effect
3	Use of a recurrence free survival hazard ratio
4	Inclusion of time dependent incidence of recurrence
5	Inclusion of all adverse events
6	Inclusion of both age and hormone receptor +/- as subgroups
7	Transparantly specify the costs
	Chapter 4
8	Inclusion of a disease free, local recurrence, soft tissue metastasis visceral metastasis, bone metastasis, death due to breast cancer and death due to other causes health states
9	Inclusion of time dependency of having metastatic disease after local recurrence
10	Inclusion of time dependency of death after having recurrence
	Chapter 6.1
11	Inclusion of time dependent costs for progressive disease health state
12	Inclusion of higher costs for last month of life

In addition, we demonstrated the use of a multi-step framework and the need for country specific quality of life and costing data as essential differences appeared between countries. Moreover, we have shown that the use of primary patient data in costing studies is essential in order to capture reliable health state costing over time (**Table 2**).

Table 2. *Other recommendations*

	Chapter 3
1	Use of the multi-step framework to eliminate cycle length induced bias
	Chapter 5
2	Collection of country specific utility values
	Chapter 6.1
3	Collection of country specific costs
	Chapter 6.2
4	Collection of patient related costing data linked to clinical progression

Perspectives

Author choices in modelling methods, structures and parameterization in early breast cancer CEAs have caused a wide spread in outcomes (**chapter 2 and 4** of this thesis), demonstrating that it is time to rethink the way we perform economic evaluations by modelling long term costs and effects in breast cancer. In addition to existing general methodological guidance[3;4], disease specific guidance is needed to decrease versatility in modelling methods, have better reflections of disease progression and thereby increase quality, credibility and comparability of early breast cancer CEAs.

To reach this goal, a reference case for breast cancer should be developed and implemented. A reference case is a standard set of methods and assumptions serving as a point of comparison across studies[5]. In 1996 Gold et al. introduced the use of reference cases by focussing on a set of minimum or core requirements such as the need for discounting, sensitivity analyses and time horizon, thereby enabling better comparison between economic evaluations[5]. In 2002 Gabriel, Drummond et al[6]. outlined a process for the development of more disease specific reference cases for economic evaluations in rheumatology as in several publications[7-9] areas were identified in which no consensus has been reached. In their publication they stated the following; "One of the primary objectives of economic evaluations is to make informed choices regarding the allocation of resources. This objective can only be achieved if the methodology of studies is broadly comparable. Otherwise, apparent differences in the relative cost-effectiveness of treatment may be attributable to differences in study methodology rather than to true differences in the cost-effectiveness of the therapies/interventions".

As outlined in this thesis, exactly the same issue has now appeared in CEAs of early breast cancer. Instead of wide varieties in study methodology, now differences in modelling methods, model structures and parameterization have caused large differences in cost-effectiveness outcomes which could even have lead to the unavailability of life-saving drugs to patients due to large differences in outcomes. We therefore should go beyond generic reference cases as specified by Gold et al. and even further then the disease specific study methodology reference case as proposed by Drummond et al. We need to develop disease specific reference cases focussing on uniform modelling methods, structures and parameterization in addition.

In early breast cancer a disease specific reference case is needed with recommendations regarding modelling methods such as time horizon, incidence of recurrence, carry over effect and inclusion of adverse events (**chapter 2**), structures and assumptions such as the inclusion of multiple metastatic health states and death due to adverse events (**chapter**

4) and at last country specific input regarding both utilities and resource use (**chapter 5 and 6**). For a complete overview of all recommendations we refer to **table 1** and **table 2** of the conclusion section.

Although recommendations for an early breast cancer reference case are described in this thesis, there is still no practical implementation of this reference case as aid for decision making. In addition, this breast cancer example could be the tip of the iceberg, as the problem is not only prevalent in this disease area[8;10-13] and reference cases for other disease areas are needed too. To eradicate the underlying problem more rigorous and practical changes to the way we perform economic evaluations are needed. Breast cancer recommendations provided in this thesis are the result of extensive literature reviews, data modelling and data collection, but to prevent the problem from occurring, reference cases for other disease areas should be developed upfront and therefore by other methods.

A relevant method to reach consensus on disease specific reference cases is the use of expert panels in international groups as presented by the OMERACT working group[6;7]. An "expert panel" is a specially constituted working group that meets for evaluation and is made up of independent specialists with well-established expertise. In this case, experts should have well-established expertise and leadership in the disease of interest (physicians), epidemiology, health services research, health policy and health economics. This expert panel should meet on a regular basis during conferences in which most essential topics are discussed. At the first conference, the research agenda should be prioritized and tasks should be distributed between members of the expert panels. During next conferences, outcomes of this research are presented and consensus on the disease specific reference case can be reached by the final selection of essential characteristics. In reality, this entire program will encompass more rounds and conferences, but for this instance the case is simplified. More detailed steps for the set up of such expert panel working groups are presented by OMERACT[14].

The next step is the publication of the disease specific reference case. The best manner would be to publish it in an open source environment managed by people from the previous explained working group. An open source environment is preferred as it enables transparent communication of adaptations to the model made by the working group over time. In addition, apart from the working group, it is also possible that other users of the disease specific reference case have reasonable arguments to adapt the structure for their specific analysis. When users (not the working group) adapt the reference case for their analysis it is essential that the differences with the reference case and the adapted model are explicitly stated in a sensitivity analysis as outlined in **chapter 4** of this thesis. Hereby impact of changes is visualized and outcomes are made more comparable and

transparency of outcomes is increased.

By only developing and publishing reference cases and guidance their impact on decision making remains low. To increase the impact of reference cases it is therefore essential that decision makers in various countries demand their use (when available) for reimbursement submissions. Decision makers should be actively involved in the development of reference cases and the working group should have contact with decision making authorities in several countries on a regular base.

To enable the development of such reference cases, network platforms are indispensable. A relevant network for this purpose would be the European network for health technology assessment (EUnetHTA)[15;16]. EUnetHTA is established to create an effective and sustainable network for health technology assessment across Europe that could develop and implement practical tools to provide reliable, timely, transparent and transferable information to contribute to decisions in member states. Such network platforms should enable the crosstalk between different disciplines and the production of various disease specific reference cases. When reference cases become available only adaptations to be made are the country specific input parameters such as utilities and resource use (**chapter 5 and 6**) to make outcomes relevant for various countries.

