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PHARMACOECONOMICS IN DECISION MAKING

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Whoever you are, or whatever is that you do, when you really want something, it's because that desire originated in the soul of the universe.

"The Alchemist" Paulo Coelho

I wish to express my gratitude for the assistance and guidance given to me by my promotor, **PharmDr. LENKA PRÁZNOVCOVÁ, PhD.** and by **Prof. MAARTEN J POSTMA, PhD.** for giving me an opportunity to carry out research in The Netherlands. The kind encouragement given to myself whilst performing this work, the introduction of the appropriate scientific methods to me, as well as necessary procedures and requirements, and the provision of the opportunity for its successful completion and presentation was invaluable.

I, Natasa Ivanovic, declare that all work conducted in this doctoral thesis is my own, with appropriate references submitted to the reference list.

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INTRODUCTION

The social science of pharmacoeconomics is quite a new and rapidly changing field. The roots of pharmacoeconomics are in health economics – a specialized aspect of economics developed in the 1960s. The concepts involved in pharmacoeconomics, such as cost-effectiveness (CEA) and cost-benefit analysis (CBA), have been developed from the late 1970s. Beginning in the 1980s, measurement tools for health and clinical outcomes assessment were created and have subsequently been improved. Pharmacoeconomics emerged in the late 1980s as an independent entity among the varied specialized economic methods. [1]

Over the past 20 years, pharmacoeconomics has become more important due to an increased emphasis on efficient drug therapies for disease, which increase health costs, etc. [2] Rising health expenditures have led to the necessity to find the optimal therapy at the lowest price. Pharmacoeconomics is an innovative method that aims to decrease health expenditures, whilst optimizing healthcare results. [3]

The science of pharmacoeconomics presents analytic methods to answer such question in economic terms. Pharmacoeconomics, as a term present in literature since 1986, has been defined as "the description of the costs of drug therapy to health care systems and society". [4]

As scientific branch pharmacoeconomics and its roots developed in 1970's. One of the first techniques introduced were cost analyses i.e. by Bootman and co workers from University of Minnesota in 1978. [5] Pharmacoeconomic research involves evaluation of pharmaceutical products and services, measuring of its costs in form of given resources, and outcomes resulting in clinical, economic or at societal level. Pharmacoeconomic methods are cost-minimization (CMA), cost-benefit, cost-effectiveness, and cost-utilization analyses (CUA). Basically, pharmacoeconomics is focusing on impact of medical or therapeutic interventions and compare to alternatives.

Described by Postma pharmacoeconomic techniques mostly used are: CBA, CEA and CUA. [6]

Nowadays trend is that costs for health care are increasing in most of European countries. New upcoming agents are expensive and so increase cost of drugs in society and health care costs in general. Health economics is now central tool of health policy makers' attempts to introduce more efficiency into health care organization, financing and resource allocation since budgets are limited. Pharmacoeconomic analyses signify relevance of assessment, registration and reimbursement of drugs.

Economic evaluations analyze the consequences of using new or established therapies, in terms of both their benefits and their costs, compared to alternatives. The methodology to be used in economic evaluations has been defined according to the state of the art by guidelines for pharmacoeconomic studies. Since value for money is now of central concern in health policy, analysis of the consequences of the use of new and existing therapies, both in terms of benefits and costs, are crucial for decisions on resource allocation. Purchasers of health care are increasingly requesting proof of the value for money of competing technologies, in particular of new pharmaceutical products, in order to decide on their adoption and reimbursement status, and cost-effectiveness has become an important criterion for selection of therapies by providers and payers of health care.

Economic evaluations have therefore become an important source of information to aid decision making about the allocation of resources to technologies, and also to decisions about the development of new pharmaceuticals.
Pharmaceutical companies have long performed economic evaluations at the time of launch of a new product. In most pharmaceutical companies these studies are integral part of research portfolio management and drug development in order to bring products to the market that meet goal of value for money, meaning how much health gain for how much money. In many Western countries as in The Netherlands the pharmacoeconomic evaluation is obligatory for the reimbursement process.

AIM OF THESIS

Theoretical part

The first objective of this thesis is to explore pharmacoeconomics and its application.

- Firstly to consider pharmacoeconomy as a science.
- Secondly to describe pharmacoeconomic methods and models.

The second objective of this thesis is to focus on Dutch pharmacoeconomic guidelines.

- Firstly to revise guidelines from 1999, from a methodological point of view and their comparison to Australian or Canadian guidelines.
- Secondly to present new pharmacoeconomic guidelines from 2006 and reason for their actualization.

Practical part

The main and the third objective of this thesis is to analyze a specific example and its pharmacoeconomic evaluation.

- Firstly for this purpose is a selected example on venous thromboembolism primary prevention after total hip replacement surgery in Europe, from a clinical point of view.
- Secondly, is to assess the total hip replacement surgery in Europe from a pharmacoeconomic point of view.

The final objective of this thesis is to evaluate the use of the national guidelines in published literature in The Netherlands.

- For this purpose firstly will be to assess the use of methodological guidelines from 1999, in the pharmacoeconomic research in a limited period.
- Secondly adherence of guidelines allows for consideration of where main improvements are to be made.

METHODS

The methods used in this doctoral thesis are mainly literature searches in electronic form of web sites, or in the form of published articles, journals, books, manuals, databases and software programs.
Each section of the thesis had a different approach according to objectives that had to be met.

The first section is oriented toward the theoretical part.
The approach used was of literature searches from various sources to define:

- a pharmacoeconomics as science and its methods with implementation of statistical techniques, Meta- and Sensitivity analyses, Markov model, BUGS and DATA,
- pharmacoeconomic guidelines by Dutch database CVZ (College voor Zorgverzekeringen).

The second section of thesis is oriented toward a practical part involving research articles.

- Firstly, the main analysis was performed on thromboprophylaxis in hip replacement surgery for Europe as well as with a literature search available on the Pub Med database (English language) for clinical trials using any of the following agents after hip-replacement surgery: acenocoumarol, fondaparinux and direct oral inhibitors. Given the European perspective of the analysis, such trials also had to be relevant for the specific European clinical practices, in particular with respect to the timing of Low Molecular Weight Heparin (LMWH) and fondaparinux (the European clinical practice, for example, implied that the European Pentasaccharide Hip Elective Surgery Study (EPHESUS) would be included, whereas the North American-based PENTATHLON 2000 study was not. Additionally, literature was searched for combinations of all previously

mentioned agents with any of the following key words: pharmacoeconomics, economy, economic studies, hip replacement and cost. Additional references from the bibliographies from the selected papers were also considered. LMWH was primarily considered the comparator drug since it is standard treatment for preventing Deep Venous Thrombosis (DVT).

- Secondly, the Dutch pharmacoeconomic guidelines were revised. In 1999, Dutch Health Care Insurance Board (CVZ) presented Dutch guidelines for pharmacoeconomic research. This review covers all Dutch pharmacoeconomic studies that were published in English during 2003–2004. Nine methodological guidelines were selected for investigation with respect to their application to pharmacoeconomic studies. Each pharmacoeconomic study was reviewed by a minimum of two reviewers for objectivity and accuracy of results. The search methodology and inclusion criteria for qualified studies: A search was oriented to pharmacoeconomic studies that were published in English for the Netherlands from 1st January 2003 to 31st December 2004. The databases used were MEDLINE and EMBASE. The search used the terms ''cost (-) effectiveness'', ''pharmaco (-) economic(s)'' and ''(the) Netherlands''. The formal inclusion criteria for this review were that studies should be: (a) Pharmacoeconomic evaluations; (b) cost-effectiveness or a cost-utility analysis; (b) Original research; and (c) That full text reports would be available (rather than merely abstracts alone).

1 THEORETICAL PART

1.1 Pharmacoeconomics and Outcomes Research

Pharmacoeconomics is collection of techniques used in evaluation not only of pharmacotherapy, in which it is a point of interest, but also in evaluating surgical procedures, medical devices or clinical services. [7]

It is important to distinguish between outcomes research and pharmacoeconomy. Outcomes research is the process that evaluates different therapies or drug regimens in order to measure the extent to which a goal of therapy or desirable outcome can be reached. Outcomes are economic, clinical, and humanistic, defined by Kozma et al. [8] Methods used in outcomes research are involving retrospective review, prospective clinical trials, and observational studies. These methods are based on software models which assume cost and efficacy data from published literature and cost-effectiveness is determined.

Pharmacoeconomics is a part of health care economics which focus on allocation of resources for health care. [9] As such pharmacoeconomics is a tool designed to provide decision makers with information of for instance cost-effectiveness of different pharmacotherapy. When used in combination with outcomes research, pharmacotherapy gives most optimal results and uses different mathematic techniques.

Aim of pharmacoeconomic analyses is to recommend the most cost-effective option in achieving desired outcome in specific population. "What is cost-effective?" could be explained as a level of efficacy in reaching an outcome for the lowest possible cost. When one therapeutic option is both more effective and more expensive it gives us information of an incremental cost per outcome to be obtained as usually applied cost of extra life year saved. [7]

Over the past decade, the importance of pharmacoeconomics has been escalating as a result of numerous factors. Governments worldwide are spending more money on healthcare than on nearly anything else. These worldwide expenditures increase at a faster rate than the global gross domestic product. Pharmaceutical expenditures, which constitute a large part of healthcare expenditures, have been increasing much faster than total healthcare expenditures. [10] Numerous drug alternatives and empowered consumers also fuel the need for economic evaluations of pharmaceutical products. [11]

The increasing cost of healthcare products and services has become a great concern for patients, healthcare professionals, insurers, politicians and the public. [12] This increasing concern has prompted demand for the use of economic evaluations of alternative healthcare outcomes. This escalation in healthcare spending is due to increased life-expectancy, increased technology, increased expectations, increased standards of living and an increased demand in healthcare quality and services. [13]

Healthcare resources are not easily accessible and affordable to many patients; therefore pharmacoeconomic evaluations play an important role in the allocation of these resources. Pharmacoeconomics strives to guide the utilization of healthcare resources optimally. [14]

The processes by which a drug evolves from an idea to a patented, marketed drug involve a great deal of consideration. Randomized, controlled clinical trials are utilized by the US Food and Drug Administration (FDA) or European Agency for the Evaluation of Medicinal Products (EMEA) to determine whether or not a drug is safe and effective for the patient. These trials determine whether drugs should be marketed to the public. A drug's effect on the health of the population once the drug is marketed, in addition to the financial consequences to the healthcare system as a result of using the drug, is not addressed by randomized, controlled trials. FDA randomized, controlled trials simply lead to efficacy, which does not provide sufficient information by which to choose a drug product. The outcome of these research studies determines effectiveness. When pharmacoeconomic studies are also implemented, including costs, the ultimate answer

emerges: efficiency. FDA or EMEA approval merely means that a drug is safe and effective compared with a placebo. This newly approved drug could be inferior to existing products in the same therapeutic class. Direct comparisons must be carried out with other drug products to truly test this drug. These pharmacoeconomic comparisons are called 'Phase IV' or 'post-marketing studies'. Today, large buyers of drug products, for example health maintenance organizations, hospitals, Department of Veterans Affairs, government agencies and the military, have sophisticated staff that analyze and evaluate alternative products. It is these pharmacoeconomic evaluations that can determine which drug is optimal. [1]

Pharmacoeconomics addresses both economic and humanistic outcomes. Pharmacoeconomics includes ideas and methods from a variety of domains including statistics, clinical epidemiology, economics, decision analysis and psychometrics, etc. Pharmacoeconomics and outcomes research are two related disciplines that focus on these areas of investigation. Pharmacoeconomics is a specialized 'twin' of outcomes research, which focuses more on pharmaceutical drugs as opposed to general healthcare services. [3]

Outcomes research is the scientific study of the effects of medical care on individuals and society. A variety of disciplines are utilized by outcomes research, including clinical epidemiology, informatics, anthropology, economics, health services research, health policy and biostatistics. Outcomes research has a patient and policy-relevant focus and is essential to the formulation of clinical practice guidelines, assessing the quality of medical care and informing health policy decisions. [15]

a. Clinical outcomes: Mortality (saving or prolonging lives); Morbidity (hospital admissions, disability); Curing disease (i.e. Bacterial infections); Prophylaxis (preventing recurrent infection, acute exacerbation of chronic disease); Surrogate or proxy outcomes (lab values), but need to correlate to real clinical measure.

b. Humanistic outcomes: Quality of life, as evaluated by general and disease specific questionnaires; Can combine with clinical outcomes (i.e. quality adjusted life years); Do decision makers care enough to spend more to achieve them, or sacrifice clinical outcomes for humanistic ones?

c. Economic outcomes: Translating the impact of clinical/humanistic outcomes into dollars; Easy method: Look at the additional, or reduced, costs of care/healthcare for a patient with a defined disease state; problem: Translating non-dollar clinical outcomes into $$$ (value of life or a year of life saved or improved quality of life). [16]

Attention by the healthcare community has been shifted from traditional clinical research to outcomes research due to the rapid rise of healthcare costs and the inefficiency of evidence-based medicine. Traditional clinical research studies the mechanisms of disease through biological mechanisms in the pharmaceutical setting, for example drug versus placebo testing in a randomized clinical trial. Endpoints studied in traditional clinical research include blood pressure, cholesterol level and glucose level. Outcomes research, on the other hand, focuses on the effect of therapeutic treatments on endpoints such as survival, quality of life, satisfaction with care and cost. This patient-oriented research method is a useful complement to clinical research and results in insight into the patient's perspective. [17]

Pharmacoeconomics is a specific form of health economics that is restricted to pharmaceutical products. Pharmacoeconomics can be described as a social science concerned with the impact of pharmaceutical products and services on individuals, health systems and society, as well as the description and analysis of the costs. One of the primary goals of pharmacoeconomics is to determine which healthcare alternatives provide the best healthcare outcome per dollar spent. Pharmacoeconomics aims to improve the allocation of resources for pharmaceutical products and services. Numerous methods are utilized to determine the least expensive treatment with the best treatment

outcome. Healthcare policies worldwide are focused on increasing efficiency at a lower cost without reducing either the quality of healthcare or access to it. [18]

In addition to drug versus drug decisions, pharmacoeconomics allows us to make decisions between drugs versus surgery and drugs versus 'watchful waiting', based on the effectiveness of the treatment and the cost. The National Institute for Clinical Excellence (NICE) in the United Kingdom (UK) functions in this way as well. [11]

1.1.1 Types of pharmacoeconomic studies

Since pharmacoeconomics is a multidisciplinary field, a group involved in pharmacoeconomics would include pharmacoeconomists, epidemiologists, statisticians, data and research personnel. Data may be collected in a variety of ways, including patient self-report questionnaires and direct data abstraction from patients' medical and employment records and bills.

There are three types of pharmacoeconomic studies:

a) Prospective studies are experimental studies that can be an additional part of a randomized clinical trial or strictly an economic evaluation. Prospective studies are the least useful because they require extensive time and money.

b) Retrospective studies are data analyses of clinical trials or cohort studies that were conducted previously. This type of study involves a comparison of treatment users and non-users that are followed from some point in the past to the present. Retrospective studies are the ideal study method.

c) Model studies are performed as a method of displaying data obtained from a variety of resources if previously studied data is unavailable. Modeling is an inexpensive and effective way of illustrating existing available data regarding the costs and outcomes of alternative therapeutic interventions. Modeling frameworks include decision trees, influence diagrams, Markov analysis, discrete event simulation and systems dynamics. The goal of these methods of pharmacoeconomic evaluation is to assess the value of pharmaceutical products and services while incorporating clinical, economic and humanistic outcomes. [1]

1.1.2 Pharmacoeconomic analyses

Techniques used in pharmacoeconomics are summerized in Table1.

Table 1. types of pharmacoeconomic methods

Analysis	Cost measurement unit	Outcome unit
Cost-minimization	Money	Assume to be same in compared groups
Cost-benefit	Money	Money
Cost-effectiveness	Money	Natural units (life year gained, blood pressure, or glucose level in blood).
Cost-utility	Money	Quality-adjusted life-year or other.

Pharmacoeconomics involves the utilization of two major methodologies for health economics analysis: cost analysis and cost outcomes. Cost analysis considers the costs of providing healthcare products or services, but does not consider the outcomes experienced by patients or providers. Cost-outcomes analysis is the most commonly used of the pharmacoeconomics methodologies. [1]

1.1.2.1 Cost-minimization analysis

CMA is specific in outcomes where two or more interventions are evaluated and which are assumed to be equivalent in terms of an outcome, consequence or costs associated with an intervention may be examined and compared. [19]

This is typical cost-analysis. Example of this pharmacoeconomic technique can be comparison of two generically same drugs with same outcomes but different the acquisistion and administration costs. Using CMA is routine in collecting and analyzing costs associated with adverse drugs events (ADE) and adverse drug reactions (ADR). [7]

Simplified, CMA chooses the cheaper option in decision making process.