Another essential task of the EUnetHTA which deserves more attention is the harmonization of evidence requirements between jurisdictions to improve efficiency. Harmonization has the potential to avoid duplication of effort for both manufacturers and HTA bodies involved in preparing and reviewing HTA submissions for innovative technologies. In addition to harmonization in modeling methods, harmonization in reimbursement requirements is extremely wanted as a boost to the HTA field.

An overview of the previously explained process for reference case development is provided in **figure 1** in which the different steps are split up in six main components.

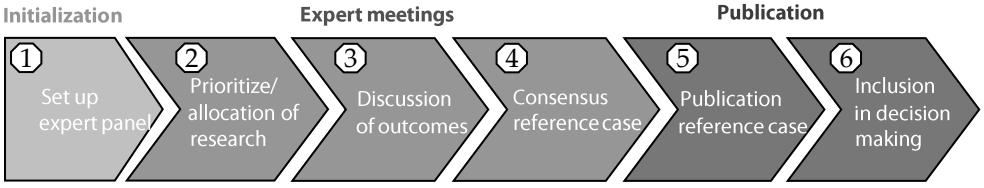


***Figure 1**. Implementation reference case*

In this thesis shortcomings of published early breast cancer CEA models are identified and solutions are presented to overcome these problems. Although different steps in

figure 1 were followed to come to publication of recommendations, some limitations of our work deserve mentioning. First of all, our group of experts was relatively small and no experts from other countries were included in prioritization of research and discussion of outcomes. To overcome this, discussion with experts over the world should be initialized who further discuss targets of future research. Outcomes found in this thesis could be a good starting point for these regular expert meetings and steps explained in this thesis (**figure 1**) should be followed during these meetings to adequately address and implement a complete reference case.

Second, we only focussed on modelling methods and input in early breast cancer thereby not covering the whole disease. Future expert meetings, explained in the first limitation, should therefore focus on expansion of current recommendations to the whole disease. Recently Tappenden et al[17]. have published a methodological framework on how to develop whole disease models. Such an approach can provide a consistent mathematical infrastructure for the economic evaluation of virtually any intervention from screening to end of life treatment across the entire breast cancer pathway. Linking this framework with the implementation of a reference case would therefore result in an extremely useful and transparent economic model.

Third, we did not discuss our outcomes with decision makers. To enhance implementation decision makers should be involved in future expert meetings. Starting with discussing outcomes and implementation with decision makers from the Netherlands it should be enabled to further expand and include decision makers from other countries as well. This would also possibly enable a boost of European wide reimbursement decisions, a previously explained target from the EUnetHTA.

At last, we only explored real world costing of MBC, but a wider implementation of real world data should be explored to enhance generalisability of CEA outcomes to the entire population. In addition to real world costing data also real world effectiveness should therefore be incorporated in models. Although improved generalisability is a major advantage, the main limitation of using real world data is the potential for bias, as observations studies do not meet the methodological rigor of RCTs[18;19]. More research is therefore needed to improve real world data incorporation in future reference CEAs.

In addition to the implementation of a reference case, we have recommended the use of scripting languages such as R for economic evaluations to increase transparency (**chapter 3** of this thesis). Although the learning-curve of R is potentially slightly steeper compared to for instance Excel or TreeAge, it has a lot of advantages. Currently a majority of economic courses are focused on introducing students with software packages as Excel or Treeage

for performing economic evaluations. In addition to the introduction with these often user friendly but not transparent software packages it is essential that students are also introduced with scripting languages in an early stage of their study. Thereby scripting languages will be gradually introduced and students can become familiar with them during their study. An increase in the use of scripting languages for economic evaluations will eventually lead to increased transparency and thereby credibility.

In this thesis several recommendations for a breast cancer reference case were outlined. In the future, reference cases should be developed and implemented before several different models are published and used with widely diverging outcomes and consequences. Expert meetings should be initialized focussing on whole disease reference cases and incorporation of real world data. Thereby it should be possible to prevent the problems described in this thesis from occurring, instead of constantly fighting fires.

References

(1) http://www.ispor.org/htaroadmaps/

(2) *Annemans L. Methodological issues in evaluating cost effectiveness of adjuvant aromatase inhibitors in early breast cancer: a need for improved modelling to aid decision making. Pharmacoeconomics* ***2008****; 26(5):409-423.*

(3) *Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ* ***1996****; 313(7052):275-283.*

(4) *Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess* ***2004****; 8(36):iii-xi, 1.*

(5) *Gold M.R, Siegel J.C, Russel L.B, Weinstein M.C. Cost-effectiveness in health and medicine. New York: Oxford University Press.* ***1986****.*

(6) *Gabriel SE, Tugwell P, Drummond M. Progress towards an OMERACT-ILAR guideline for economic evaluations in rheumatology. Ann Rheum Dis* ***2002****; 61(4):370-373.*

(7) *Gabriel S, Drummond M, Suarez-Almazor ME, Ruff B, Guillemin F, Bombardier C et al. OMERACT 5 Economics Working Group: summary, recommendations, and research agenda. J Rheumatol* ***2001****; 28(3):670-673*

(8) *Gabriel SE. Controversies in economic evaluation in the rheumatic diseases. J Rheumatol* ***1999****; 26(9):1859-1860.*

(9) *Ruff B. OMERACT: economic evaluations and health policy. J Rheumatol* ***2001****; 28(3):666-669.*

(10) *Cranney A, Coyle D, Welch V, Lee KM, Tugwell P. A review of economic evaluation in osteoporosis. Arthritis Care Res* ***1999****; 12(6):425-434.*

(11) *Maetzel A, Ferraz MB, Bombardier C. A review of cost-effectiveness analyses in rheumatology and related disciplines. Curr Opin Rheumatol* ***1998****; 10(2):136-140.*

(12) *Tugwell P. Economic evaluation of the management of pain in osteoarthritis. Drugs* ***1996****; 52 Suppl 3:48-58.*

(13) *Drummond MF, Barbieri M, Wong JB. Analytic choices in economic models of treatments for rheumatoid arthritis: What makes a difference? Med Decis Making* ***2005****; 25(5):520-533.*

(14) *Tugwell P, Boers M, Brooks P, Simon L, Strand V, Idzerda L. OMERACT: an international initiative to improve outcome measurement in rheumatology. Trials* ***2007****; 8:38.*

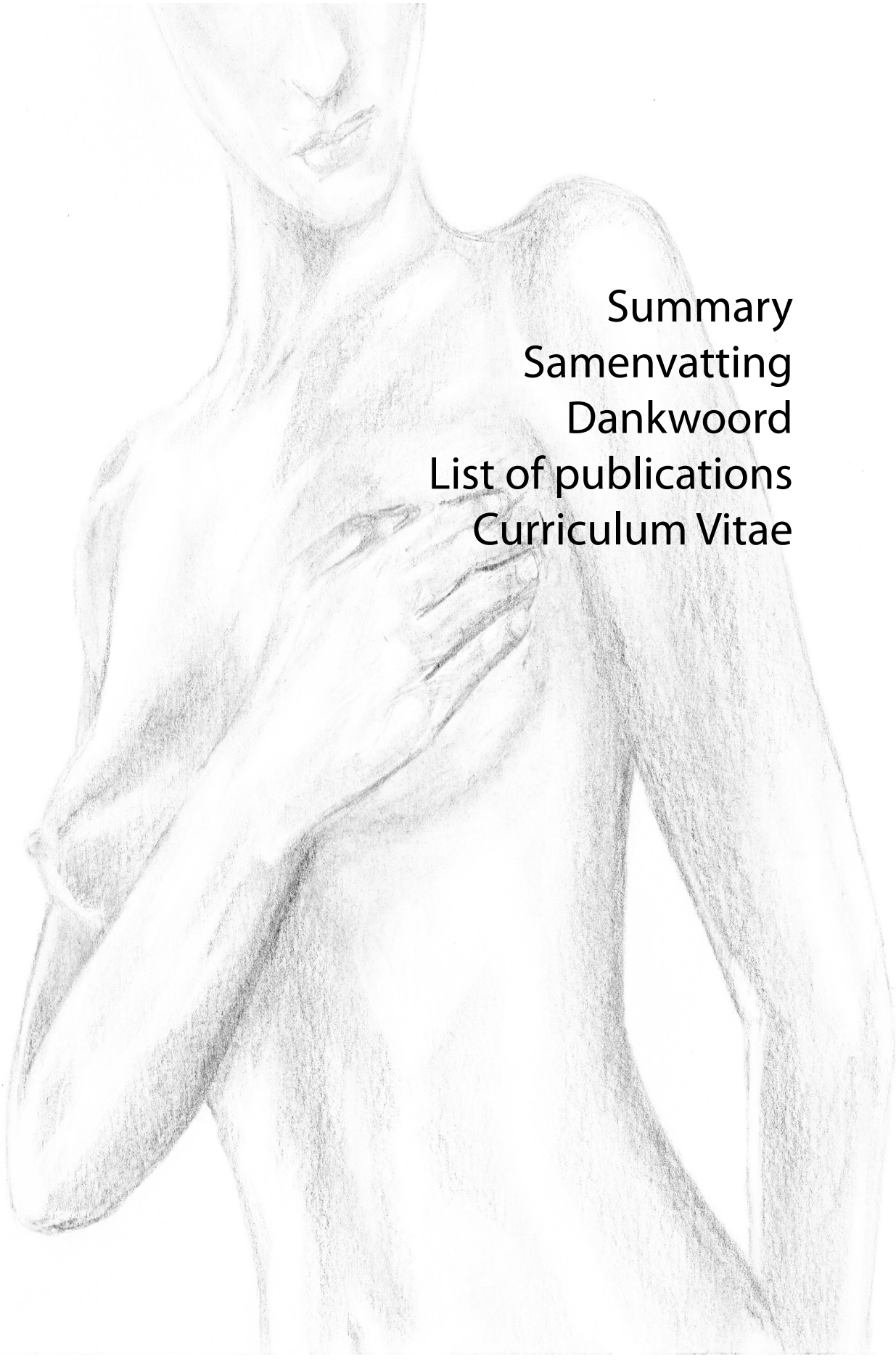
(15) *Kristensen FB, Chamova J, Hansen NW. Toward a sustainable European Network for Health Technology Assessment. The EUnetHTA project. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz **2006**; 49(3):283-285.*

(16) *Kristensen FB, Makela M, Neikter SA, Rehnqvist N, Haheim LL, Morland B et al. European network for health technology assessment, EUnetHTA: planning, development, and implementation of a sustainable European network for health technology assessment. Int J Technol Assess Health Care **2009**; 25 Suppl 2:107-116.*

(17) *Tappenden P, Chilcott J, Brennan A, Squires H, Stevenson M. Whole disease modeling to inform resource allocation decisions in cancer: a methodological framework. Value Health **2012**; 15(8):1127-1136.*

(18) *Garrison LP, Jr., Neumann PJ, Erickson P, Marshall D, Mullins CD. Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. Value Health **2007**; 10(5):326-335.*

(19) *Schneeweiss S, Gagne JJ, Glynn RJ, Ruhl M, Rassen JA. Assessing the comparative effectiveness of newly marketed medications: methodological challenges and implications for drug development. Clin Pharmacol Ther **2011**; 90(6):777-790.*



Summary

Cost-effectiveness analyses (CEAs) are widely considered to be helpful tools for making informative decisions in a resource constrained environment. Since the introduction of economic evaluations in reimbursement submissions in Australia as a formal requirement in 1993, CEAs have become widespread with approximately half the countries in the European Union requesting economic data to varying degrees in their reimbursement decision process.

To ensure appropriate quality of CEAs, guidelines were developed and published several years ago, with the Drummond guideline in the British Medical Journal (BMJ) as the most widely applied one. Regardless of the implementation of these guidelines, several studies have shown that CEAs differ markedly in quality. As CEAs could have a direct effect on the reimbursement of therapies and patient access to medication is strongly related to reimbursement it is of utmost importance that analyses and outcomes are of high quality, robust, comparable, and credible.

In this thesis, we aimed to study whether current model based CEAs in early breast cancer have sufficient quality, whether modelling methods are comparable between published articles and whether they reflect "real world" disease progression. In addition we aimed to assess utility and real world observational costing data for metastatic breast cancer (MBC) in different countries. Research is presented on various subjects such as, reviewing early breast cancer CEAs, introducing new cost-effectiveness frameworks, quality of life in MBC and at last real world observational costing studies for MBC from patient population levels.