1.1.2.2 Cost-benefit analysis

CBA is only pharmacoeconomic method that includes only monetary costs and benefits. Costs may be drug cost, administration cost, and cost of ADR or pharmacist fee. Benefits may be for example costs saved on hospitalization or on general practitioner (GP) visit avoided. These would be direct costs. Indirect costs/benefits are those that are in relation to production losses due to inability to work.

Usually outcome of CBA is cost minus benefit resulting in net cost. Negative net costs (<0 meaning that benefits are higher than costs, so from pharmacoeconomic point of view the intervention (for example new drug) should be applied giving positive health effects as outcome. Net costs >0 should be considered due to health gains achieved. In general it is important to know perspective of pharmacoeconomic study which types of costs and benefits will be involved (perspective of the health-care insurer, the health-care payer or society as whole). [6]

CBA can be also seen as yield of an investment. A single intervention may be evaluated or multiple interventions with different outcomes may be compared with CBA. All benefits and costs that occur at different times must be adjusted to reflect comparable dollar values. Dollar amounts are converted to present values through the use of an interest rate known as the discount rate. Other important point is use of sensitivity analysis which is a method of determining whether the conclusion of an economic evaluation changes when the value of one variable is varied as all other variables are held constant. [19]

Besides cost and benefits, two other cost-related calculations can be made. The first is benefit/cost ratio, which is equal to the total of benefits divided by the cost. Ratio >1 means that each dollar invested produces more than one dollar of benefits. Other number to calculate is the return on investment, which is equal to the net benefits divided by costs, presenting that rate of return the institution earns on its investment in the project. Choice of the best alternative depends on perspective, and the use of CBA offers a

strategy for example for deciding which ADE would be the best for an institution to target. [7]

Simplified, CBA includes cost (drug, ADR...) minus benefit (averted hospital days or GP visits) when giving negative value <0 than it is acceptable in decision making process.

1.1.2.3 Cost-effectiveness analysis

CEA health gains, as opposed to CBA, are expressed in terms of natural units as for example infections averted, complications prevented, and cases of chronic disease averted or number of life-years gained (LYG). The concept of LYG combines mortality and remaining life expectancy at population level for those groups where fatalities have been averted. Averted death at young age yields more LYG than averted death at an older age. The advantage of the use of LYG is that comparison of outcomes of different types of interventions (therapeutic or preventive) and different disease becomes feasible to a certain degree. A disadvantage is the potential discriminating implications of the techniques, for example with the respect to the elderly where by definition fewer life-years may be gained. Also, given longer remaining life expectancies for women over men, a CEA may favor an intervention for women over men, despite similar risk reductions achieved for both genders. [6]

In general CEA are designed to assist decision maker to identify a preferred choice between possible alternatives. The term cost-effectiveness should be used to imply value for money. It is also important to distinguish between the concepts of efficacy (how well the drug works under ideal conditions) and effectiveness (how well it works under conditions of average use- meaning real life use). Discounting costs and effectiveness, as in all economic variables (present and future), are adjusted for inflation, it is still necessary to discount future costs. The reason is that a dollar not spent now can be invested to yield a larger number of dollars in the future.

Many of the estimates used in CEA are uncertain so there is need to test the sensitivity of the results to changes in these estimates. A useful approach to sensitivity analysis is the establishment of confidence intervals around the various estimates and than allowing the estimates to take on the upper and lower bonds of the interval. Basically, if one drug costs less and it is more effective than another, it is clearly more cost-effective of the two. However, when one drug both costs more and is more effective than another, the decision of relative cost-effectiveness depends on weather the decision-maker believes the extra effectiveness is worth the extra costs.

Decision trees or other modeling techniques are important for identifying alternative interventions and for describing the production relationship between resource inputs and resource and health outcomes. Simple cost-effectiveness ratio (CER= C/E) is misleading, but incremental cost-effectiveness ratio (ICER= ΔC (C1-C2)/ ΔE (E1-E2)) must be applied. [19]

An example of use of CEA could be in selection of drugs for therapeutic substitution, which involves choosing among alternatives, for a certain disease or a condition. The goal is to select the agent that provides an acceptable (but not necessary the highest) level of effectiveness at the lowest possible cost. In cases when drug is more expensive and more effective the question that arises is "If it is worth the extra price for the level of effectiveness?"

Pharmacoeconomic analysis is a toll to help in selection of drugs by identification which drug gives the most effectiveness per dollar spent. In principle it is cost divided by effectiveness, giving ratio and the drug with lowest ratio is drug of choice. When another drug has a higher CER but is more effective, than decision maker must come to conclusion, by calculating the extra cost of increasing the efficacy by one unit, what is the amount of reasonable price to pay for added efficacy or effectiveness? [7]

Simplified, CEA are used in analyzing one specific condition or disease, comparing intervention and non- intervention or two or more alternative interventions that compete.

It has monetary costs and health gains as benefits (averted infections, case cured, LYG). Resulting amount depends on given threshold as ex €20,000 in the Netherlands per LYG.

1.1.2.4 Cost-utility analysis

CUA use the concept of quality adjusted life-years (QALYs) meaning evaluation of health status: perfect health corresponds to a value of 1 and death to 0. Intermediate values correspond with various diseases and disease stages. The concept of LYG is of no use as an outcome when if the intervention considered does not prevent mortality, despite improving the health state of patients. For this purpose one may apply a CUA, where health gains are transformed into utilities as QALY. [6]

CUA is a tool in which intervention consequence is measured in terms of quantity and quality of life. CUA is a technique that assesses the efficiency of healthcare interventions. In comparison to other techniques CUA has advantages, CBA has difficulties in translating all sots and consequences into monetary terms; CEA is limited in incorporation of multiple outcomes from the same intervention or too compare interventions with different outcomes. In contrast, CUA incorporates the quality of the health outcome achieved by use of QALYs where pharmaceuticals can produce QALYs by lengthening life or improving the quality of life, or both. Incremental cost/utility ratio is changes in cost divided by changes in QALYs (utilities) resulting in dollar value per QALY gained. [19]

Simplified, CUA are comparing different conditions or diseases where health gains are transformed to utilities as QALY. QALY=1 perfect health. QALY=0 is death.

1.1.3 Different types of cost

Cost is defined as the magnitude of resources consumed, monetary value of resources consumed in production or delivery of product or service. [19]

Pharmacoeconomic studies consider the total costs incurred from the disease – both direct and indirect costs.

Direct costs consist of pharmaceutical drugs, medical devices, physician visits, emergency room visits, diagnostic testing services, education and research.

Indirect costs comprise lost school and work days, lost productivity, travel time and waiting time.

Direct costs have been shown to exceed indirect costs, both in Canada and the United States (US). Therefore, pharmacoeconomic analysis must include more than just the costs of drugs. Many costs are not seemingly obvious, i.e. education and non-compliance costs. [20]

Use of CER's and translating them into criteria for resource allocation has couple of views. First view is concerned with comparability between CER's based on different definitions of cost and also derived from different perspectives in decision making process. Second view is application of incremental CEA in evaluation of new drugs. Third point is choice of critical value of CER.

From societal perspective, differences in interpretation of cost can lead to different interpretations of CER. This means exclusion or inclusion of cost elements that can have dramatic effect on resulting CER. The most direct and theoretically correct criterion for judging the acceptability of CER is the shadow price of an explicit budget constant. [21]

To summarize cost:

- Direct cost: medical (for intervention, drugs or hospital stay) or non-medical (for transportation to hospital), borne by insurers and patients.
- Indirect cost medical (medical cost in LYG) and non-medical (sickness leave, life-years lost) production losses through morbidity and mortality, borne by society and employer.
- Fixed cost (reimbursement level).
- Variable cost (cost of ADR of therapy).
- Average cost (one therapy option in different populations).
- Opportunity cot is affected by market (pricing level).
- Intangible cost is non-monetary (pain, disability, invalidity).
- Incremental cost as most important (two or more alternatives compared for the same condition).

Benefits in general are GP visits or hospital costs averted, travel costs and production loss averted.

1.1.4 Discounting

The reason for converting future dollars into today's dollars is based on assumption that a dollar in the future is worth less than dollar today. Rationale behind this is that the costs of goods or services will continue to rise in future due to inflation. By discounting costs and benefits of the future are converted or discounted into "present value" dollars of today. For that we need discount rate, the number of years until the future payment and the future value. [7]

National guidelines for pharmacoeconomic research recommend discounting, both of money and health against the same rate. The new theory in the pharmacoeconomic research area indicates that it would be appropriate from a societal perspective to choose discount rates for health that are lower than those for money.
This rate is generally assumed to range from 2 to 7% annually, indicating that €x now equals between €x * (1.02) and x * (1.07) next year. [22]

At the moment national guidelines for pharmacoeconomic research are being updated and new more appropriate discount rate are suggested where rates differ in monetary and are lower in health gains (utility) values. If the value in health changes over time, this may not be properly reflected in a cost-effectiveness analysis with similar discount rates for health and money.

As in regular economics, future costs, benefits and health gains are discounted in pharmacoeconomics. This technique reflects existing time preference, preferring future costs over current costs, and current benefits and gains over those in the future. The specific discount rate to use in calculus should reflect the societal time preference. [23]

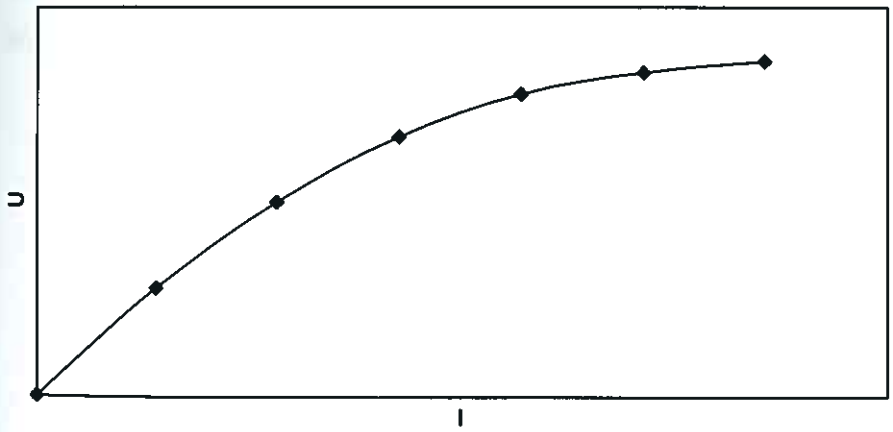
Basically, discounting is applied to correct for different types of time preference. Time preference is a complex composite of pure time preference (impatience and uncertainty about the future) and decreasing marginal utilities of different utility arguments over time

(money and health). This decreasing marginal utility reasoning assumes a growth of the utility arguments over time. [24]

Formulations from eighties, indicates that if health gains are discounted at a lower rate than money, the CER of a healthcare intervention with investment prior to health gains will always improve by delaying the implementation as delay lowers the nominator of the CER more than the denominator. In fact, theoretically this would result in the endless postponing of health interventions (thus paralyzing decision making). [25]

In terms of finding a new theoretical basis on which to base discount rates for money and, in particular health, Van Hout has made an important suggestion arguing that the discount rate for health should be based on the expected growth in life expectancy and the diminishing marginal utility related to such additional health. [26]

Figure 1. Illustration of utility (U) as a function of income (I).



For utility as a function of health (L), a similar graphical illustration can be presented.

In order to give an indication of the range in which the appropriate discount rate for health effects might be expected to lie, defined by use two separate cases:

- Health is not related to income and value of health is constant in time.
- Health and income are related, causing the growth in the value attached to health is equal to the growth in welfare. [27]

Using this method for The Netherlands, discount rates of 4% for money and 1.5% for health were estimated in the Dutch context and implemented from 2006, as stated in new guideline 9 of pharmacoeconomic guidelines for decision making, specified in section 1.2.1. (New Dutch guidelines for pharmacoeconomic research).

In summary, rationale for discounting is time preference.
€100 (t=0) is preferred over €100 (t=1); €100 (t=0) = €100*(1+r) (t=1);
Discount rate r varies between 3-6%. Netherlands: 4%. The exact rate is derived from real rate-of-return on investment. Discounting relates to real economic growth and uncertainty.

1.1.5 Pharmacoeconomics in decision making process

Using of pharmacoeconomics for policy making by evaluation of medical intervention is the regular practice in many countries in Europe. CEA and CUA are tools in priority setting in health care, and are implemented in reimbursement procedure or in recommendations for clinical guidelines. For example in The Netherlands the threshold is given for cost-effectiveness of €20,000 per LYG and in the up to US $100,000 per LYG or QALY. These thresholds are given formally and in many cases values are under or above given threshold. For this reason decision rules are set up for decision maker to evaluate what alternative is worth of desired outcomes.

Timing for pharmacoeconomic analyses differ from countries, for instance it is performed in The Netherlands directly after registration prior to reimbursement, meaning that CEA must be proved for drug to be reimbursed. In the UK pharmacoeconomics is applied after reimbursement and so has only influence on guideline development.

In CBA apply rule of maximum willingness to pay (WTP), but in other techniques it is not such a case (WTP per LYG or QALY is not possible). In CEA and CUA are evaluating maximum health gains under restricted budget choosing between different interventions by eliminating dominated and weakly dominated options. Solution is the value of the maximum WTP per unit of health gain per group of interventions could be defined as the rule for decision making. [28]

Cost of illness (COI) studies estimate the overall economic burden of a specific disease, rather than simply treatment-related costs. While having been criticized for not allowing resource prioritization, COI studies can provide useful guidance, so long as they adhere to accepted methodology. Hence, to increase the credibility of COI studies, closer agreement among researchers on methodological principles would be desirable. [29]

1.1.5.1 Incremental cost-effectiveness analysis importance

Usually CEA are used for comparison of competing alternatives for same condition. In other examples which include analysis among various diagnostic strategies that involve different tests in different sequences and with different criteria CEA are not applicable, because alternatives are not longer independent (different drugs for the same condition). As an example, the benefits of giving two antihypertensive drugs to the same group of patients are not additive. The paradigm needs to be modified to involve the possibility of mutually exclusive competing choices for the same condition. The correct measure of cost-effectiveness is the ICER of a treatment relative to less expensive options. This is because usually more than one treatment is available for a given condition. [21]

1.1.5.2 Cost-effectiveness plane and its quadrants

Concept of cost-effectiveness plane (CEP) is explaining the ICER of the new therapy over the old treatment option, with an insight of additional costs and effects of the new treatment.

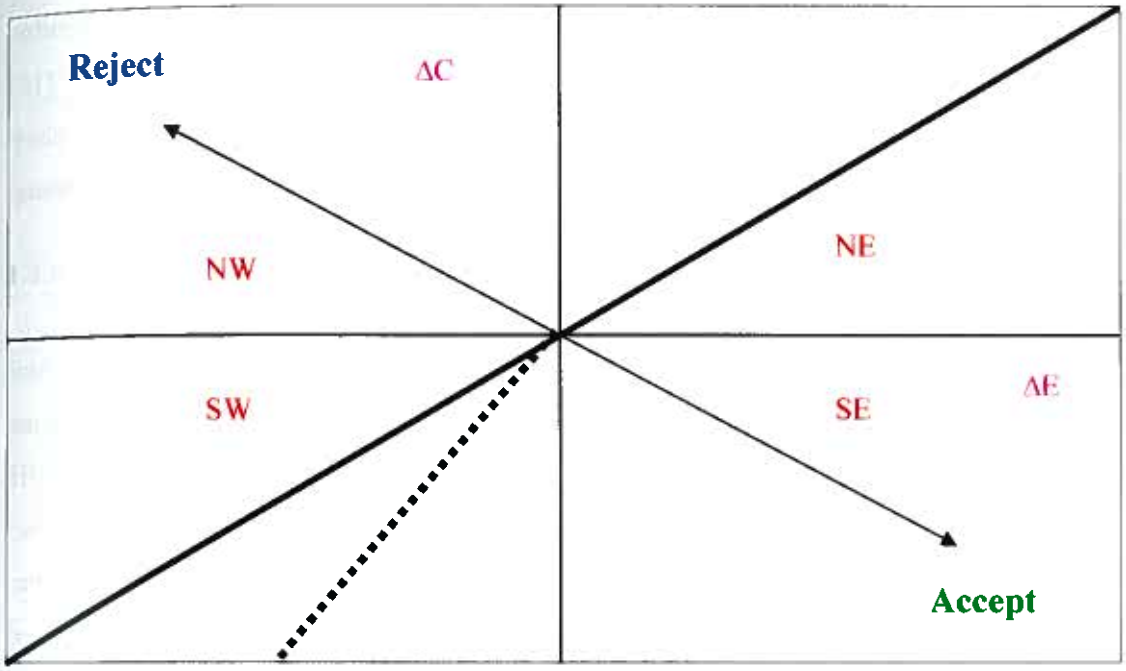
- South-east (SE) quadrant shows that new alternative is more effective and less costly than old one. New treatment dominates the old treatment.
- North-west (NW) quadrant shows opposite situation where new alternative is less effective and cost more than old one. Old treatment dominates the new treatment.