After a general introduction (chapter 1), **chapter 2.1** of this thesis provides an overview of the current scientific literature on CEAs of hormonal therapies for early breast cancer. This overview shows that, regardless of a good adherence to current quality guidelines, there is a wide variety in choice of modelling methods for the extrapolation of data. Outcomes are driven by author choices instead of underlying clinical trial data resulting in a wide variety in expected life years (LY) gained and costs. For example outcome for anastrazole vs. tamoxifen varied in Spain from 0.16 LY to 0.550 LY gained and incremental cost-effectiveness ratios (ICERs) varied from €3,958 per LY gained in Belgium to €75,331 per LY gained in Spain. The main conclusion from this chapter was that there is an urgent need for more guidance and standardization regarding modelling methods applied in breast cancer CEAs to increase credibility and reliability

While chapter 2.1 analyzed methodological differences in all CEAs of hormonal early

breast cancer therapies, **chapter 2.2** focused on the outcomes of CEAs calculating cost-effectiveness of anastrazole. In this chapter a short perspective is provided in which we aimed to increase awareness to the problem discussed in the previous chapter by focussing on the widely diverging outcomes of CEAs making use of similar clinical trial data. The need for collaboration between clinical experts and cost-effectiveness modelling experts is discussed to increase quality of CEAs in early breast cancer.

More specifically from the wide variety of modeling methods as presented in chapter 2.1, especially a wide variety in cycle length was observed in these analyses. **Chapter 3** describes the development and implementation of a framework for CEAs in the statistical scripting language R eliminating the need for specifying this cycle length upfront. The developed framework, in which the multi-step ODE solver algorithm was implemented, was demonstrated using a previously published case example model that compared adjuvant breast cancer therapies for tamoxifen and anastrazole. A single-step ODE solver algorithm was also implemented, in order to compare performance of the single-step algorithm for a range of step-sizes to the multi-step algorithm. From these results it becomes clear that incorrectly chosen cycle lengths lead to biased outcomes in life expectancy and ICERs. Furthermore, the use of the statistical scripting language R is advocated in this chapter to improve transparency and reproducibility of future CEAs.

Chapter 4 describes the wide variety and impact of differences in published model structures and parameterization for CEAs comparing tamoxifen and anastrazole. A basic model was developed consisting of the most common structures and most simple parameterizations. This structure was adapted with the identified differences in the publications and subsequently outcomes (LY gained and ICERs) were re-calculated. Various structures and parameterizations did not adequately reflect disease progression and we showed that these even resulted in diverging outcomes when compared to the basic model. Results from this chapter indicate that also more standardization and guidance is needed in structures and parameterization of early breast cancer CEAs.

The second part of this thesis, (**chapter 5 and 6**) focussed on quality of life and real world costing studies in metastatic breast cancer (MBC) patients.

In this respect, **chapter 5** describes the quality of life and productivity loss of patients diagnosed with human epidermal growth factor receptor 2(HER-2) positive MBC in the Netherlands and Sweden. To capture these utilities, validated health state vignettes were used describing stable disease, progressive disease and seven grade 3-4 adverse events. Results showed that the Swedish sample rated progressive and stable disease (0.61 (95%CI= ±0.07), 0.81 (±0.05)) higher than the Dutch sample (0.49 (±0.06), 0.69

(±0.05)). Furthermore, results from the productivity loss study demonstrated that patients currently receiving treatment reported productivity reductions of 69% (The Netherlands) and 72% (Sweden); those who had recently completed therapy reported reductions of 41% (The Netherlands) and 40% (Sweden). The differences in utility scores between both countries indicate the necessity of collecting country specific quality of life data for use in cost-effectiveness models.

Chapter 6 presents two different costing studies focusing on patients diagnosed with HER-2 positive MBC. **Chapter 6.1** describes the resource use and costs in both the Netherlands and Belgium making use of primary real world patient data. Resource use was analyzed from a health care perspective and five types of input were collected; demographics, MBC clinical history, medical treatment, other MBC related resource utilizations and clinical outcomes. Total costs of medical treatment and other resource use utilization amounted to respectively €48,301 (CI, 40,037 – 56,564) in the Netherlands and €37,343 (CI, 28,996 – 48,181) in Belgium. The majority of costs in both countries was related to the use of trastuzumab, which was 50% of total costs in the Netherlands and 56% in Belgium, respectively. In addition, we noticed essential differences in resource use between both countries such as length of hospital stays and number of physician visits, demonstrating the need for country specific resource use data instead of transferring volume data from other countries.

In **chapter 6.2** we describe phase related costing of HER-2 positive MBC. Resources collected in the previous chapter were used and MBC disease state was determined by collecting date of MBC diagnosis, disease progression and death for each individual patient. Costs of stable disease were constant over time, with monthly average costs of €3,236. Monthly costs and factors contributing to the costs for progressive disease demonstrated a wide variety over time whereby as expected the highest costs were achieved in the first two months after diagnosis amounting to €4,339 and €4,366, respectively. Costs and factors contributing to the last months of life also varied over time, whereby as expected the last month of life turned out to be the most expensive one, with average costs of €4,521. This analysis demonstrated that time dependent costs for progressive disease and death should be included in Markov modeling to obtain an adequate reflection of costs of the disease over time.

In conclusion, this thesis presents the varying use of modelling methods, structures and parameterization in CEAs of early breast cancer. In the various chapters recommendations are presented that should increase credibility, external validity, robustness and quality of future CEAs. This thesis demonstrates that it is for instance essential to include life long time horizons, a carry over effect, time dependent incidence of recurrence and

various metastatic health states. In addition, quality of life data in HER-2 positive MBC patients for both the Netherlands and Sweden is presented and furthermore real world costing data for similar patient populations in the Netherlands and Belgium. Apart from identifying quality of life and costs, these studies demonstrate the necessity of collecting country specific data and real world costing outcomes over time linked to clinical disease progression.

Samenvatting

De behoeften van de mens zijn per definitie oneindig maar de middelen om aan deze behoeften te voldoen zijn beperkt. In de gezondheidseconomie gaat dezelfde regel op, het budget binnen de gezondheidszorg is eindig ook al worden er steeds meer nieuwe middelen geïntroduceerd. De uitdaging bestaat er dan ook uit om binnen het kader van het beperkte budget op de best mogelijke manier gezondheid te winnen voor de bevolking. Om de kosten en de gezondheidseffecten van interventies te onderzoeken wordt daarom gebruikt gemaakt van gezondheidseconomische evaluaties.

Een vorm van deze economische evaluaties is de kosten effectiviteit analyse (KEA) waarbij het verschil in kosten tussen twee interventies en het verschil in effectiviteit tussen dezelfde twee interventies wordt berekend. Het verschil in kosten gedeeld door het verschil in effectiviteit resulteert in de "incrementele kosten effectiviteit ratio" (IKER) welke staat voor de prijs per gewonnen levensjaar, één van de primaire eindpunten van economische evaluaties.

Sinds de introductie van economische evaluaties als formeel onderdeel bij vergoedingsbesluiten in Australië in 1993, is de implementatie en het gebruik van KEAs wijd verspreid waarbij ongeveer de helft van de Europese landen economische data heeft opgenomen in richtlijnen voor vergoedingsbesluiten. Deze opname heeft ervoor gezorgd dat bij vergoedingsbesluiten, naast uikomsten van klinische trials, ook de uitkomsten van economische evaluaties worden meegenomen. In deze landen worden dan ook belangrijke besluiten omtrent maatschappelijke aanvaardbaarheid van de kosten genomen aan de hand van de hoogte van de berekende IKER. In het Verenigd Koninkrijk worden bijvoorbeeld interventies over het algemeen niet vergoed als deze een IKER hoger dan £30.000 hebben.

Om de kwaliteit van economische evaluaties te garanderen zijn jaren geleden richtlijnen ontwikkeld en gepubliceerd. Ondanks het navolgen van deze richtlijnen hebben verschillende studies aangetoond dat KEAs zeer in kwaliteit verschillen. Deze grote mate van kwaliteitsverschil is een zorgwekkende ontwikkeling aangezien uitkomsten van KEAs, een direct effect op vergoeding besluiten kunnen hebben en toegang tot medicatie voor de patiënt sterk gerelateerd is aan deze vergoeding. Het is dan ook van essentieel belang dat analyses en uitkomsten van goede kwaliteit, robuust, vergelijkbaar en betrouwbaar zijn.

Ziekteprogressie en kwaliteit van leven zijn vaak primaire eindpunten van grote klinische trials. Binnen huidige KEAs worden deze ziekteprogressie, kwaliteit van leven en daarbij

behorende kosten vaak aan elkaar verbonden door wiskundige modellen. Op deze manier is het mogelijk om eindpunten te voorspellen wanneer men geïnteresseerd is in uitkomsten die ver achter het einde van de klinische trial liggen (extrapolatie van data). Patiënten worden bijvoorbeeld voor vijf jaar in een klinische trial gevolgd, maar overleven gemiddeld voor twintig jaar. Om deze overleving te kunnen berekenen moet de data na vijf jaar geëxtrapoleerd worden naar tijdspunten die verder in de toekomst liggen. Dit wordt gedaan door deze vijf jarige data te modelleren over de tijd waarbij vele verschillende aannames gedaan moeten worden.

Het doel van dit proefschrift is drieledig; 1) het in kaart brengen van de kwaliteit van huidige model gebaseerde KEAs van vroege borstkanker, 2) of modellering methoden en aannames vergelijkbaar zijn tussen publicaties en of deze progressie van ziekte correct weerspiegelen en als laatste 3) het vaststellen van de kwaliteit van leven en kosten voor gemetastaseerde borstkanker in verschillende landen uit de dagelijkse klinische praktijk, beide essentiële parameters binnen KEAs.

Na een algemene samenvatting (hoofdstuk 1), geeft **hoofdstuk 2.1** van dit proefschrift een overzicht van de huidige wetenschappelijke literatuur betreffende KEAs van hormonale therapieën voor vroege borstkanker. Dit overzicht laat zien dat, ondanks het correct navolgen van huidige richtlijnen, er zeer grote verschillen zijn in de keuze van modellering methoden voor de extrapolatie van data. Uitkomsten worden gedreven door keuzes van auteurs in plaats van onderliggende klinische trial data welk resulteert in grote verschillen in verwachtte gewonnen levens jaren (LJ) en kosten. Bijvoorbeeld uitkomsten voor anastrazole vs. tamoxifen varieerden in Spanje van 0.16 gewonnen LJ tot 0.550 gewonnen LJ en IKERs varieerden van €3,958 per gewonnen LJ in België tot €75,331 in Spanje. De voornaamste conclusie van dit hoofdstuk was dat er een urgente behoefte is aan meer richtlijnen en standaardisatie betreffende modellering methoden om zo de betrouwbaarheid en geloofwaardigheid van uitkomsten te verbeteren.

Terwijl hoofdstuk 2.1 de nadruk legt op modellering verschillen in alle KEAs van hormonale vroege borstkanker therapieën, legt **hoofdstuk 2.2** de nadruk op de uitkomsten van KEAs die alleen de kosten effectiviteit van anastrazole berekenen. In dit hoofdstuk is een kort perspectief weergegeven waarin we proberen het bewustzijn omtrent het probleem beschreven in het vorige hoofdstuk te verbeteren. Dit is gedaan door te focussen op de zeer uiteenlopende uikomsten van KEAs die gebruik maken van dezelfde klinische trial data. De behoefte aan een verbetering van samenwerking tussen klinische- en KEA experts wordt hier bediscussieerd, wat uiteindelijk zou moeten leiden tot een verbetering in de kwaliteit van KEAs bij vroege borstkanker.

Naast het grote verschil in methoden van extrapolatie van data zoals gepresenteerd in hoofdstuk 2.1 was er in de gepubliceerde modellen ook een zeer groot verschil in gekozen lengte van Markov cycles en waren modellen gematigd transparant. Met Markov cycles word de tijd bedoeld wanneer patiënten in het wiskundig model geëvalueerd worden, dit kan iedere dag, iedere maand of ieder willekeurig gekozen lengte van tijd zijn. Een te korte lengte van de Markov cycle kan ervoor zorgen dat bijvoorbeeld ziekenhuis opnames of terugkeer van ziekte bij een patiënt gemist worden. **Hoofdstuk 3** beschrijft de ontwikkeling van een raamwerk voor KEAs in het statistische programma "R" welke het gebruik van vooraf gekozen Markov cycles overbodig maakt. Dit raamwerk, waarin een multi-stap differentiaal vergelijker is gebruikt, wordt uitgelegd aan de hand van een gepubliceerde KEA van tamoxifen en anastrazole, twee hormonale therapieën voor vroege borstkanker. Een differentiaal vergelijker met een enkele stap werd ook ontwikkeld om zo het gebruik van verschillende stappen te vergelijken met het multi-stap raamwerk. De resultaten laten zien dat een verkeerd gekozen lengte van Markov cycle tot bias in levensverwachting en IKERs leidt. Daarnaast wordt in dit hoofdstuk het gebruik van het statistische programma "R" bepleit voor het verbeteren van de transparantie en reproduceerbaarheid van KEAs.