ICER has only a negative value in SE and NW quadrants.

- South-west (SW) quadrant explained that new treatment saves money compared to the old one but it is at the cost of health, meaning less effective.
- North-east (NE) quadrant shows that new treatment is more effective and more costly.

ICER has positive values in SW and NE quadrants.

Figure 2. Incremental costs (ΔC) and effects (ΔE) of a new technology over an old one and the maximum acceptable ICER in solid line and with a dotted line.



Most interesting is NE quadrant, where maximum acceptable ICER to pay falls into. The maximum differs between countries, as mentioned before, for US$50,000 per QALY, in the UK£30,000 per QALY, and in The Netherlands €20,000 per LYG. This corresponds to WTP for the gain of one unit of health and applied only in NE quadrant.

Most of the results fall into mix between SW and SE quadrant, so threshold representing maximum ICER presented in NE is extended in bold diagonal line to the SW quadrant and concluded that all options bellow that line are acceptable and without importance which quadrant is in question. Only section between solid line and dotted line would also be concerned as non acceptable when concerned from societal level from budget allocations in terms of achieved health gains. [30]

1.1.6 Using different statistical models in reading CEA results

The past decade has seen a rapid increase in the use of clinical trials as a vehicle for collecting economic information and estimating the cost-effectiveness of interventions. [31] The existence of patient-level information on both costs and effects from clinical trials has generated interest in statistical methods for CEA, with a key focus on the quantification and presentation of uncertainty. [32]

1.1.6.1 Application of cost-effectiveness plane in uncertainty

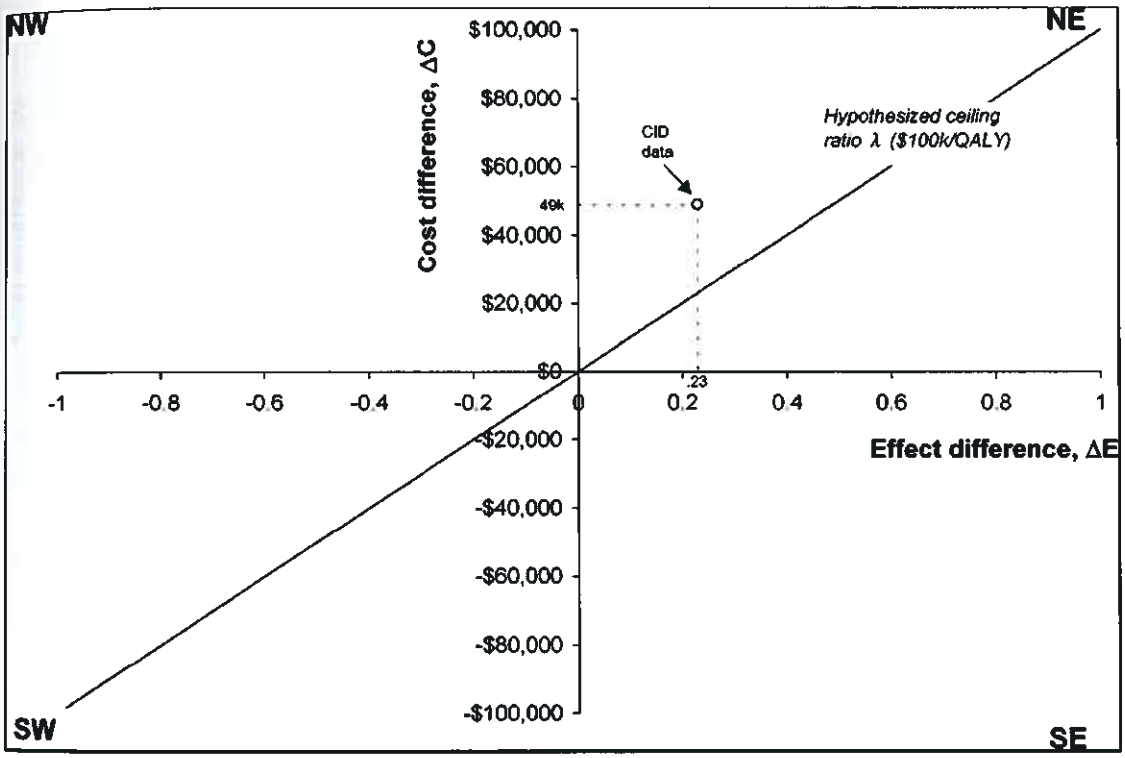
Introducing the CEP as a device is useful for presenting and relating the two central parameters of interest in economic evaluation: the difference (treatment minus control) in effectiveness (ΔE) and the difference in cost (ΔC). It is shown how the CEP is useful for presenting uncertainty in the location of these two parameters and also uncertainty in the ratio between them, $\Delta C/\Delta E$, known as the ICER. Using the CEP, are reviewed methods for estimating and presenting the uncertainty that can arise in cost-effectiveness results.

Most new therapies locate in the NE quadrant where increased effectiveness is achieved at increased cost. In this situation, the decision to adopt the new therapy will depend on where the (x, y) coordinates fall in the NE quadrant and whether this point lies below the acceptable "ceiling ratio" of the decision maker. As illustrated by the ray extending from the origin, the assumption is that the dollar amount that the decision-maker is willing to pay for a unit of effectiveness is known (call this λ). If the ICER of the new therapy is ($\Delta C/\Delta E$), i.e., the slope of a straight line from the origin that passes through the (ΔC, ΔE) coordinate, is less than the decision-maker's WTP (λ), then the treatment should be adopted. [32]

Using example, if we assume, for the moment, that data had no uncertainty, and then the true cost difference per patient would be C$49,100 and the true increase in survival would be 0.23 years for an ICER of C$214,000 per LYG. If we assume that the maximum that society is willing to pay for a year of life is C$100,000, then new therapy should not be adopted. This is shown graphically in Figure 3 by the point estimate of

cost-effectiveness falling above and to the left of the line with slope , λ =C$100,000. Of course, the problem is that all the parameters are uncertain; including the amount society is willing to pay for a unit of effect. [33]

Figure 3. Incremental cost-effectiveness plane showing four quadrants, line representing the ceiling ratio for decision making and the location of the point estimate of incremental costs and effects.

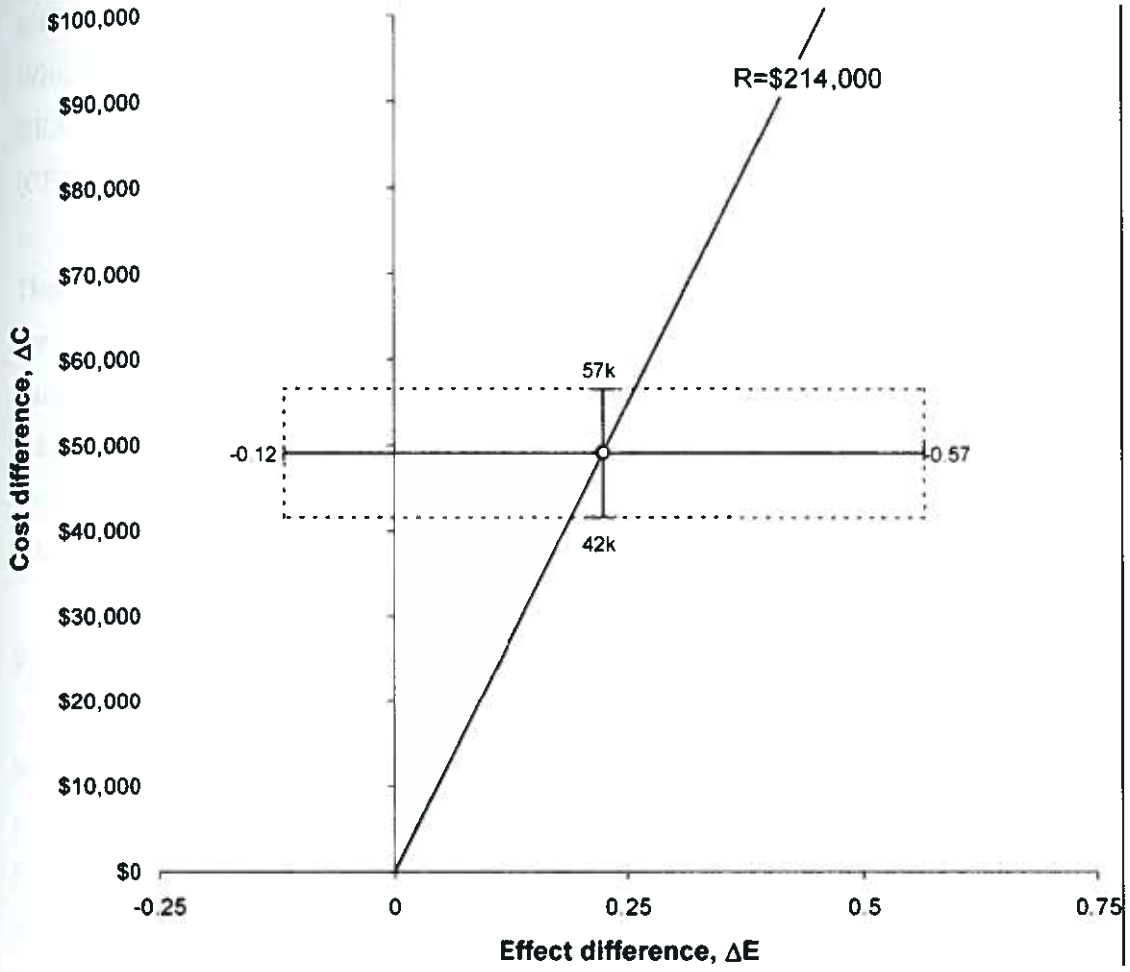


In practice, we have only estimates of the cost and effect differences, and it is important that uncertainty in those estimates is also presented.

It is straightforward to calculate confidence intervals (CI) for each of the cost and effect differences, ΔC and ΔE, using standard methods, and these intervals can also be plotted on the cost-effectiveness plane. [33]

For example referring to Figure 3, the 95% confidence intervals for ΔC are (C$41,600 to C$56,600) and for ΔE are (-0.12 to 0.57). [32]

Figure 4. Confidence limits and the confidence box on the cost-effectiveness plane for the data example.



Results are represented on the CEP in Figure 4, which, in addition to a point estimate of the cost and effect difference of therapy, also shows I-bars representing the CI around those estimates. The horizontal I-bar represents the CI for the effect difference, and the vertical I-bar represents the CI for the cost difference. Both have the point estimate of the cost and effect differences at their center and together the intervals define a box on the CEP. In example the box "straddles" the y-axis but lies completely above the x-axis, reflecting the fact that the difference in survival in the trial was not significant ($p > 0.05$) but that the difference in cost was significant ($p < 0.05$). [32]

1.1.6.2 Estimation of uncertainty

The point estimates (means) from the effect and cost distributions provide the best estimate of the treatment and cost effects and should be used in the primary analysis. While confidence intervals for CER are a valid approach to addressing uncertainty in CEA for situations SW and NE quadrant problems arise when uncertainty is such that the ICER could be negative [34].

There have been many proposed solutions to the problem of estimating confidence limits for the ICER, many of which were simply approximations that could perform rather poorly in some situations. However, a general consensus has emerged in support of two main approaches: the parametric method introduced by Fieller [35] half a century ago and the nonparametric approach of bootstrapping [36], both of which have been described in relation to CEA.

Fieller's theorem confidence interval:

In Fieller's approach, it is assumed that the cost and effect differences (represented by ΔC and ΔE, respectively) follow a joint normal distribution. The standard CER calculation of $R = \Delta C/\Delta E$ can be expressed as $R\ \Delta E-\Delta C=0$, with known variance
R^2 var (ΔE) + var (ΔC) -2R cov (ΔE, ΔC).

Figure 5a shows the assumption of joint normality on the CEP for the given example data by plotting ellipses of equal probability covering 5%, 50%, and 95% of the integrated joint density. Also plotted are the estimated confidence limits using Fieller's theorem (C$86,800 to C$-408,000), represented by the slopes of the lines on the plane passing through the origin. By contrast, Fieller's approach automatically adjusts to ensure that 95% of the integrated joint density falls within the wedge, which makes Fieller's approach an exact method (subject to the parametric assumption of joint normality of costs and effects holding). [32]

Bootstrap confidence intervals:

The approach of nonparametric bootstrapping has been gaining in popularity with the advent of powerful desktop computing. It is a re-sampling procedure that employs raw computing power to estimate an empirical sampling distribution for the statistic of interest rather than relying on parametric assumptions. Bootstrap samples of the same size as the original data are drawn with replacement from the original sample and the statistic of interest is calculated. Repeating this process a large number of times generates a vector of bootstrap replicates of the statistic of interest, which is the empirical estimate of that statistics' sampling distribution.

In terms of the cost-effectiveness application, the approach involves a three-step procedure:

Sample with replacement n_C cost/effect pairs from the patients in the control group (where n_C is the number of observed patients in the control group) and calculate the mean cost and effect in this bootstrap resample.

Sample with replacement n_T cost/effect pairs from the patients in the treatment group (where n_T is the number of observed patients in the treatment group) and calculate the mean cost and effect in this bootstrap resample.

Using the bootstrapped means from the steps above, calculate the difference in effect between the groups, the difference in cost between the two groups, and an estimate of the incremental cost-effectiveness.

This three-step procedure provides one bootstrap replication of the statistic of interest; repeating this process a large number of times (at least 1000 times is recommended for CI calculation) generates the empirical distribution of cost-effectiveness.

Each of 1000 bootstrapped effect and cost differences from step 3 above are plotted on the CEP in Figure 5b for data example. Confidence limits can be obtained by selecting the 26th and 975th of the 1000 replicates [which excludes 25 (or 2.5%) of observations from either end of the empirical distribution]; this effectively ensures that 95% of the estimated joint density falls within the wedge on the CEP defined by the confidence limits. [32]

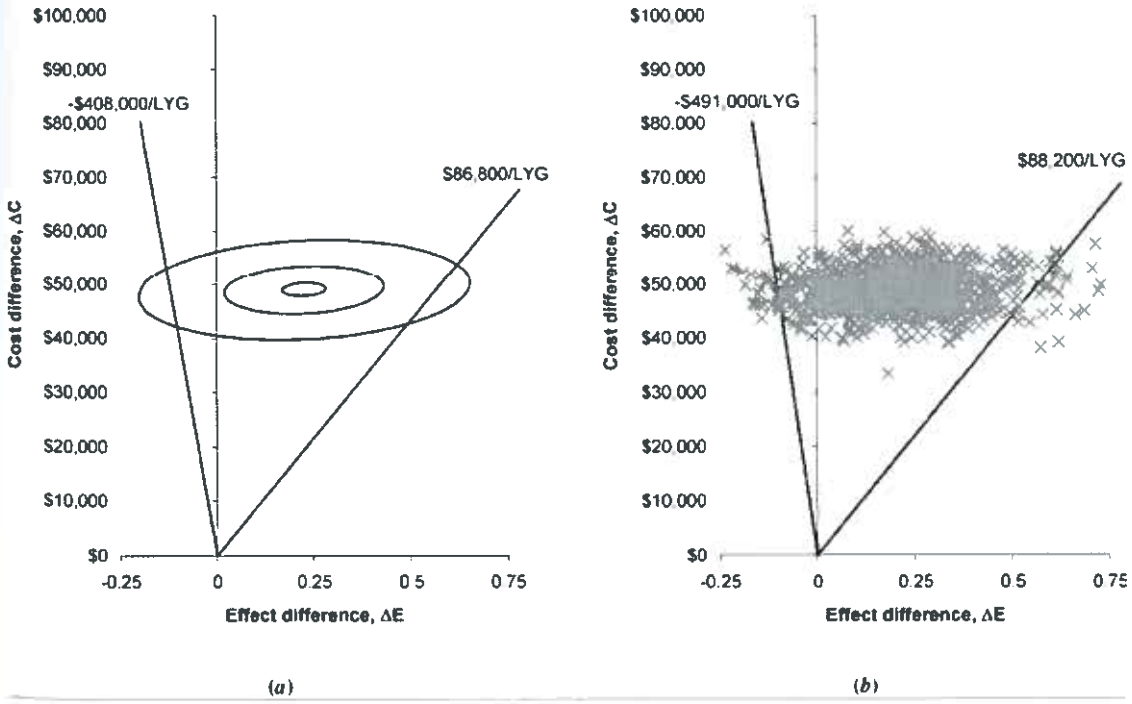
As is clearly apparent from Figure 5b, the bootstrap estimate of the joint density and the bootstrap confidence limits (C$88,200 to C$¡491,000) are very similar to those generated by Fieller's theorem. This suggests that for this particular example, the assumption of joint normality for the cost and effect differences is reasonable.