Naast de extrapolatie van klinische trial data moet de structuur van het model ook het ziekteproces correct weerspiegelen. Met de structuur wordt hier bedoeld hoe de ziekte uitgebeeld is in het wiskundige model aan de hand van geïncludeerde gezondheidstoestanden van een patiënt, bijvoorbeeld gezond, metastase, bijwerking etc. **Hoofdstuk 4** beschrijft het grote verschil in gepubliceerde model structuren en parameterisatie (manier van gebruik parameters) van KEAs die tamoxifen en anastrazole vergelijken. Een basis model werd ontwikkeld bestaande uit de meest algemene structuren en meest simpele vorm van parameterisatie. Deze structuur werd aangepast middels gevonden verschillen in de publicaties en gewonnen LJ en IKERs werden herberekend. Verschillende structuren en parameterisatie weerspiegelden progressie van ziekte niet op een adequate wijze en resulteerden zelfs in verschillen in uitkomsten wanneer deze vergeleken werden met het basis model. Uitkomsten van dit hoofdstuk laten zien dat er ook meer standaardisatie en richtlijnen nodig zijn voor structuren en parameterisatie van vroege borstkanker KEAs.

De nadruk van het tweede deel van dit proefschrift (hoofdstuk 5 en 6) ligt op de kwaliteit van leven en kosten studies bij gemetastaseerde borstkanker patiënten.

In **Hoofdstuk 5** wordt de kwaliteit van leven en het productiviteitsverlies van patiënten gediagnosticeerd met humane epidermale groei factor receptor 2 (HER-2) positieve gemetastaseerde borstkanker in Nederland en Zweden beschreven. Zowel kwaliteit van

leven als het productiviteitsverlies van een patiënt zijn belangrijke input paramaters voor KEAs. Om de kwaliteit van leven van een patiënt te berekenen werd gebruik gemaakt van gevalideerde beschrijvingen van de volgende gezondheidstoestanden; stabiele ziekte, progressieve ziekte en zeven graad 3-4 bijwerkingen. Uit de resultaten bleek dat men in Zweden progressieve en stabiele ziekte (0.61 (95%CI= ±0.07), 0.81 (±0.05)) hoger waarderen dan de geïnterviewde personen in Nederland (0.49 (±0.06), 0.69 (±0.05)). Daarnaast lieten resultaten van het onderzoek naar productiviteitsverlies zien dat patiënten die op dit moment een behandeling ondergaan een vermindering in productiviteit van 69% in Nederland en 72% in Zweden hadden. Patiënten die recent hun therapie beëindigd hebben lieten een vermindering in productiviteit zien van 41% in Nederland en 40% in Zweden. De verschillen in kwaliteit van leven tussen beide landen benadrukken het gebruik van land specifieke kwaliteit van leven data voor KEAs.

In hoofdstuk 6 onderzochten we de kosten van patiënten gediagnosticeerd met HER-2 positieve gemetastaseerde borstkanker. Dergelijke kosten studies zijn belangrijke input parameters voor de kosten waardering van verschillende gezondheidstoestanden in model gebaseerde KEAs. **Hoofdstuk 6.1** beschrijft het zorggebruik en de kosten van patiënten in Nederland en België gebruik makend van primaire data uit de dagelijkse praktijk. Het zorggebruik werd geanalyseerd vanuit een gezondheidszorg perspectief en vijf verschillende types input werden verzameld; demografie, klinische geschiedenis van gemetastaseerde borstkanker, medische behandeling, ander borstkanker gerelateerd zorggebruik en klinische uitkomsten. Totaal van medische behandeling en ander zorggebruik bereikte een totale kostenpost van €48,301 (CI, 40,037 – 56,564) in Nederland en €37,343 (CI, 28,996 – 48,181) in België. Het merendeel van kosten in beide landen was gerelateerd aan de kosten van trastuzumab, 50% van totale kosten in Nederland en 56% in België. Daarnaast constateerden we een aantal grote verschillen in zorggebruik tussen beide landen, zoals de lengte van ziekenhuisopnames en gemiddeld aantal bezoeken aan een arts. Deze resultaten suggereren dat landspecifieke data voor zorggebruik gebruikt moeten worden in plaats van het gebruiken van volume data uit andere landen.

Het doel van **hoofdstuk 6** was het beschrijven van gezondheidstoestand gerelateerde kosten van HER-2 positieve gemetastaseerde borstkanker over de tijd. Zorggebruik, zoals verzameld in het vorige hoofdstuk, werd gebruikt en voor elke individuele patiënt gekoppeld aan data van diagnose van gemetastaseerde borstkanker, ziekte progressie en eventueel overlijden. Kosten van stabiele ziekte waren constant over de tijd met gemiddelde maandelijkse kosten van €3,236. Maandelijkse kosten en factoren die bijdragen aan de kosten voor progressieve ziekte lieten een grote verscheidenheid over de tijd zien. De hoogste kosten werden, zoals verwacht, in de eerste twee maanden na diagnose bereikt, met een totaal van €4,339 in de eerste maand en €4,366 in de

tweede. Kosten en factoren bijdragend aan de laatste maanden van leven lieten ook een verschillend patroon over de tijd zien, waarbij de laatste maand de hoogste kosten met zich meedroeg €4,521 gemiddeld per patiënt per maand. Deze uitkomsten laten zien dat het essentieel is dat tijdsafhankelijke kosten voor progressieve ziekte en sterven meegenomen worden in KEA modellen om zo een adequate weerspiegeling van kosten van de ziekte over te tijd te krijgen.

In conclusie, dit proefschrift presenteert het variërende gebruik van modellering methoden, structuren en parameterisatie in KEAs van vroege borstkanker. Aanbevelingen worden gedaan in de verschillende hoofdstukken die moeten zorgen voor een verbeterde weerspiegeling van klinische ziekte progressie van borstkanker in economische modellen. Deze aanbevelingen zouden uiteindelijk moeten leiden tot een verbetering in geloofwaardigheid, externe validiteit, robuustheid en kwaliteit van toekomstige KEAs. Daarnaast is kwaliteit van leven data gepresenteerd voor zowel Nederland als Zweden evenals zorggebruik en kosten voor dezelfde patiënt populatie in Nederland en België. Naast het publiceren van kwaliteit van leven en verschillende kosten laten beide studies zien dat het essentieel is om landspecifieke data te verzamelen en zorggebruik data over de tijd te correleren met ziekte progressie van een patiënt.

Dankwoord

Dat was het dan, mijn promotie onderzoek is afgerond en vier jaar aan werk zit veilig opgeborgen in dit boekje. Het waren vier leuke, onvergetelijke maar vooral ook leerzame jaren. Dit kwam niet alleen door de onderwerpen en het interessante onderzoeksgebied, maar vooral ook door iedereen die ik in deze tijd heb leren kennen. Ik wil dan ook graag een ieder om mij heen bedanken die heeft bijgedragen aan het tot stand komen van dit proefschrift, waarvan een aantal mensen in het bijzonder.

Allereerst wil ik mijn promotoren, Jan Schellens en Hans Severens bedanken. Beste Jan, ik sta nog altijd versteld van je ongelooflijk brede kennis en je onophoudelijke drive. Bedankt voor de grote mate van vrijheid en vertrouwen die je me hebt gegeven in deze tijd, dit waardeer ik enorm. Jouw manier van multi-tasken, begeleiden en aandacht verdelen is, om in de context van dit proefschrift te blijven, ongelooflijk effectief en daarnaast zeer leerzaam. Ik heb veel van je geleerd, bedankt!

Beste Hans, tijdens onze besprekingen in Rotterdam ging het naast de economische evaluaties toch ook wel vaak over de sportieve bezigheden in onze vrije tijd. Ik ben nog steeds in training om je tijden op zowel de 7-heuvelen als de Alpe D'Huez te gaan verbeteren, I will make it! Om elkaar te kunnen spreken, wist ik je overal te vinden, tot aan je keukentafel aan toe. Ik heb tijdens de vier jaren veel van je geleerd, bedankt voor de inspirerende gesprekken en visie, zowel op academisch als sportief gebied.

Mijn directe sparringpartner en co-promotor Anke Hövels. Beste Anke, wat zou ik in deze vier jaren zonder jou hebben gemoeten. Samen filterden we de stortvloed aan ideeën van zowel Jan, Hans en Jan om deze daarna om te zetten tot interessante en haalbare projecten. Mijn nieuwe uitdaging is een baan als post-doc aan de Universiteit in Utrecht, een stap die ik vooral dankzij jouw inzet kan zetten. Ik kijk er ontzettend naar uit om de komende tijd samen verder te werken aan alle verschillende projecten. Bedankt voor alles!

Als laatste uit mijn begeleidingscommissie, Jan Raaijmakers. Beste Jan, iedere keer dat ik je sprak wist je wel weer iets nieuws te verzinnen welk mijn enthousiasme direct weer aanwakkerde. Ik vind het prachtig en leerzaam om te zien hoe je de wereld van de academie met die van de industrie combineert en daar al het mogelijke uithaalt. Bedankt voor de inspirerende en gezellige gesprekken, ik kijk uit naar onze verdere samenwerking in Utrecht.

Onmisbaar voor mij en mijn analyses was ook Coen van Hasselt. Coen, op de dag dat ik hoorde dat ik met R moest gaan werken ben ik direct naar jou toe gesneld. Je hebt me, af

en toe bijna dagelijks, met raad en daad bij gestaan met alle vragen die ik had over deze (toen nog) voor mij onbekende programmeertaal. Ik ben je ontzettend dankbaar voor al je hulp en de plezierige samenwerking bij verschillende manuscripten.

Ook Alwin Huitema had een belangrijk aandeel in mijn zojuist beschreven "R ontdekkingsreis". Alwin, je kwam op een maandag ochtend bij de state met het idee om nu voor eens en altijd die cycle length in de economische modellen te verbannen. Het resultaat was uiteindelijk een heel mooi manuscript en een transparant kosten effectiviteit raamwerk in "R". Bedankt voor al je input en de plezierige samenwerking.

I would like to thank Nuz Quadri and Andrew Lloyd from Oxford Outcomes, United Kingdom. Nuz and Andrew, it was a pleasure working with you. Although we only had discussions by phone in a short time period, I do believe we managed to come up with a very interesting manuscript regarding the quality of life in metastatic breast cancer patients, thank you.

Ilona van Rooij, Janneke Coopmans, Sylvia Sprangers- van Campen en Joke Vanderhaegen wil ik bedanken voor het verzamelen van die ongelooflijke hoeveelheid aan data betreffende het zorggebruik van gemetastaseerde borstkanker patiënten in Nederland en België. Ik besefte me goed dat we alles gedocumenteerd wilden zien, tot aan het kleinste pilletje aan toe. Bedankt voor al dit uitpluiswerk.

Jolanda Slijkerman, personal assistent van Jan, maar toch ook zeker de onze. Voor ons als onderzoekers onmisbaar voor al het geregel binnen het NKI, een ware moeder voor de OIO's. Aangezien ik niet langer dan anderhalf uur achter elkaar rustig op mijn kont kan zitten ben ik regelmatig bij je langs gewandeld om even bij te kletsen. Jolanda, bedankt voor alles!

Ook alle collega's, directe en indirecte , zowel in de "keet" als het NKI, maar natuurlijk ook niet te vergeten mijn geliefde oud collega's, en alle collega's in Rotterdam wil ik kort bedanken. Ook al hebben we vaak geen directe input op elkaars werk, ik denk dat jullie allemaal een grote invloed hebben gehad op het "onzichtbare" deel van mijn proefschrift. Mijn onderwerp was volkomen anders, maar vaak was het schuitje waar we in zaten hetzelfde. Bedankt voor de tips, tricks en natuurlijk alle gezelligheid op de kamer, de borrels, het ISPOR congres in Berlijn en verschillende OIO weekenden. Ik ga jullie missen!

De omslag van het boek was er niet geweest zonder Jules Calis. Jules, we kennen elkaar al vanaf de kleuterschool en als kleine mannekes woonden we bij elkaar in de straat. Ik vind het dan ook een eer dat je de ideeën die ik had voor mijn omslag in een prachtig

geheel wilde verwerken. Ook de tekening van mijn huisje is prachtig geworden, een waar aandenken aan de mooie tijd in Amsterdam! Bedankt!

Paranimfen Rick en Rik (om misverstanden te voorkomen, beter bekend als Pothast en Stuurman in Amsterdam en omstreken). Rick, na de middelbare school in Boxmeer samen richting de Uni in Nijmegen en aansluitend bijna tegelijk richting Amsterdam, waar we wederom vele avonden en weekenden elkaars deur plat liepen. Wat een mooie en onvergetelijke tijd hebben we daar weer gehad. Ik ben ongelooflijk blij jou als goede vriend te hebben en ben er trots op dat je mijn paranimf wilt zijn. Ik kijk uit naar de volgende avonturen. Rik, voorafgaand aan onze promotie-trajecten in Amsterdam kenden we elkaar nog niet, maar het pleit was al direct in de eerste week beslecht. Regelmatig hebben we de "hardloop - biefstuk - voetbal combinatie" gehouden en hoop dat we deze nog regelmatig gaan doen! Ik ben ontzettend blij dat ik je heb leren kennen en je tegenwoordig tot een goede vriend mag beschouwen. Super dat je mijn paranimf wilt zijn.