The Fieller limits are therefore preferred in this case for two main reasons:

(a) Parametric methods are commonly more powerful than their nonparametric counterparts when the parametric assumptions hold; and

(b) Fieller's approach always generates the same result; two analysts both employing the bootstrap method with the same data will generate slightly different results due to the play of chance. [32]

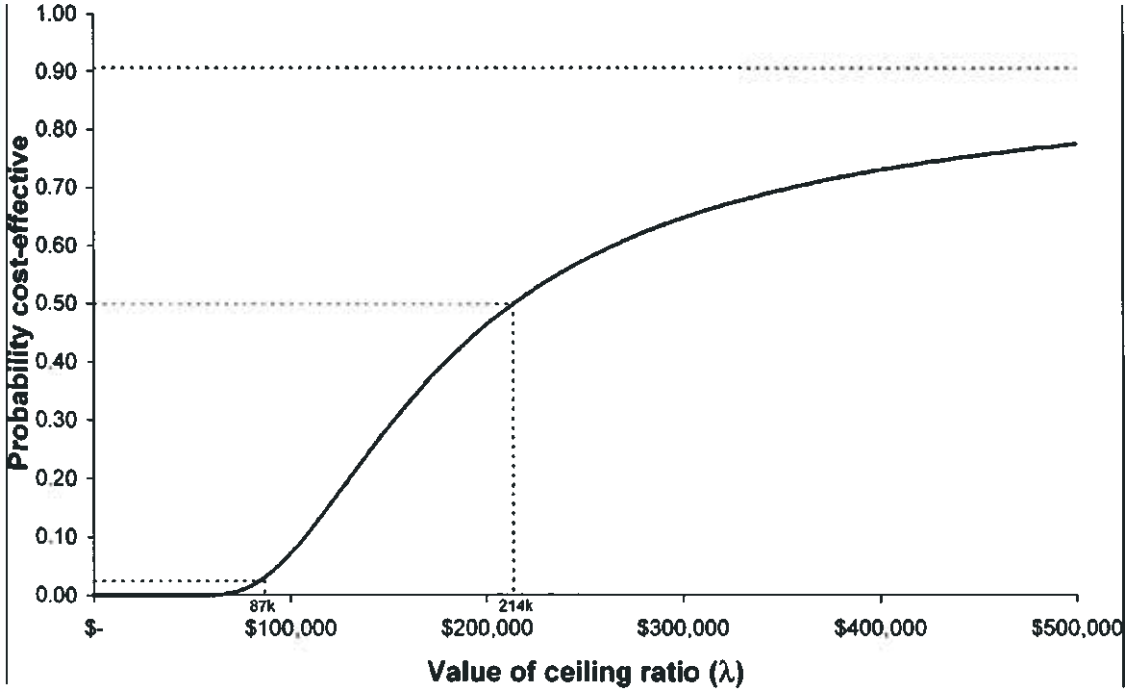
Figure 5. Fieller's theorem (a) and bootstrap (b) confidence limits on the CE plane for data example.



1.1.6.3 Acceptability curve better solution

The acceptability curve (AC) presents much more information on uncertainty than do confidence intervals. The curve cuts the vertical axis at the p-value (one-sided) for the cost difference (which is $p < 0.0001$ in example) since a value of zero for , implies that only the cost is important in the cost-effectiveness calculation. The curve is tending toward 1 minus the p-value for the effect difference (which in the example is $p= 0.10$), since an infinite value for λ implies that effect only is important in the cost-effectiveness calculation. The median value ($p=0.5$) corresponds to the base-case ICER, which is C$214,000 in our example. As well as summarizing, for every value of λ, the evidence in favor of the intervention being cost-effective, acceptability curves can also be employed to obtain a CI on cost-effectiveness. For the example, the 95% upper bound is not defined and the 95% lower bound is equal to C$86,800. [32]

Figure 6. Parametric cost-effectiveness acceptability curve for data example (assuming joint normality of cost and effect differences).



Therefore, formal tests of hypothesis are unlikely to be useful in economic evaluation studies; however, the use of CI for representing uncertainty in the ICER is limited. Rather, it is more appropriate the use of AC that directly addresses the concern of the decision-maker: How likely is it that the intervention is cost-effective? This interpretation requires a Bayesian view of probability, but a Bayesian approach is the most natural approach for decision-making. [32]

The technique of representing uncertainty in CEA through the use of cost-effectiveness acceptability curves (CEAC) has been widely adopted method to quantify and graphically represent uncertainty in economic evaluation studies of health-care technologies. [37]

CEAC were originally introduced to represent the uncertainty concerning the cost-effectiveness of a health-care intervention in the context of decisions involving two interventions, as an alternative to confidence intervals around ICER. [38] The CEAC is derived from the joint density of incremental cost (ΔC) and incremental effect (ΔE) for the intervention of interest, and representing the proportion of density where the intervention is cost-effective for a range of values of λ. Parametric estimation is possible by assuming a parametric functional form for the joint density (ΔC, ΔE). Where bootstrapping or Monte Carlo simulation is employed, the CEAC is determined as the proportion of the (ΔC, ΔE) points where the intervention is cost-effective. [37]

1.1.7 Epidemiology as base for economic evaluations

Base for any pharmacoeconomic research is epidemiology. Epidemiology determines the baseline and current state of diseases within populations, describing characteristics of the patients with particular diseases, and identifying exposures that have a positive or negative impact on the occurrence and outcome of the diseases. The role of epidemiology is complementary to that of economics; it encompasses rubrics ranging from health services research to Pharmacoepidemiology, Outcomes Research and Clinical epidemiology. Epidemiology describes the distribution of diseases and exposures in populations and draw conclusions regarding association between the exposures and diseases. [19]

1.1.7.1 Clinical trials

A properly planned and executed clinical trial is a powerful experimental technique for assessing the effectiveness of an intervention. A clinical trial is defined as a prospective study comparing the effect and value of an intervention(s) against a control in human beings. The ideal clinical trial is that it is randomized and double-blinded. Randomized clinical trials (RCT) compare the effectiveness of one or more interventions with a control, including I (in-vitro or animal models), II (biologic activity, ADR, dosing in human), III (assess effectiveness and safety short term)/IV (long-term surveillance without control groups) phase of study. Study population is the subset of the population with the condition or characteristics of interest defined by the eligibility criteria. Scientific investigation always demands that a control group be used against which the new intervention can be compared. Randomization is the preferred way of assigning participants to control and intervention groups. Confirmed RCT are strongest in study design because randomization removes potential bias in the allocation of participants to the intervention group or control group; randomization tends to produce comparable groups and validity of statistical tests of significance is guaranteed. A clinical trial should, ideally, have a double-blind design to avoid potential problems of bias during data collection and assessment. [39]

Evaluation of validity of published randomized clinical trials

Firstly it is assessed if published study possesses all essential components, study design.

Background of study discusses different alternative therapies for treating a disease state and indicates where there may be a room for improvement.

The goal of the study should be to determine if the therapy being evaluated solved the problem better than either an alternative therapy or doing nothing at all.

The objectives are a critical part of a study. They should be specific, measurable and relevant subsets of the main goal and if satisfied than the goal has been met. The methodology should be designed around the objectives.

The results section presents what happened after performing the methodology.

The discussion section allows interpretation of the trends and interrelationships of the results.

The conclusion section should relate the discussion back to the original problems and tell readers if the therapy under study actually solved the problem.

Validity of the study is second step in evaluating RCT, determining whether the study results (i.e., the effect) are really due to drug under study (i.e., the cause) or due to some other cause or factor present among the study participants who received the treatment.

Study bias is when a study includes selecting tests and techniques designed to favor one group over another or choosing a measurement tool that shows an improvement in one group but is of no clinical significance.

Lack of placebo group which means appropriate comparator is important point in evaluation of validity. Comparator group received no treatment or different treatment.

Index of accomplishment is criterion selected to determine if an objective is met. This index is measured by techniques using golden standard or best available methodology.

Following and handling the patients who drop-out from study voluntarily or due to sickness. Best solution is intention-to treat analysis by taking the average of the group.

Duration of the study is important for reflection of objectives and for negative effects take time to occur.

Confounding variables is important to establish true cause-and-effect relationships in a study, it is necessary to exclude or account for other reasons why a drug or a therapy may have been associated with a certain effect.

Statistical validity it is important that appropriate statistical analysis be used to ensure that differences between treatments groups were not due to chance or to a random sampling error (was the real patient population appropriately represented in the sample selected?). It is equally important to know that the sample size was large enough to detect a difference when results indicate that no differences were discovered between treatment groups. Traditionally, for a difference to be "statistically significant", the chance that the difference is due to sampling has to be less than 1 in 20, or $p<0.05$. Thus, the "p value" should be provided for all differences cited. Compliance is important so study design must be such that compliance is assured and that the individual patients follow-up the therapy. [7]

By bringing together the results of research in systematic way, apprising its quality in the light of the question being asked, synthesizing the results in an explicit way and making this knowledge base more accessible, it is hoped to foster a greater sensitivity to evidence by researchers, policy makers, practitioners and the public. The absence of an adequate knowledge base for much of care was highlighted in 1972 by the British epidemiologist Archie Cochrane. The rise of the Evidence Based Medicine (EBM) movement stresses the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. If systematic reviews provide the research evidence input into the process of evidence-based decision making, the meta-analysis is the analytical or statistical part of systematic reviews, with a set of guidelines for good meta-analytic practice. [40]

Outcome data from a different type of a single trial are in Table 2 and 3.

Table 2. RCT

	Failure/ Dead	Success/ Alive
New treatment	a	b
Control	c	d

Table 3. Case-control study

	Diseased (Cases)	Non diseased (Control)
Exposed	a	b
Not Exposed	c	d

Odds outcome is easy to calculate:

ln (ODDS) = ln (no. of patients having event / no. of patients not having event).

The odds ratio (OR): OR= ad / bc.

Relative risk (RR): rate ratio/ relative rate

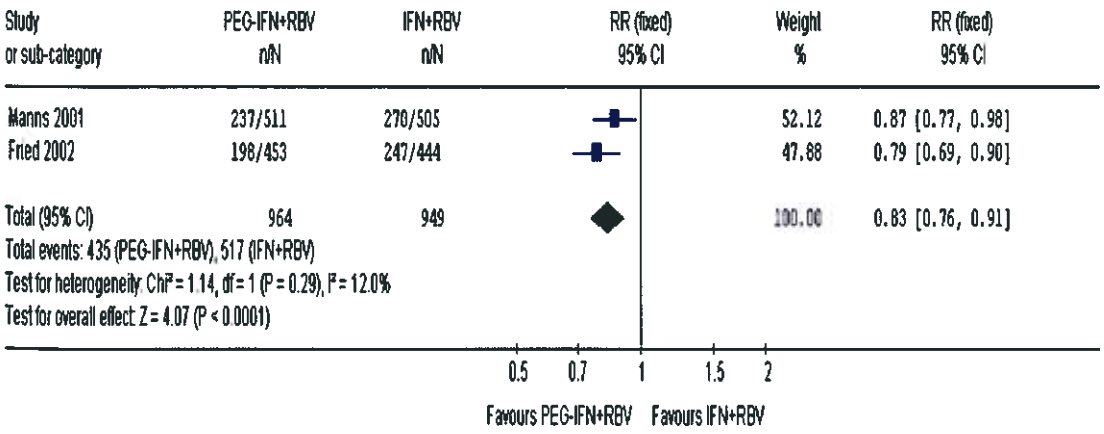
RR= (a / (a+b)) / (c / (c+d)). [40]

1.1.7.2 Meta-analysis

A meta-analysis is a two-stage process. The first stage is the extraction of data from each individual study and the calculation of a result for that study (the 'point estimate' or 'summary statistic'), with an estimate of the chance variation we would expect with studies like that (the 'confidence interval'). The second stage involves deciding whether it is appropriate to calculate a pooled average result across studies and, if so, calculating and presenting such a result. Part of this process is to give greater weight to the results from studies which give us more information; because these are likely to be closer to the truth we are trying to estimate. The results of meta-analyses are often presented in a forest plot. [41]

Simple presentation of forest plot usually used in meta-analysis applied in graphical presentation of results can be shown in Figure 7.

Figure 7: Meta-analysis: Forest Plot and pooled relative risk (RR). [42]



1.1.7.3 Sensitivity analysis

Sensitivity analyses provide reviewers with an approach to testing how robust the results of the review are, relative to key decisions and assumptions that were made in the process of conducting a review. Each reviewer must identify the key decisions and assumptions that are open to question, and might conceivably have affected the results, for particular review. Sensitivity analysis should be used to assess robustness of the results to specific methods used and decision made. [40]

Sensitivity of results to inclusion criteria was revised by Cochrane Collaboration and their handbook is used as advice in performing sensitivity analyses, as follows:

Changing the inclusion criteria; Including or excluding studies were there is some ambiguity as whether they meet the inclusion criteria; Including or excluding unpublished studies; Impact of studies of lower methodological activity; Re-analyzing the data where uncertainties concerning value extracted exist; Publication bias assessment; Re-analyzing the data were missing values exist; Simulation of extra trials. [43]

1.1.7.4 Frequentist versus Bayesian approach

Although a strict frequentist interpretation of CEAC's is possible through the consideration of the p-value on net benefits, the natural way to interpret these curves is as the probability that the intervention is cost-effective. A number of commentators have stressed that such a view of probability in CEA is only possible in a Bayesian framework.

Fundamentally, the Bayesian approach includes a learning process whereby beliefs concerning the distributions of parameters (prior distributions) are updated (to posterior distributions), as information becomes available, through the use of Bayes' Theorem. Historically, advocates of the Bayesian approach were seen to inhabit a different scientific paradigm that was at odds with the frequentist paradigm:

Frequentists considered Bayes methods as subjective and highly dependent on the prior beliefs employed, whereas frequentist methods were objective and robust. The empirical Bayes methods and Bayesian analysis based on uninformative prior distributions are not subjective and have much to offer the frequentist analyst.

At present, and most likely in the immediate future, health economists conducting economic analyses alongside clinical trials will have to work within the sample size constraints imposed by clinical investigators. This is likely to generate the situation where important economic differences cannot be detected at conventional levels of power and significance. A number of commentators have suggested that it may be appropriate for economic analysts to work with "error rates" (in the frequentist sense) that are higher than those employed in clinical evaluation.

This suggestion indicates the desire of economic analysts to consider the weight of evidence relating to the cost-effectiveness of the intervention under evaluation rather than relying on showing significance at conventional levels. This is most easily achieved through the use of CEAC, which show the weight of evidence for the intervention being cost-effective for all possible values of the ceiling ratio, λ. Furthermore, a Bayesian view of probability allows analysts to directly address the study question: How likely is it that the intervention is cost-effective? [32]
Beside CEAC's Bayesian approach is used in all aspects of statistical analysis as well as meta-analysis.

Bayesian methods can be considered as an alternative to the Classical approach to statistical analysis. The name originates from Rev. Thomas Bayes (1702-1761), who in papers published posthumously outlined an alternative approach for making statements regarding probabilities and random phenomena. A Classical statistical analysis of single RCT would make use of only the data contained in the trial. By contrast, a Bayesian analysis would proceed by first summarizing the evidence external to trial, perhaps from laboratory, animal or non-randomized studies, or based on subjective beliefs. This

external evidence is than combined with the observed data to arrive at the current state of knowledge regarding the intervention in the question.

A key element of a Bayesian approach is that different individuals have their own view of the world, and this introduces the idea of subjective probability, in contrast to the objective probabilities traditionally attached to specific, often repeatable, events. The prior beliefs of the individual are than combined with the evidence generated by the trial. Classical analyses use CI but Bayesian analyses apply credibility intervals (CrI) which are intervals within which the quantity of interest (i.e. the log odds ratio for mortality) lies with a specific probability. Disadvantages of Bayesian approach are: prior beliefs lead to illusion of objectivity; elicitation of prior beliefs is non-trivial, and at the present there are few guidelines; There is no automatic or conventional single measure of statistical significance; Bayesian analysis can be computationally complex to implement, and thus time consuming to perform. [40]

At the moment Bayesian approach is used as complementary to Frequentist Classical approach.