Lieve Pap en Mam, ik ben ervan overtuigd dat jullie de basis voor dit proefschrift vormen. Jullie hebben het voor Maike, Cas en voor mezelf altijd mogelijk gemaakt om vol te kunnen gaan voor alles wat we nastreven, wat ik zie als een ongelooflijk mooi voorrecht. Ik ben jullie enorm dankbaar, welk met een aantal zinnen in een proefschrift niet uit te drukken is. Fijn dat jullie er altijd voor ons zijn. Dank jullie wel voor alles!

Lieve Marieke, last but certainly not least. Ik ben je ontzettend dankbaar voor al je liefde, grote steun en geduld. Vier jaren lang hebben we de reis Amsterdam – Nijmegen en Nijmegen – Amsterdam gemaakt om bij elkaar te kunnen zijn, al was het af en toe maar voor welgeteld twee hele weekenden in de maand. De reizen die we vanaf nu gaan maken doen we samen, ik heb er zin in!

Geert

List of publications

Articles

Frederix GW, Severens JL, Hövels AM, Raaijmakers JA, Schellens JH. Reviewing the cost effectiveness of endocrine early breast cancer therapies: influence of differences in modeling methods on outcomes. *Value Health 2012; 15(1):94-105*

Frederix GW, Quadri N, Hövels AM, Wetering F, Tamminga H, Schellens JH, Lloyd A. Utility and work productivity data for economic evaluation of breast cancer therapies in the Netherlands and Sweden. *Clinical Therapeutics. 2013 April; 35(4):e1-e7*

Frederix GW, Hasselt JG, Severens JL, Hövels AM, Huitema AD, Raaijmakers JA, Schellens JH. Development of a framework for cost-effectiveness analysis cohort simulation using a multi-step ordinary differential equation solver algorithm in R. *Medical Decision Making. 2013 March; Epub ahead of print*

Frederix GW, Severens JL, Hövels AM, Hasselt JG, Raaijmakers JA, Schellens JH. Time dependent resource use and costs associated with different states of disease in patients diagnosed with HER-2 positive metastatic breast cancer. *Breast Cancer Research and Treatment*: In Press

Frederix GW, Severens JL, Hövels AM, Raaijmakers JA, Schellens JH. The cloudy crystal ball of cost-effectiveness studies. *Submitted for publication*

Frederix GW, Hasselt JG, Severens JL, Hövels AM, Huitema AD, Raaijmakers JA, Schellens JH. Uncertainty of model structure and parameterization: the need for a standardized cost-effectiveness model for adjuvant breast cancer therapies *Submitted for publication*

Frederix GW, Severens JL, Hövels AM, Hasselt JG, Hooiveld MJ, Neven P, Raaijmakers JA, Schellens JH. Resource use of HER-2 positive metastatic breast cancer in the Netherlands and Belgium: a longitudinal incidence based observational costing study. *Submitted for publication*

Abstracts

Frederix GW, Hasselt JG, Severens JL, Hövels AM, Huitema AD, Raaijmakers JA, Schellens JH. Development of a framework for cost-effectiveness analysis cohort simulation using a multi-step ordinary differential equation solver algorithm in R. *International Society for Pharmacoeconomics and Outcomes Research. 2012. Berlin*

Frederix GW, Hasselt JG, Severens JL, Hövels AM, Huitema AD, Raaijmakers JA, Schellens JH. Uncertainty of model structure and parameterization: the need for a standardized cost-effectiveness model for adjuvant breast cancer therapies .*International Society for Pharmacoeconomics and Outcomes Research. 2012. Berlin. Awarded best student podium presentation*

Curriculum Vitae

Geert Frederix is geboren op 8 januari 1985 te Boxmeer. Na het behalen van zijn VWO-diploma in 2003 aan het Elzendaal College te Boxmeer is hij begonnen met zijn studie Medische Biologie aan de Radboud Universiteit Nijmegen. In 2006 behaalde hij zijn bachelordiploma. Tijdens zijn masteropleiding liep hij een wetenschappelijke stage op de afdeling Farmacologie-Toxicologie van het Universitair Medisch Centrum St. Radboud in Nijmegen waar hij onderzoek deed naar de invloed van cafeïne op ischemie/reperfusie schade bij gezonde mannelijke vrijwilligers. Zijn laatste stage was onderdeel van de management & toepassing variant. Deze stage voltrok zich bij Intervet Schering Plough te Boxmeer waar hij onderzoek deed naar optimalisering van de productie van dierlijke vaccins, gebruik makend van een kosten-baten analyse. In november 2008 ontving hij zijn masterdiploma. In mei 2009 begon hij aan het onderzoek dat beschreven staat in dit proefschrift. Het onderzoek werd uitgevoerd binnen het Nederlands Kanker Instituut – Antoni van Leeuwenhoek ziekenhuis (NKI-AvL) in Amsterdam onder begeleiding van Prof. dr. J.H.M. Schellens, Prof. dr. J.L. Severens, co-promotor Dr. A.M. Hövels en Prof. dr. J.A.M. Raaijmakers. Vanaf juni 2013 werkt hij als post-doc onderzoeker bij de afdeling Pharmacoepidemiologie en Klinische Farmacologie van de Universiteit Utrecht.

Geert Frederix was born in Boxmeer on January 8, 1985. After his high school graduation in 2003 at the Elzendaal College in Boxmeer, he started studying Medical Biology at the Radboud University Nijmegen. He received his Bachelor's degree in 2006. During his Masters programme he completed a scientific research project at the department Pharmacoloy & Toxicology of the Radboud University Nijmegen Medical Centre. During this internship the influence of caffeine on ischemia/reperfusion damage in healthy male volunteers was investigated. His last master internship was part of the management & technology track of his study Medical Biology. This internship took place at Intervet Schering Plough in Boxmeer were he performed research regarding the optimalization of animal vaccine production using a cost-benefit analysis. In November 2008 he obtained his Master of Science degree. In May 2009 he started his PhD project described in this thesis at the Netherlands Cancer Institute – Antoni van Leeuwenhoek hospital in Amsterdam. This research project was supervised by Prof. dr. J.H.M. Schellens, Prof. dr. J.L. Severens, joint supervisor Dr. A.M. Hövels and Prof. dr. J.A.M. Raaijmakers. From June 2013 he works as a post-doc researcher at the division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University.


1731