1.1.8 Modeling in pharmacoeconomic research

1.1.8.1 Markov model

Software program available can be found on web sites and download is for free, for the Bayesian inference Using Gibbs Sampling (BUGS) project is concerned with flexible software for the Bayesian analysis of complex statistical models using Markov Chain Monte Carlo (MCMC) methods. The project began in 1989 in the MRC Biostatistics Unit and led initially to the `Classic' BUGS program, and then onto the WinBUGS software developed jointly with the Imperial College School of Medicine at St Mary's, London. Development now also includes the OpenBUGS project in the University of Helsinki, Finland. [44]

Decision trees are a simple way to structure problems of decision making under uncertainty. They describe the major factors involved in decision making. For decision making, estimates of the parameters are needed: the costs or benefits and health outcomes of the various branches and probability of their occurrence. Once the estimates have been made, simple calculations suffice to combine them. Modern medical treatments are very powerful, entailing large financial costs and even potential health costs. If those who would benefit from treatment were known in advance, only those people would need to be treated, and the cost of the treatment of the others could be saved. Decision trees have been widely used to model screening and testing decisions.

Simplified decisions are easy because consequences of treatment were immediate. Treatment decisions with long term consequences are harder to analyze. Solution is software packages that allows the analyst to design sub trees and than paste them where needed onto the main tree. Most of the large models used for computing long-term outcomes in the literature are Markov models. These models are a technique for analyzing events that repeat (i.e. headache, mental health treatment) or events that play out over an extended period of time (i.e. cancer, HIV, heart disease). Basic idea of Markov model is that individuals at any time are in one of finite set of states of health, and that health changes from state to state according to set of transition probabilities. In the simplest form, called a Markov chain, the transition probabilities are constant. In

particular, the probability of dying is assumed to be the same for twenty-years-olds and for sixty-years-olds. Because age is important, it is common in models of continuing disease to have transition probabilities that are not constant and are called Markovian assumptions or semi-Markov process. In modeling health outcomes, MCMC simulation is used to transform the health of individual patients by applying a random device to generate random shocks to see what happens to those at chance nodes, until they reach the node of the tree. Repeating these calculations thousands of times on identical patients, using fresh flips of the coin each time, leads to distribution of outcomes which should coverage to the expected distribution of outcomes for such a patients. [45]

The advantages of decision-analytical models are described by 4 stages in decision making. Modeling has major role in Stage I which is characterized by significant uncertainty about particular variables, mostly about cost and effectiveness of the new intervention. Pharmaceutical companies are beginning to use this form of analysis prior to large investment in phase II and III trials In order to begin to understand the likelihood of a new drug being cost-effective at particular price levels.

Stage II economic evaluation is required on all technologies which, on the basis of analysis undertaken Stage I, were considered to offer some scope for being more cost-effective than existing interventions. One major role of the model is to assist in the design of the trial-based economic evaluation that tends to be undertaken subsequently. Models can identify particular parameters to which the cost-effectiveness of the new intervention is likely to be sensitive, and thus will help the decision regarding data collection and sample size determination in later trials.

Stage III is the most prevalent in terms of publication and based on the synthesis of data from various sources. Randomized trial is seen as ideal data collection vehicle for this stage of analysis. Trial data are only concerned with an intermediate measure of outcome. Models can estimate the effects of changes in the clinical outcome on the long term costs, morbidity and mortality of disease. Economic evaluations will most likely be concerned with lifetime costs and effectiveness.

Stage IV is concerned with evaluating cost-effectiveness of interventions when they are used in routine clinical practice.

Markov states are definition of the diseases in terms of different states. These states should be chosen to represent, clinically and economically, important events in the disease process that is to be modeled. One of the requirements for Markov modeling is that a patient cannot be in more than 1 state at any of time. [46]

To summarize there are two basic types of Markov models:

I. First and more traditional approach is Markov chain model with constant transition probabilities.
II. The other method for evaluation is Markov Chain Monte Carlo which is individual simulation.

The difference between these two methods is that although individual patients are subjected to the same probabilities of transition as the cohort of patients, since an individual patient can only be in one stage at given time , they may or may not transit between states in any given cycle.

1.1.8.2 Decision tree by DATA

Decision analysis by TreeAge (DATA) has been designed to implement the techniques of decision analysis in an intuitive and easy-to-use manner. It transforms decision analysis from a potentially tedious exercise into an easily applied and highly visual means of

(1) Organizing the decision making process,

(2) Analyzing the problem at hand, and

(3) Communicating both the structure of the problem and the basis for decision reached.

The decision tree is a subject to a few guidelines:

1) Time flows from left to right. Horizontal structure of tree proceeding from left to right. Each successive branch represents an event or decision as it occurs in time.
2) All outcomes must be represented. Each final outcome must be represented as an endpoint on the right side of the tree.
3) Several types of nodes may be used. In general, a node represents a decision, an uncertain event, or an outcome. Each branch of the tree has an associated node located at the right hand end of the branch. A decision node (square in blue) is used to indicate a decision facing the decision maker. A chance node (circle in green) is used to represent an event of uncertain outcome. A terminal node (triangle in red) is used to denote a final outcome: the end of the path often referred as scenario. All of the nodes at the right edge of the tree must be terminal nodes.
4) Branches emanating from decision node represent the options. All available choices must be represented, and the choices must be designated in a way that none overlap.
5) Branches emanating from a chance node represent the possible outcomes of the event. All possible outcomes must be represented, and the outcomes must be in a way that none overlap.

Basic skeleton structure of a tree

I. First are described treatment options: What is appropriate treatment for this patient?

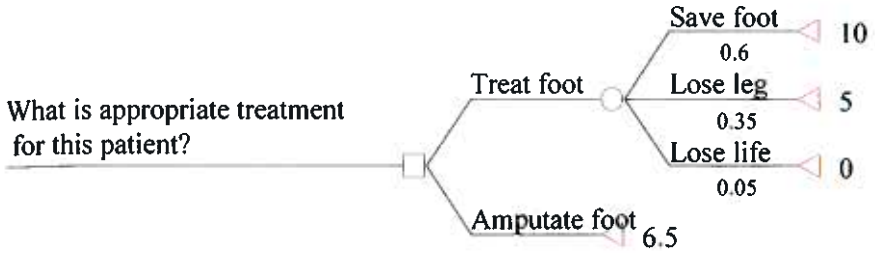
II. Two options considered 1. Treat foot or 2. Amputate foot.

1. Option Amputate foot has no uncertainty, and finish in final outcome terminal node.

2. Option Treat foot has an uncertain event: if treatment with antibiotics (ATB) will be successful and, if not, the extend of the adverse consequences.

This option is followed by a circular chance node where all possible outcomes are represented: a) Save foot, b) Lose foot and c) Lose life. Each is final outcome, so they are represented by terminal nodes.

Figure 8. Example on decision tree, with basic features. [47]



Inserting values in the tree

There are two types of values: probabilities and pay offs.

Probabilities are assigned to the branches emanating form chance nodes, and payoffs are assigned at every terminal node.

- Probabilities are specified below the branch line of the event they represent.
- Payoffs are specified to the right of the terminal node.

In this tree, payoffs are to be made by the patient, based on his subjective view of the utility (quality of life) offered by each outcome. The payoff value is assigned under the assumption that the outcome represented at that terminal node is reached. Utilities can be assigned on any appropriate scale (0-10).

a) Save foot is 10,
b) b) Lose foot is 5 and
c) c) Lose life is 0.

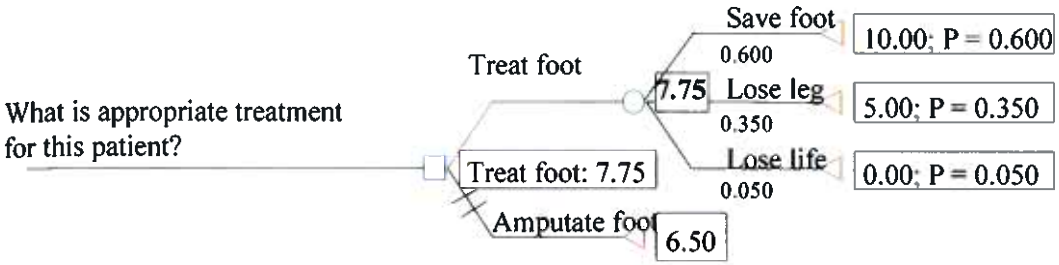
On this scale patient assign utility of 6.5 to the outcome resulting from Amputate foot.

Probabilities are

a) Save foot 0.6 (60%),
b) Lose foot 0.35 (35%) and
c) Lose life 0.05 (5%),

Probabilities are meeting requirements that the probabilities of the branches emanating from a chance node must sum to 1.0 (100%).

Figure 9. Example on calculation of the tree, with values of rolling back function. [47]



Calculation of the tree

For calculation one must go backward, from right to left, called rolling back the tree.
The value of decision node (blue) is equal to the value of its best option.
The value of a terminal node (red) is equal to the value of its payoffs.
The value of a chance node (green) is equal to expected values of each of its branches by their respective probabilities.

A value of each terminal node is already displayed. Only left to calculate is expected value of the node Treat foot (10x0.6) + (5x0.35) + (0x0.05); where 10 is payoff of Save foot and 0.6 is its probability; where 5 is pay off of Lose leg and 0.35 is its probability; where 0 is payoff in Lose life and 0.05 is its probability. Expected value of Treat foot = 6 + 1.75 + 0= 7.75.

A value 7.75 doesn't mean outcome valued by patient in option Treat foot, but it means that 7.75 would be an average utility if decision maker were to repeat this treatment on large number of identical patients. This distinction is critical to understanding of decision analysis. The expected value of an uncertainty is a probabilistic calculation, making it possible to compare one uncertainty with another or an uncertainty against a certain outcome. In a decision node (blue) is the value 7.75 as well, because decision node is equal to the value of its best option. [47]

1.2 Pharmacoeconomic guidelines

In The Netherlands, in 1999, the Dutch Health Care Insurance Board (advisory body on the reimbursement of new drugs) presented the guidelines for pharmacoeconomic research. [48] These guidelines are explained in details in practical section of thesis.
The advanced methods, such as Bayesian analyses and Value-of-Information analyses are not yet in the guidelines, up to date.

Since January 2005, the Ministry of Health in The Netherlands implemented the use of pharmacoeconomics as a supplementary aspect in the evaluation for drug reimbursement. Pharmacoeconomic evaluation was optional in the past, but obligatory since then, to be included in all applications when new drug with proven therapeutic added value claims reimbursement. [49]

This policy was already in practice for many years in other countries, such as the UK, Australia and Canada.

The Dutch guidelines for pharmacoeconomic research consisted initially of 19 recommendations with some of a methodological nature (# 2, 6, 8, 9, 10, 12, 15, 16, 17) and some merely of a procedural nature. Currently, methodological and procedural ones are being separated in distinct booklets.

It is well known that there is a difference between the actual practice in performing the pharmacoeconomic research and guidelines in theory. Also it is important to have in mind that reimbursement procedures differ per country.

Table 4. Comparing the Dutch, Canadian and Australian guidelines for the selected methodological issues [50]

Selected guidelines	Dutch guidelines	Canadian guidelines	Australian guidelines
Perspective	Societal perspective	Perspective of decision makers and/or societal perspective	Perspective of society
Subgroup analysis	The subgroup analyses for patient groups, disease subtypes, degree of seriousness, presence or absence of co-morbidity, etcetera, must all be stated	Generalizability to various subgroups	Not applicable
Incremental analysis	Cost and effect must be reported in the form of incremental values	Incremental cost, clinical outcomes, cost utility and cost-effectiveness	Incremental cost, outcomes and cost effectiveness
Time horizon	The time horizon of the study should enable capturing of all relevant aspects of costs and effects, validly and reliably	Based on current empirical data and long enough to structure all relevant outcomes and costs	Related to the treatment pattern and natural history of the disease
Efficacy and effectiveness	Effectiveness rather than efficacy	Effectiveness rather than efficacy	Effectiveness rather than efficacy
Outcome	QALY or life-year gained (LYG)	QALY or Willingness To Pay (WTP)	LYG or QALY gained
Reference prices	Manual for cost research. Methods and recommended prices for economic evaluations in health care	Unit prices for the resources need to be estimated in Canada, but may allow for the use of quantities of individual services to be estimated from non-Canadian studies	Manual of resources and their associated costs
Discounting	Future outcomes and costs should be discounted at equal rates. Current discount rate in Netherlands is 4%. Also use 0%, 3% or 5% in sensitivity analysis	Discount rate of 5%	Discount rate of 5%
Sensitivity analysis	When conditions and assumptions are uncertain, at least univariate sensitivity analysis using different discounting rates	Sensitivity analyses are used to assess the robustness of the qualitative conclusions and identify areas where further research is needed to more precisely estimate cost effectiveness	One way and two way sensitivity analysis, using different discounting rates or substituting the upper and lower 95% confidence limits of the difference in outcomes achieved

1.2.1 New Dutch guidelines for pharmacoeconomic research

Guidelines for pharmacoeconomic research, actualized version by the Ministry of Public Health, Well-being and Sport. These are recommendations how pharmacoeconomic studies should be performed and which aspects should be taken into account. By help of guidelines optimal use of new therapeutic alternatives is applied. With the aim of better application of guidelines in practice The Ministry of health, well-being and sport actualized the pharmacoeconomic guidelines in two phases. The final responsibility was taken by the group of experts for methodology of economic evaluations.

The directives are not for The Netherlands specifically, but form a reflection of the current score of methodology for the implementation of economic evaluation.

There is no difference in interpretation of the contents of the directives between the CVZ and the manufacturers. There are however differences in the appraisal and application of the directives. The new guidelines were assessed 1st April 2006. Commencing date up to 1 April 2006 CVZ assess the pharmaco-economic evaluations which are part of a compensation file still by means of the original directives from 1999. After this date are the actualized directives effective. [51]

Reasons for actualization:

1. The guideline must be actualized on the basis of the current (international) methodology concerning the implementation of economic evaluations;

2. The guideline to add to other guideline (s) and needs in particularly textual reconsiderations that becomes a univocal interpretation of the guidelines;

3. The guideline is in nature procedural and it is related to information which supplies the manufacturer for the appraisal of mutual substitution and therapeutic value of medicine the guideline is moved to CVZ-publishing of the ' procedure application compensation medicines '.

All pharmaco-economic evaluations, submitted for the support for a compensation application, must be carried out according to these directives. Only when in the file with arguments it is founded why the evaluation not in accordance with the directives it has been carried out or is carry out, is deviate from the directives permitted.

Table 5. Overview of directives actualized including the reason for actualization. [52]

Directive	directive actualized Yes/No	Reason actualization
1 target groups	no, moves	3
2 the perspective	no	–
3 timing of the studies	no, moves	3
4 executants of the study	no, removes	–
5 analysis technique	yes	1
6 indications	yes and moves	3
7 the comparing treatment	yes and moves	3
8 Incremental - and total analysis	no	–
9 analysis period	no	–
10 activity versus effectiveness	no, moves	3
11 quality of life and utility	yes	2
12 outcomes for cost-utility analysis	yes	2
13 cost identification	yes	2
14 cost measuring	yes	2
15 cost appreciations	yes	2
16 discounting for future outcomes and cost	yes	1
17 reliability and validity of results	yes	1
18 reporting of results	yes, moves	1
19 modeling of results	yes	1

There are now only 11 pharmaco-economic guidelines.

Guideline #1 (The perspective of the evaluation), states that the societal perspective should be applied and that the most important characteristic of this perspective is the inclusion of the indirect costs from production losses. It is related to the allocation of financial resources and the consequences on the public health.

Guideline #2 (Choice of comparing treatment/indication), states that new medicines must be compared with the standard treatment, or (if not present) with the usual treatment for compensation, and for a certain indication. Primarily the treatment of which the effectiveness has been proved is considered to be a comparator treatment. Indication must be specified which narrower indication for registration procedure.

Guideline #3 (Analysis technique), states that for the implementation of an pharmaco-economic evaluation can be chosen from three analysis techniques: a 1) cost-utility analyses (CUA) involving the difference costs (incremental costs) compared to the difference in consequences on health are measured life years corrected for quality of life (QALY's), 2) cost-effectiveness analysis (CEA) involving the difference in costs (incremental costs) become compared to the difference impact (incremental impact), or 3) cost-minimization analyses (CMA) involving comparison of only costs of two treatments and it is applicable when the clinical outcomes of treatments are same.

Guideline #4 (Analysis period), states that the impact and costs of the treatment to compare must be measured over the same period. It concerns both impact and costs but also including cost of side effects, as a result of therapy, for treatment to compare.

Guideline #5 (Cost identification, - measuring and- appreciation) states that the identification of cost is carried out from social perspective, the measuring and the appreciation of costs must, wherever possible use the National Guide for cost research, with the aim of the of the uniformity and standardizing of cost measuring is and appreciations in pharmaco-economic evaluations. Types of cost involved are: direct

medical and non-medical costs, indirect medical and non-medical cost, with importance of involving productivity cost, as well. For calculating the costs as a result of productivity losses are two methods applied: Human capital approach and the friction cost method. All cost categories must be mentioned separately and measured in monetary entities.

Guideline #6 (Appreciate of quality of life and QALY's), states that for the improvement of the quality of life cost utility analyses (CUA) must be performed. Appreciations for the medical condition of patients are stipulated for the number of quality adjusted life years (QALY) to calculate. Both the appreciations and the survival data must be reported separately. The combination from these two elements to QALY must be made transparent.

Guideline #7 (To model), states that the model used in pharmaco-economic analyses must be transparent in supporting decision-making process and preferably connected to clinical research. There are 3 main reasons for implementation of modeling: 1) the impact and costs during a time horizon longer than those of clinical research, 2) obtained for the clinical data translation to estimates of the effectiveness in practice daily, 3) and to compare the effectiveness and costs between resources which have not been compared directly in empirical study. The validity of the model (face validity, internal and external validity) must be examined and described. Also the results must become compared with study for other countries and with results of possibly available other pharmacoeconomic models for the same medicine.

Guideline #8 (Incremental analysis), states that incremental analysis must be performed on the basis of the incremental differences in impact and costs between the treatment to compare.

Guideline #9 (Discounting of future impact and costs), states that for data concerning the impact and costs collected over a period longer than one year must the impact and costs generated after the first year be discounted. Primary analysis use

constant cost discounting at rate of 4%, and future impact is discounted with a constant rate of 1.5%.

Guideline #10 (uncertainty analysis), states that the sensitivity analysis must be carried out to examine how the results depend on made assumptions. Sensitivity analyses used are: univariate in case of uncertainty of deterministic variables, and probabilistic sensitivity analysis in case of stochastic variables modeling. Cost, impact and cost-effectiveness ratio are methodologically presented and valued. Sensitivity analysis examines parameters in lower and upper limits and to what extended cost, impact and cost-effectiveness ratio changes when assumption is changed.

Guideline #11 (Use expert panel), states that if research data are lacking and as a result for obtaining data for input in a model or forming a model for pharmaco-economic evaluation to be scientifically described and accepted must be applied an evaluation from expert panel which is composed of experts and it is an independent body. [52]

2 PRACTICAL PART

2.1 Thromboprophylaxis in total hip-replacement surgery in Europe: acenocoumarol, fondaparinux, dabigatran and rivaroxban.

The research was focused to show on example in practice use and application of pharmacoeconomics on specific disease and clinical practice for decision making.

The analysis was performed on thromboprophylaxis in hip-replacement surgery for Europe. Results were published in Future Drugs section on Expert Review of Pharmacoeconomics & Outcomes research. February 2007, Vol. 7, No. 1, Pages 49-58.

Thromboprophylaxis in total hip-replacement surgery in Europe: acenocoumarol, fondaparinux, dabigatran and rivaroxban

Natasa Ivanovic, Maarten Beinema, Jacobus RBJ Brouwers, Mark Naunton and Maarten J Postma[1]

This paper reviews the clinical and pharmacoeconomic studies that have been conducted within Europe for patients undergoing elective hip-replacement surgery. Additionally, we offer a perspective on the possible future clinical use of new agents in orthopedic surgery, such as dabigatran and BAY 59–7939 (rivaroxban). Low-molecular weight heparins are standard therapy for patients requiring thromboprophylaxis and, therefore, we compare these with the other agents: vitamin K antagonists, fondaparinux and the direct oral inhibitors (thrombin or factor Xa inhibitors). The most evidence on the cost-effectiveness and efficacy is available for the low-molecular weight heparins and fondaparinux. Their major limitation is that they require parenteral administration. Only fondaparinux has undergone an extensive pharmacoeconomic evaluation. The direct thrombin inhibitors and direct factor Xa inhibitors are possibly the drugs of the future, but it must be borne in mind that they are still in Phase III clinical trials and, therefore,their safety and efficacy profile is not completely understood, neither are the pharmacoeconomic aspects.

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CONTENTS

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Joint replacement surgery, especially total hip-replacement (THR) surgery, is the most common surgical treatment in older persons with osteoarthritis and results in pain relief, enhanced patient functioning and an improvement in quality of life. Importantly, it is considered a cost-effective intervention [1]. Studies using national registries from Finland, Denmark, Sweden and The Netherlands have shown that the annual incidence of primary THR is approximately 93–113 per 100,000 inhabitants, while in the USA, the incidence is 164–294 per 100,000 [2]. In Europe, by the year 2020, the demand for THR is expected to increase by 25–50% compared with the current level, primarily owing to the aging of the population [3]. Musculoskeletal conditions have an enormous impact on the public health expenditure. In The Netherlands, more than 18,090 THR [4a] and 5000 total knee replacements (TKR) [4] cost US$274 million (€217 million) in the year 2000, which is 9.4% of the total healthcare budget [1].

Patients who undergo THR are at high risk of venous thromboembolism (VTE); in patients undergoing elective THR, reported incidences of asymptomatic deep-venous thrombosis (DVT) and symptomatic VTE are 50–85% [4a] and 2–5%, respectively [4]. DVT may lead to life-threatening pulmonary embolism (PE), disabling morbidity in the form of the post-thrombotic syndrome (PTS) and risk of recurrent thrombotic events. Fatal PE occurs in approximately one per 1000 elective hip arthroplasties in the absence of thromboprophylaxis [4a]. When used for 7–14 days following THR surgery, the percentages of patients with venographically confirmed VTE for the various available agents

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are: no treatment (placebo) 54%, vitamin K antagonists (VKA) 22%, low-molecular weight heparins (LMWH) 16% and fondaparinux 6% [101].

A number of randomized studies have been published over the last 20–30 years demonstrating clearly that primary prophylaxis reduces DVT, PE and fatal PE [4]. Moreover, it has been shown that primary prophylaxis is cost effective [4]. Although thromboprophylaxis is cost effective in general, specific agents approved for use still need to be assessed for cost–effectiveness in addition to safety and efficacy.

The aim of our current study is to summarize some of the European antithrombotic clinical and pharmacoeconomic studies and practices in THR surgery, and to provide an integrated perspective on the present guidelines for clinical practice and possible use of novel anticoagulants.

There have been a number of guidelines produced specifying recommendations for thromboprophylaxis in patients undergoing THR. The American College of Chest Physicians (ACCP) published guidelines in 2004 [4], and recently, Samama and colleagues also published their guidelines [5]. The latter guidelines may be labeled European, although we do note that for various European countries, country-specific guidelines also exist. For example, the national Dutch evidence-based guidelines by CBO (The Dutch Institute for Healthcare Improvement) were updated recently [101]. Each of these guidelines differs from the other, with the exception of the use of fondaparinux. Each guideline recommends that fondaparinux is commenced at 2.5 mg 6–8 h after surgery. The ACCP guidelines recommend that VKAs can be used as first-line therapy [4] in contrast to Samama and colleagues who recommend that VKA should not be first-line therapy [5]. The above-mentioned Dutch guidelines for thromboprophylaxis were published initially in 2000 and updated in 2006. In 2000, the guidelines recommended that thromboprophylaxis with a LMWH should be continued for 6 weeks after major orthopedic surgery and VKAs can be considered as an alternative [6]. However, the recently updated guidelines state that LMWH, fondaparinux or VKA may be used interchangeably [101].

A key difference among the guidelines regards the timing of LMWH administration. Specifically, the ACCP guidelines recommend that LMWH is given at a relatively high dose, starting 12 h before or 12–24 h after surgery. Alternatively, the dose can be halved and given approximately 4–6 h after surgery and then the usual full dose can be given the following day [4]. Samama and colleagues recommend that LMWHs can be administered 12 h before or after surgery at the usual full dose [5]. The ACCP currently recommend using extended thromboprophylaxis (28–35 days) in those patients undergoing THR [4] with LMWH. The recent guidelines by Samama also recommend that prophylaxis is continued for 4–6 weeks after a THR [5].

A recent survey (data were collected from 2002–2004) by Ettema and colleagues of Dutch orthopedic departments (126 hospitals) identified that LMWHs were used as the primary agent for thromboprophylaxis and that they were usually commenced preoperatively (like most European countries) [7]; which is in contrast to the North American situation, where, generally, LMWHs are administered postoperatively [4]. Nearly all Dutch orthopedic departments (97%) used some form of extended prophylaxis. In total, 17% of respondents indicated that LMWHs were used for 5–6 weeks following surgery and acenocoumarol was used for 2 or 3 months in 64% of cases. Acenocoumarol was generally given with LMWH as 'bridge therapy' (87% of respondents) until a therapeutic international normalized ratio (INR) was achieved. The authors concluded that, in general, Dutch orthopedic departments comply poorly with the national guidelines of 2000 [7].

Methods

In this review, we searched the PubMed database (English language) for clinical trials using any of the following agents after hip-replacement surgery: acenocoumarol, fondaparinux and direct oral inhibitors. Given the European perspective of our analysis, such trials had to also be relevant for the specific European clinical practices, in particular with respect to the timing of LMWH and fondaparinux (this did, for example, imply that the European Pentasaccharide Hip Elective Surgery Study (EPHESUS) [9] would be included, whereas the North American-based PENTATHLON 2000 study was not [25]). Additionally, literature was searched for combinations of all previously mentioned agents with any of the following key words: pharmacoeconomics, economy, economic studies, hip replacement and cost. Additional references from the bibliographies from the selected papers were also considered. LMWH was primarily considered the comparator drug since it is standard treatment for preventing DVT [8].

Results

Clinical studies

We identified six relevant European randomized clinical studies (excluding LMWH studies, except when it was the comparator drug), which evaluated thromboprophylaxis in patients undergoing hip-replacement surgery. Specifically, we identified three studies for acenocoumarol [10–12], one for fondaparinux [9], one study on dabigatran [13] and one on BAY 59–7939 [14]. We also considered the results/findings from the meta-analysis performed by Mismetti and colleagues [15] and Turpie and colleagues [16].

Acenocoumarol

Results from large clinical trials have demonstrated that adjusted-dose warfarin is safe and effective when compared with LMWHs [4]. Acenocoumarol is a VKA used in many European countries for thromboprophylaxis. There have been only few clinical trials assessing the safety and efficacy of acenocoumarol in patients undergoing THR.

One of the initial clinical trials investigating acenocoumarol was a prospective randomized study (n = 101) performed in The Netherlands. This study was designed to investigate whether acenocoumarol commencing 4 days preoperatively was more effective than commencing it 1 day preoperatively in patients

undergoing THR. The investigators showed that there was no difference in the incidence of proximal DVT. There were no postoperative hemorrhagic complications and the authors found that blood loss did not depend on the exact level of anticoagulation. No fatal PE occurred during the study [10]. This study included a small sample size and therefore has limited value in clinical practice.

In 1995, Hamulak and colleagues published the results of their single-blinded randomized trial (n = 672), comparing the safety and efficacy of acenocoumarol and nadroparin (LMWH) in patients undergoing THR (n = 391) and TKR surgery [12]. A dose of acenocoumarol 4 mg was administered on the day before surgery, as well as 2 mg on the evening of surgery, followed by dose-adjusted therapy to achieve an INR of 2–3 for 10 days. Nadroparin was given subcutaneously 0.3 ml (3075 anti-Xa-units) on the evening before surgery and, subsequently, the dose was adjusted to each patient's weight and continued for another 10 days. Specifically, patients who weighed less than 60 kg received 0.3 ml; 0.4 ml (4100 anti-Xa-units) was given to those weighing 60–80 kg; and 0.6 ml (6150 anti-Xa-units) was given to those who weighed more than 80 kg. The incidence of DVTs (measured by bilateral venography) was the same in each group at 13.8%. Proximal DVT was slightly lower in the acenocoumarol group (4.6 vs 6.2%). However, clinically important bleedings were higher in the acenocoumarol group (2.6 vs 1.2%) for those patients undergoing THR [12].

The largest randomized trial involving acenocoumarol was published recently by Samama and colleagues. In the Study Comparing Oral Anticoagulants With Reviparin (SACRE), 1279 patients undergoing THR were randomized over two different regimens [11]:

- Bridge therapy: dose-adjusted acenocoumarol was commenced postoperatively following 3–5 days of 4200 IU reviparin and an LMWH commenced preoperatively
- 4200IU of reviparin, commenced preoperatively

Both groups received thromboprophylaxis for 6 weeks. The intent-to-treat results are summarized in TABLE 1. The primary end point was the failure rate, defined as the combined clinical events of a confirmed symptomatic VTE, a major hemorrhage or death. The primary objective was to compare the observed cumulative failure rate in the LMWH with the acenocoumarol group.

Among the patients treated with reviparin, 2.3% developed at least one thromboembolic event compared with 3.3% of acenocoumarol users. During the study, statistically significantly fewer major bleeding events occurred for patients in the reviparin group, 1.4 versus 5.5% patients in the acenocoumarol group. In the intention-to-treat analyses, there was a statistically significant 55% risk reduction in the primary end point for the reviparin group, with 3.7 compared with 8.3% in the acenocoumarol group. In addition, the primary end point in the per-protocol analysis was significantly lower at 4.2% for reviparin than for acenocoumarol at 10.3% ($p = 0.001$). In summary, a significantly higher benefit–risk ratio was observed for THR patients who received extended out-of-hospital prophylaxis with LMWH versus acenocoumarol. LMWH prophylaxis was at least as effective as oral anticoagulants, but with a marked improvement in safety [11]. A potential limitation of LMWH prophylaxis in the out-of-hospital setting is the need for subcutaneous administration, which may be difficult for some patients, and more costly.

A meta-analysis of all randomized trials in orthopedic surgery (THR and/or TKR) on the risk–benefit ratio of VKA versus LMWHs found that VKAs were less effective than LMWHs in the prevention of both total and proximal DVT (RR: 1.51; 95% confidence interval [CI]: 1.27–1.79 and RR: 1.51; 95% CI: 1.04–2.17, respectively). There were no significant differences in the risk of clinical PE, death, major hemorrhage or wound hematoma between the two treatments [15]. A subgroup analysis indicated that neither the type of surgery, nor the timing of LMWH administration relative to the surgery, modified these results.

Fondaparinux

The pentasaccharide fondaparinux is the first of a new class of synthetic antithrombotic agents that act by specifically inhibiting factor Xa. There has been only one major clinical trial in Europe investigating the safety and efficacy of fondaparinux in patients undergoing THR [9]. The EPHESUS study was a double-blind randomized trial comparing fondaparinux 2.5 mg (started 6 h postoperatively) with enoxaparin (LMWH) 40 mg subcutaneously once daily (starting preoperatively) for 6 weeks in patients undergoing THR surgery [9]. The primary efficacy outcome was VTE (defined as documented symptomatic DVT and/or PE) at day 11. The secondary efficacy outcomes were total, proximal and distal DVTs, and symptomatic VTE up to day 11 and day 49. The EPHESUS investigators found that overall fondaparinux was more efficacious than enoxaparin (TABLE 1). By day 11, significantly fewer patients treated with fondaparinux 4% had VTE, detected by scheduled bilateral venography than those on enoxaparin at 9% ($p < 0.0001$). However, while the incidence of venographic VTE was reduced significantly, the incidence of symptomatic VTE did not differ between the two groups; by day 49, 1% of patients in each group had experienced a symptomatic venous thromboembolic event. The two groups did not differ in the frequency of death or clinically relevant bleeding. In summary, the administration of fondaparinux 2.5 mg starting postoperatively had a more favorable risk–benefit compared with LMWH only if asymptomatic VTEs were included in the analysis [9].

A meta-analysis of four randomized trials investigating the efficacy of fondaparinux (2.5 mg administered once a day 6 h postoperatively) found that it was superior to enoxaparin for the prevention of VTE in major orthopedic surgery. Fondaparinux significantly reduced the incidence of VTE by 55% compared with enoxaparin by day 11 (6.8 vs 13.7%, respectively). Major bleeding occurred more frequently in the fondaparinux group than the enoxaparin group (2.7 vs 1.7%;

Table 1. Summary of clinical studies in thromboprophylaxis of THR.

Study	Study design	Medication program	Follow-up (weeks)	Efficacy outcome per protocol thromboembolic accidents (%)		Safety outcome per protocol (%)			Ref.
				Venography	*Symptomatic*	*Major bleeding*	*Nonmajor bleeding*	*Deaths*	
SACRE (THR)	Randomized, open	Acenocoumarol for 6 weeks postoperative (n = 645)	9		A: 4.0 NS, Patients with ≥1 thromboembolic accident: 3.3	7.8	2.7	0.2	[11]
		Reviparin for 6 weeks preoperative (n = 644)			R: 2.8; Patients with ≥1 thromboembolic accident: 2.8	1.6 ($p < 0.001$)	2.0	0.0	
EPHESUS (THR)	Randomized, double-blind	Fondaparinux 2.5 mg for 11 days postoperative (n = 1155)	6	4.0 ($p < 0.0001$);	0.4 NS	4.0 NS	4.0	0.2	[9]
		Enoxaparin 40 mg for 11 days preoperative (n = 1154)		9.0	0.3	3.0	3.0	0.4	
BISTRO II (THR or TKR)	Randomized, double-blind, Phase II	Dabigatran 50, 150 and 225 mg bid and 300 mg od for 6–10 days postoperative (n = 1576)	4–6	THR only: 50 mg: 23.6; 150 mg: 3.4; 225 mg: 8.3; 300 mg: 13.1	THR only: 50 mg: 1.0; 150 mg: 1.0; 225 mg: 0.0; 300 mg: 1.0	50 : 0.0; 150 mg: 3.8; 225 mg: 4.4; 300 mg: 4.7	50 mg: 4.2; 150 mg: 8.6; 225 mg: 10.4; 300 mg: 8.5	50 mg: 0.3; 150 mg: 0.0 225 mg: 0.3; 300 mg: 0.0	[13]
		Enoxaparin 40 mg od for 6–10 days preoperative (n = 397)		THR only: 14.9	THR only: 0.0	2.2	5.2	0.0	
BAY59-7939 (THR)	Randomized, double-blind, double-dummy, Phase II	BAY 59-7939 2.5, 5 , 10, 20 and 30 mg* bid for 5–9 days postoperative (n = 573)		2.5 mg: 15.4 NS; 5 mg: 13.8 NS; 10 mg: 11.9 NS; 20 mg: 18.2 NS; 30 mg*: 6.9 NS	-	2.5 mg: 0.8; 5 mg: 2.2; 10 mg: 2.3; 20 mg: 4.5; 30 mg*: 5.4	2.5 mg: 4.5; 5 mg: 10.3; 10 mg: 10.6; 20 mg: 14.9; 30 mg*: 5.4	2.5 mg: 0.8; 5 mg: 0.8; 10 mg: 0.0; 20 mg: 0.0; 30 mg*: 0.0	[14]
		Enoxaparin 40 mg od, 5–9 days preoperative (n = 133)		17.0		1.5	4.5	0.0	

NS: Not significant *when significance was not stated in table it is because it was not given by original studies).
bid: Twice daily; od: Once daily; THR: Total hip replacement; TKR: Total knee replacement.
*Dose arm suspended owing to regulatory request.

p = 0.008); however, clinically relevant bleedings (resulting in death, reoperation or occurring in a critical organ) did not differ between the groups [16].

New anticoagulants

Administration of LMWH is generally not convenient for use in the outpatient setting. VKAs, however, can be administered orally, but require careful patient monitoring and dose adjustments owing to their variable dose–response relationship. The development of new anticoagulants has been pursued with the aim of improving efficacy, predictability, consistency of response, safety and convenience.

Recently, a new class of anticoagulants, direct thrombin inhibitors (DTIs), have undergone extensive clinical Phase II and III trials (Di Nisio and colleagues [17]). There are now many injectable DTIs available and used in clinical practice (e.g., hirudin, argatroban, bivalirudin and desirudin). A recently marketed oral anticoagulant was ximelagatran, a prodrug, which is converted to melagatran. Melagatran, given intravenously or subcutaneously, was studied extensively in patients undergoing orthopedic surgery and found to offer a favorable risk benefit over the LMWHs [18]. However, in February 2006, ximelagatran and melagatran were removed from the market following liver toxicity concerns. There are other oral inhibitors undergoing clinical investigation, including dabigatran etexilate (DTI) and BAY 59-7939, a direct factor Xa inhibitor.

Dabigatran

Dabigatran is also a prodrug. The BISTRO II study was a Phase II, double-blind, randomized, controlled trial (n = 2039) comparing dabigatran used in a range of doses (50 mg twice daily, 150 mg twice daily, 225 mg twice daily and 300 mg once daily) with enoxaparin 40 mg once daily in patients undergoing THR or TKR [13]. Dabigatran was commenced 1–4 h postoperatively and continued for 6–10 days, while enoxaparin 40 mg once daily was started 12 h preoperatively and continued for 6–10 days after surgery. A significant dose-dependent decrease in VTE occurred with increasing doses of dabigatran ($p < 0.0001$). The lowest rate of VTE (13.1%) and proximal DVT (2%) occurred in the 225 mg twice-daily group. Compared with enoxaparin, VTE was significantly lower in those patients receiving 150 mg twice daily, 300 mg once daily and 225 mg twice daily (TABLE 1). Compared with enoxaparin, major bleeding was significantly lower with 50 mg twice daily (0.3 vs 2.0%; p = 0.047), but elevated with higher doses, nearly reaching statistical significance with the 300 mg once-daily dose (4.7%; p = 0.051) (TABLE 1).

During the treatment period, 0.1% of the total study population developed a symptomatic VTE and during the follow-up period, a further three patients developed symptomatic VTE. Symptomatic VTE occurred in all except the 225 mg twice-daily group.

In summary, administration of dabigatran in the postoperative period was effective and safe across a range of doses. Importantly, the three higher doses of dabigatran were significantly more effective in VTE prevention following major joint replacement surgery than enoxaparin, although this could be at the expense of elevated bleeding risks [13]. Dabigatran is undergoing Phase III clinical trials to assess the safety/efficacy balance and results are envisaged for 2007. In particular, the trial is investigating the efficacy and safety of oral dabigatran (150 or 220 mg once daily) compared with enoxaparin 40 mg once daily in patients who are undergoing primary elective THR surgery [102]. The study is designed such that each treatment is given for 28–35 days. The patients randomized to dabigatran receive half the dose (i.e., 75 or 110 mg) on the day of the surgery.

BAY 59-7939 (rivaroxban)

A recent study completed by Eriksson and colleagues (double-blind, a double-dummy and dose-ranging study) investigated the safety and efficacy of BAY 59-7939, an oral direct factor Xa (FXa) inhibitor (Bayer Health Care AG, Wuppertal, Germany) [14]. Patients undergoing THR (n = 722) were randomized to BAY 59–7939 at administered doses of 2.5, 5, 10, 20 and 30 mg twice daily, starting 6–8 h after surgery, or enoxaparin 40 mg once daily, commenced on the evening before surgery. The treatments were continued until bilateral venography 5–9 days after surgery. The primary efficacy end point was the incidence of any DVT, nonfatal PE and all-cause mortality up to 9 days after surgery. The rates were 15, 14, 12, 18 and 7% for the respective doses compared with 17% of patients treated with enoxaparin (TABLE 1). There was no statistical evidence of a trend in the dose–response relationship between BAY 59–7393 and the primary efficacy end point (p = 0.932).

There was a statistically significant increase in the frequency of major bleeding with increasing doses of BAY 59-7939 at 0.8, 2.2, 2.3, 4.5 and 5.4% for the respective dosages. The incidence of major bleeding in the enoxaparin group was 1.5%. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than three-times the upper limit of normal occurred in 11.2 and 8.8% in the enoxaparin group, respectively, compared with 3.9–6.4, and 3.3–8.3% in the BAY 59–7939 groups, respectively. There was no evidence of a dose–response relationship of BAY 59–7939 and increased liver enzymes [14]. This finding is important as ximelagatran, the first oral DTI, was removed from market owing to liver toxicity concerns. In summary, BAY 59–7939 compared favorably with enoxaparin in both efficacy and safety, at doses ranging from 2.5 to 10 mg twice daily [14].

Pharmacoeconomic studies

We were unable to identify any relevant pharmacoeconomic studies directly relating to acenocoumarol and thromboprophylaxis following THR surgery, as well as for the new oral inhibitors, DTIs and FXa inhibitors (however, they are still in Phase III clinical trials and early pharmacoeconomic assessments are scarce). From the studies that investigated the cost–effectiveness of fondaparinux, four related to THR surgery in Europe [19–22] and one concerned the cost–effectiveness of the timing of administration [23]. All currency conversions were performed by using [103] on the 14th July (2006).

Fondaparinux

Lundkvist and colleagues performed a cost–effectiveness and cost–consequence analysis from the Swedish perspective on the use of fondaparinux and enoxaparin following THR, as well as TKR [22]. The authors simulated 10,000 patients to receive 7 days of either fondaparinux or enoxaparin and followed these patients for 5 years, and then estimated costs, clinical DVTs and PEs and VTE-related deaths. The authors used a discount rate of 3% in their base-case analyses. Sensitivity analyses showed that fondaparinux use incurred higher costs than enoxaparin after THR at the 5-year follow-up. The cost per clinical VTE event (DVT or PE) prevented was €239 (TABLE 2). Extensive sensitivity analyses were performed, for example, a 20% higher price of fondaparinux increased the cost per VTE prevented to approximately €1500, and surgery was approximately €4000 per VTE prevented after THR [22].

Bjorvatn and colleagues performed cost–effectiveness and cost–consequence analyses of fondaparinux versus enoxaparin from a Norwegian perspective in patients undergoing THR, TKR and HFS [20]. The authors used Norwegian data from 55,000 patients who had undergone major orthopedic surgery in the period 1999–2001. The costs were obtained from the Norwegian Insurance Services. The analysis was based on a specifically developed decision tree simulation model of 10,000 patients over 5 years [21] and is derived from fondaparinux Phase III trials, as well as Norwegian resource use. The model was divided into two phases: an acute phase, from surgery to 30 days postoperatively, and a chronic phase, from day 30 to 3 months. The follow-up period was from 3 months to 5 years. The costs were discounted at 3% per annum. The authors found that the total costs for patients undergoing THR surgery were greater for fondaparinux than enoxaparin in the inpatient setting (€210 for fondaparinux vs €158 enoxaparin per patient). Fondaparinux also incurred greater costs at day 30 (€259 for fondaparinux vs €227 for enoxaparin per patient) and day 90 (and €299 for fondaparinux vs €279 for enoxaparin per patient). The costs per death avoided for using fondaparinux instead of enoxaparin after THR were €172,700 at discharge, €53,100 at day 30 and €25,100 at day 90 (TABLE 2). The model showed clearly that fondaparinux was not a cost-saving option in postoperative VTE prophylaxis following THR, from discharge up to day 90. However, incremental costs per death avoided or VTE event avoided decreases as follow-up time increases. Sensitivity analyses were robust to changes in crucial parameters [20] and the authors conclude that fondaparinux is likely to be cost saving after a time horizon of 5 years.

Annemans and colleagues performed a cost–consequence analysis in Belgium of fondaparinux versus enoxaparin in patients undergoing major orthopedic surgery (THR, TKR and HFS) [19]. The study was designed from the perspective of the Belgian healthcare payer. A hypothetical cohort simulation of 10,000 patients receiving either fondaparinux or enoxaparin was performed, and outcomes were assessed at 90 days, 1 year and 5 years. The 7-day use of fondaparinux was more expensive

Table 2. Summary of pharmacoeconomic studies in thromboprophylaxis in THR for EU countries.

Perspective	Comparator[§]	Analytical technique	Time	Cost € (THR only)	ICER for THR	Discounting (%)	Surgery	Ref.
Payer (Sweden)	Fondaparinux (2.5 mg) and enoxaparin (40 mg) od	CEA,CCA	6 years	‡	€239 per VTE prevented by use of fondaparinux	3	THR; TKR	[22]
Payer (Norway)	Fondaparinux (2.5 mg) and enoxaparin (40 mg) od	CEA,CCA	Discharge; 1 month; 3 months	Fondaparinux per patient: At discharge: €52; 1 month: €32; 3 months: €2	Per death avoided: At discharge: €172,700; 1 month: €53,100; 3 months: €25,100 by use of fondaparinux	3	THR; TKR; HFS	[20]
Payer (Belgium)	Fondaparinux (2.5 mg) and enoxaparin (40 mg) od	CCA	3 months; 1 year; 5 years	Fondaparinux per patient: 3 months: €12; 1 year: €10; 5 year: (€6)*	‡	No	THR; TKR; HFS	[19]
National Health Service (UK)	Fondaparinux (2.5 mg) and enoxaparin (40 mg) od	CCA	Discharge; 1 month; 3 months; 1 year; 5 years	‡	‡	6	THR; TKR; HFS	[21]

*Savings are expressed in brackets.
‡Single results for THR could not be derived.
§Each of these were administered for 7 days.
CCA: Cost consequence analysis; CEA: Cost-effectiveness analysis; VTE: Venous thromboembolism; od: Once daily; THR: Total hip replacement; TKR: Total knee replacement; HFS: Hip fracture surgery; ICER: Incremental cost–effectiveness ratio.

than enoxaparin (€72.7 vs 26.2). With respect to THR, the total costs were €248 for fondaparinux versus €236 enoxaparin per patient at day 90 (€259 vs 249) at 1-year follow-up and €324 versus 330 at 5 years (TABLE 2). Hence, savings were achieved over the long term (5 years). In sensitivity analyses, the results were found to be robust to variations in important parameters. The authors concluded that their analysis of health and economic consequences over a long-term period demonstrates the value for money of fondaparinux versus enoxaparin for the prevention of VTE events after THR, TKR and HFS.

Gordois and colleagues performed a cost–consequence analysis from the UK perspective for patients undergoing THR, TKR and HFS [21]. This study did not differentiate between the types of surgery and it is not possible to identify whether fondaparinux or enoxaparin was cost effective in those patients undergoing THR. At discharge up to day 30, fondaparinux was shown to be cost neutral, and cost saving thereafter. The sensitivity analyses for combined THR, TKR and HFS surgery demonstrated that fondaparinux was cost saving at day 90, 1 year and 5 years. The costs were discounted at rate of 6% (TABLE 2) [21]. The sensitivity analyses were robust to changes in key parameters. The authors concluded that fondaparinux is more effective and reduces costs to the healthcare system compared with enoxaparin.

Fondaparinux versus preoperative & postoperative enoxaparin

There are major differences between European and North American practices in thromboprophylaxis, in particular with the exact timing of administration. On the one hand, the widely held European view is that thromboprophylaxis should be commenced preoperatively (12 h prior to surgery). On the other hand, concerns about risk of bleeding during surgery and the interference with regional anesthesia led the North Americans to commence thromboprophylaxis postoperatively (12–48 h after surgery).

A review done on the timing of prophylaxis by Dutch and Italian researchers showed that there is no convincing evidence that starting LMWHs prophylaxis preoperatively is associated with a lower incidence of VTE. In addition, the perioperative regimen (2 h before up to 4 h after operation) may decrease the risk of postoperative DVT, but it is associated with an increase of major bleeding [24].

A study performed by Wade and colleagues addressed the cost–effectiveness of fondaparinux once daily with enoxaparin administered 30 mg twice daily postoperatively and enoxaparin administered 40 mg once daily preoperatively [23]. The analysis utilized data from the PENTATHLON 2000 [25] and EPHESUS [9] clinical trials. The cost data were derived from the literature and enabled calculation of the mean cost of proximal DVT, nonfatal PE and bleedings. The authors found that the costs of fondaparinux 2.5 mg once daily (given for 7–8 days), enoxaparin 30 mg twice daily (for 7 days) and enoxaparin 40 mg daily (for 8 days) were €258, 203 and 160 per patient, respectively. Overall, the incremental costsaving per VTE avoided was €39,700 by using the enoxaparin twice-daily regimen postoperatively over the fondaparinux regimen. On the other hand, when fondaparinux was compared with the enoxaparin 40 mg regimen, the incremental cost saving per VTE avoided was €5200 in favor of fondaparinux. The cost per death averted was €156,600 if fondaparinux was used, €109,000 if enoxaparin 30 mg of twice daily was used and €131,500 if enoxaparin 40 mg once daily was used. Versus no prophylaxis, the cost per life year gained (LYG) was €9850 for fondaparinux, €7390 for enoxaparin 30 mg twice daily and €7690 for enoxaparin 40 mg once daily. Hence, fondaparinux once daily is more cost effective than enoxaparin 40 mg once daily, but it is less cost effective than enoxaparin 30 mg twice daily. In sensitivity analyses, these results appeared robust [23].

Conclusion

Studies have shown that during the first 10 days, low molecular heparins started preoperatively or fondaparinux commenced postoperatively are preferred over the vitamin K antagonists. Clinical results included in the new Dutch CBO evidence-based guidelines have shown that LMWHs, VKA and fondaparinux are equally effective in the extended period. Pharmacoeconomic studies indicate that fondaparinux is only cost saving in the long term; for example over a 5-year period. Fondaparinux appears more cost effective than LMWH 40 mg once daily commenced preoperatively, but appears to be less cost effective then LMWH 30 mg twice daily commenced postoperatively.

Expert commentary & five-year view

During the last 10 years, many evidence-based guidelines for orthopedic thromboprophylaxis have been published [26–32]. Owing to the inconsistent study design of many trials, it is difficult to conclude which strategy fits best with a safety balance between major bleeding disorders and efficacy to prevent DVT and PE. Orthopedic surgeons argue that a bleeding is much more harmful than a DVT, which can be treated with therapeutic doses of anticoagulants when symptomatic. The design of modern trials with VKAs included symptomatic as well as asymptomatic DVTs. The question arises of whether there is a difference in symptomatic versus asymptomatic DVT in the prediction for a fatal PE. A controlled clinical trial including at least 10,000 patients is required to answer this question reliably, which is logically very difficult and financially challenging.

During the first 10 days, LMWHs started preoperatively or fondaparinux commenced postoperatively are preferred over the vitamin K antagonists. The LMWHs, VKAs and fondaparinux are equally effective [101] in the extended period and differences in major bleeding are only marginal. LMWHs and fondaparinux have the disadvantage that they are required to be given subcutaneously. In addition, the effects of LMWHs (and possibly fondaparinux) in patients with certain morbidities (e.g., obesity and decreased renal function) is unpredictable and few evidence-based guidelines exist to manage these patients appropriately. Hence, one can conclude that since VKAs are available at low cost, can be orally administered, computerized dosing schedules are available and can be monitored by simple laboratory tests

(including patient self monitoring) in patients with certain morbidities (e.g., obesity and decreased renal function), they are perhaps the most appropriate option for the extended period at present. Furthermore, individualized risk assessment strategies for DVT-PE should be included to make the appropriate prophylactic approach in surgical patients [33]. The quality of coumarin dose adjustment in earlier-mentioned studies was poor. Anticoagulant clinics, for example, in The Netherlands provide better VKA management in the sense of better control and individual adjustment of INR in patients [34]. From our present knowledge regarding the metabolism of coumarins, which depend on CYP2C9, fixed doses of coumarins are not evidence based owing to the variable response and risk of bleeding. CYP2C9 genotyping could be useful to identify potential candidates who may require lower starting doses in order to minimize problems with acenocoumarol during the initiation period [35].

Direct oral inhibitors are possibly the drugs of the future and, although ximelagatran was withdrawn from the market owing to safety concerns (liver enzyme elevation), the next generation of oral agents (still in Phase III trials) appear promising. One of the most interesting new compounds is dabigatran, which has been proven effective; liver enzyme elevation has not been observed to the same extent as ximelagatran and, therefore, there is a strong possibility that it could be used routinely in clinical practice to prevent DVT following major orthopedic surgery.

This review covered clinical trials for drugs of interest within applications that would be relevant for the European situation: SACRE for acenocoumarol, EPHESUS for fondaparinux and dabigatran and BAY 59–7393. The latter two drugs are still in Phase III study, yet are expected to appear shortly on to pharmaceutical market and were therefore included in this review, with some speculations on use in the future and the experiences up to now.

From the presented clinical and economic data, it is impossible to make evidence-based statement on the best available cost-effective strategy for THR prophylaxis; all the given options are speculative. We must also realize that some of the pharmacoeconomic analyses are company driven and are only available for fondaparinux. We recommend additional studies within noncompany sponsored projects. Additionally, we note that many economic studies focus on symptomatic DVTs only, whereas the prevention of asymptomatic events may also be expected to, in the end, lead to health gains. So, full integrative and independent economic studies are lacking and urgently needed. These studies might also already anticipate on the use of the new classes of drugs in other fields of indication (such as cardiology).

Conflict of interest

Authors have no conflicts of interest to declare.

Key issues

- The demand for total hip replacement (THR) is increasing owing to a growing number of elderly people in Europe and it remains a costly intervention for the health care budget.
- Low-molecular weight heparins (LMWHs) started preoperatively or fondaparinux commenced postoperatively are clinically preferred over the vitamin K antagonists (VKAs) if used during the first 10 days after surgery.
- Current clinical guidelines in THR thromboprophylaxis state that LMWHs, VKAs and fondaparinux are equally effective if used for extended periods (10–42 days).
- Fondaparinux is only cost saving compared with LMWH in the long term (> 5 years).
- Orally administered direct thrombin and factor Xa inhibitors are promising drugs for the future.

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2.2 Application of national guidelines to pharmacoeconomic research in the Netherlands

The research was focused to revise the pharmacoeconomic guidelines and their application in the published literature.

The analysis was performed on studies published in The Netherlands concerning methodological guidelines.

Results were published in Farmakoekonomika a lieková politika, ročník 3, 2007, číslo 1. Pharmacoeconomics and Drug Policy, year 3, 2007, No. 1, Pages 33-40.

APPLICATION OF NATIONAL GUIDELINES TO PHARMACOECONOMIC RESEARCH IN THE NETHERLANDS

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Abstract

Objective: This study investigates the application of the Dutch national guidelines to pharmacoeconomic studies in the Netherlands.
Methods: In 1999, Dutch Health Care Insurance Board presented Dutch guidelines for pharmacoeconomic research. Our review covers all Dutch pharmacoeconomic studies that were published in English during 2003–2004. Nine methodological guidelines were selected for investigation with respect to their application to pharmacoeconomic studies. Each pharmacoeconomic study was reviewed by minimum two reviewers for objectivity and correctness of results.
Results: From 56 studies identified only 13 studies satisfied the inclusion criteria.
An appropriate time period for analysis was applied in all studies (100%), as well as an incremental analysis. Sensitivity analysis was present in 11 studies (85%). In 10 from 13 studies (77%) following three criteria were taken into account: societal perspective, discounting (of costs, benefits and health gains), and efficacy versus effectiveness distinction. LYGs or QALYs as effectiveness expression were used in 7 (54%) and reference prices in 9 studies (69%). Adequate subgroup analyses were presented in only 5 studies (38%).
Conclusions: We found in this review that the application of some of the Dutch guidelines for pharmacoeconomic research to pharmacoeconomic studies is good.
Main changes are needed in areas of suitable subgroup analysis and utilization of the preferred outcomes life-years gained (LYGs) or quality-adjusted life years (QALYs).

Key words: guidelines, - application of guidelines, - pharmacoeconomics, - The Netherlands

Authors have no conflicts of interest to declare

Introduction

Every country is facing problems in financing a health care. In particular, expenditures on health care are often increasing constantly. Pharmacoeconomics has recently come up to control expenditures and enhance economically rational drug use. In such pharmacoeconomic analyses, appropriate methods must be used for a fair evaluation of new drugs. For example in the Netherlands, in 1999, the Dutch Health Care Insurance Board (advisory body on the reimbursement of new drugs) presented the guidelines for pharmacoeconomic research.
One of the most outstanding points of the Health Care Insurance Boards guidelines was that a pharmacoeconomic study was said to should always be a cost-effectiveness analysis and/or a cost-utility analysis, whereas a cost-minimization is never sufficient 1–4. These analyses are supposed to be supportive tools in the decision-making. In fact, the Health Care Insurance Board adopts an independent position: in between policy and practice, in between central government on the one hand and the health insurers, care-providers and citizens on the other 2. In recent years, new supplementary methods are arising, such as Bayesian analyses and Value-of-Information analyses. The advanced methods are not yet in the guidelines.
Since January 2005, the Ministry of Health in the Netherlands implemented the use of pharmacoeconomics as a supplementary aspect in the evaluation for drug reimbursement. Pharmacoeconomic evaluation was optional in the past, but obligatory since then, to be included in all applications when new drug with proven therapeutic added value claims reimbursement 5. This policy was already in practice for many years in other countries, such as the UK, Australia and Canada.
Our review analyses the application of Dutch natio-

nal guidelines to recently published pharmacoeconomic studies in the Netherlands.
The Dutch guidelines for pharmacoeconomic research consisted initially of 19 recommendations with some of a methodological nature and some merely of a procedural nature. Currently, methodological and procedural ones are being separated in distinct booklets. Below, we focus on the guidelines that are referring to methodology.
It is well known that there is a difference between the actual practice in performing the pharmacoeconomic research and guidelines in theory. Also it is important to have in mind that reimbursement procedures differ per country. Still, we believe that these guidelines could always be used as tool for pharmacoeconomic evaluation, as is now done in many western countries.

Methods

Search methodology and inclusion criteria for qualified studies
A search was oriented to pharmacoeconomic studies that were published in English for the Netherlands from 1st January 2003 to 31st December 2004. The databases used were
MEDLINE 6 and EMBASE 7. The search used the terms "cost (-) effectiveness", "pharmaco (-) economic(s)" and "(the) Netherlands".
The formal inclusion criteria for this review were that studies should be:
(a) Pharmacoeconomic evaluations;
(b) A cost-effectiveness or a cost-utility analysis
(b) Original research; and
(c) That full text reports would be available (rather than merely abstracts alone).
This review covers 9 methodological guidelines, chosen by the investigators, and considered as the most important criteria for pharmacoeconomic studies in the sense that they reflect good scientific practice rather than procedures (Table 1). In particular, guidelines studied are numbers 2, 6, 8, 9, 10, 12, 15, 16 and 17 (see (Appendix 1 for detailed information).

Table 1: The Dutch guidelines for pharmacoeconomic research
1. Target groups
2. The societal perspective*
3. Timing of the studies
4. Perpetrator of the study
5. Analytical technique
6. Indications (subgroup analysis)*
7. The comparative treatment
8. Incremental and total analysis*
9. Analysis period/time horizon*
10. Efficacy versus effectiveness*
11. Quality of life and utilities
12. Outcomes for cost-utility analysis (LYG or QALY)*
13. Cost identification
14. Cost measurements
15. Cost evaluation using reference prices*
16. Discounting for future outcomes and costs*
17. Reliability and validity (sensitivity analysis)*
18. Reporting the studies
19. Modeling of the results

*Selected for this review.

Guideline 2 states that the societal perspective should be applied and that the most important characteristic of this perspective is the inclusion of the indirect costs from production losses.
Guideline 6 describes that subgroup analysis should be presented especially when there are differences in clinical effectiveness or costs concerning indications and groups (for example, regarding age or exact indication) that warrant separate evaluation.
Guideline 8 points out the importance of the incremental cost-effectiveness ratios, their reporting and adequate comparison to the relevant alternatives. In principle, comparison of the investigated drug should be with the standard treatment which is evidence-based and may be in the clinical guidelines. Alternatively, the comparator could be the drug that is most widely used (as assessed in drug use databases, such as IADB.nl from the University of Groningen).
Guideline 9 involves the specification of the appropriate time horizon which should be such to cover all important aspects of cost, benefits and health effects.
Guideline 10 states that one should distinguish between efficacy and effectiveness. Effectiveness refers to clinical use of the drug in wide variable populations and real world conditions, whereas efficacy involves carefully selected populations included in the clinical trial. Economic evaluation should ideally relate to effectiveness and not to efficacy.
Guideline 12 recommends that health effects should be expressed as life-years gained (LYGs) or quality-adjusted life-years (QALYs). These outcome measures are presented to make comparison of health outcomes possible across health-care interventions.
Guideline 15 promotes that reference prices (estimated cost prices), should be used in economic evaluation, and only in the absence of these tariffs can be used instead. National average cost price estimates are specified in the guidelines for hospital inpatient days, outpatient visits to GP or hospital and the pharmacist's fee.

Guideline 16 states that costs, benefits, and health effects distributed over time should be discounted at an annual rate of 4%. Discounting is a standard procedure in economic evaluations. In sensitivity analysis lower discount rates for health effects should be investigated.
Guideline 17 recommends that uncertainty is always present in the analyses and that at least a univariate sensitivity analysis must be included to investigate this uncertainty.
After inclusion, each study was examined regarding these nine methodological guidelines. This was elaborated by two reviewers independently. Consensus was achieved if reviewers disagreed and had different opinions.

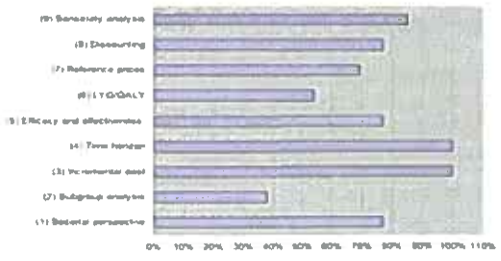
Results

The search conditions were initially met by a total of 56 studies. The MEDLINE search for 2003 and 2004 identified 5 and 11 studies, sequentially. The EMBASE search resulted in 14 and 26 studies in 2003 vs. 2004, respectively. Table 2 presents the 13 studies that met the inclusion criteria. The application of the national guidelines to identified pharmacoeconomic studies is shown in Figure 1.

Table 2 Pharmaco-economic studies in the Netherlands selected for investigation of application of the Dutch guidelines for pharmaco-economic research

Authors Ref	Disease area	Drug(s)
Publication Year 2003		
Bos JM et al. 14	Pneumococcal infection	Universal vaccine vs. Pneumococcal vaccine
Postma MJ et al. 15	Cardiac surgery	Leucocyte depletion of red cell transfusions
Postma MJ et al. 16	Hepatitis A	Hepatitis A vaccine
Redekop WK et al. 17	Diabetic foot ulcer	Apligraf
Stant AD et al. 18	Schizophrenia	Hallucination focused integrative treatment
van den Hout WB et al. 19	Bone cancer	Radiotherapy
van Dieten HE et al. 20	Reflex sympathetic dystrophy	Acetylcysteine vs. Dimethyl sulfoxide
Publication Year 2004		
Knijff-Dutmer EA et al. 21	Inflammation	Cox-2 inhibitors vs. nonselective NSAID
Korthals-de Bos IB et al. 22	Lateral epicondylitis	Corticosteroids
Oostenbrink JB et al. 23	COPD	Tiotropium vs. ipratropium
Maitland-van der Zee AH et al. 24	Hypercholesterolemia	Screening of genotype before HMG-CoA (statins)
Welsing PM et al. 25	Rheumatoid arthritis	TNF-blocker vs. leflunomide
Welte R et al. 26	Meningococcal infection	Meningococcal vaccine

Figure 1: Application of nine selected guidelines for pharmaco-economic research to the included studies: percentage of adherence



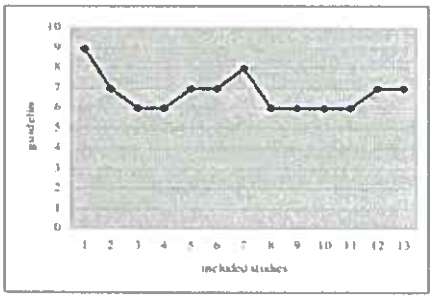
The highest compliance with guidelines, detected in these studies, related to the time period and the incremental analysis (both 100%). The lowest compliance was found for the criterion of subgroup analysis. Sensitivity analysis was reported in 11 studies (85%). The societal perspective was applied in 10 studies (77%), as well as for the effectiveness vs. efficacy criterion and for discounting (applied for costs, benefits and health gains). Reference prices, as recommended in detail from the Dutch manual on cost, were used in 9 studies (69%). Effectiveness was expressed in LYGs or QALYs in 7 studies (54%). Subgroup analysis was done poorly and was performed only in 5 studies (38%).

Table 3 Dutch pharmaco-economic studies included with respect to number of methodological guidelines applied

Included studies Ref	Guidelines applied (no.)
Bos JM et al. 14	9
Postma MJ et al. 15	7
Postma MJ et al. 16	6
Redekop WK et al. 17	6
Stant AD et al. 18	7
van den Hout WB et al. 19	7
van Dieten HE et al. 20	8
Knijff-Dutmer EA et al. 21	6
Korthals-de Bos IB et al. 22	6
Oostenbrink JB et al. 23	6
Maitland-van der Zee AH et al. 24	6
Welsing PM et al. 25	7
Welte R et al. 26	7

The included studies are listed in Table 3 according to the number of guidelines adhered to per study. One study applied all nine criteria and one study, eight out of nine, respectively. The median number of criteria applied to studies was seven. There were five studies that applied seven, and finally six studies applied six of the nine selected methodological guidelines. The respective number of national guidelines applied to included pharmacoeconomic studies can be seen in Figure 2.

Figure 2: Adherence of included studies to the methodological guidelines



Discussion

This review involves all pharmacoeconomic studies published in the Netherlands in period 2003-4, analyzed with respect to selected national methodological guidelines for pharmacoeconomic research.
Adherence to guidelines in the published literature was found at 75% on average, which may be considered satisfactory. The guidelines that were mostly adhered to were: time horizon, incremental analysis, sensitivity analysis, efficacy versus effectiveness, discounting and perspective. Lower compliance of studies with guidelines was found for: reference price, LYG or QALY as preferred outcome and especially in the case of subgroup analysis.
An appropriate time horizon is of essential importance in performing pharmacoeconomic research from point of view to cover all relevant outcomes. All studies included in this analysis comply with the time horizon requirement.
All studies in this review applied a qualified incremental analysis. This illustrates the relevance of the use of an incremental cost effectiveness ratio (ICER) rather than just a CER. It is simply calculated by dividing the incremental cost by incremental effect for each successfully more effective treatment alternative 8, involving all changes in cost versus all changes in effects.
Sensitivity analysis was used in most of the studies. Sensitivity analysis provides reviewers with an approach to testing how robust the results of the analysis are, relative to key decisions and assumptions that the researcher makes in the process of conducting an analysis. Each reviewer must identify the key decisions and assumptions that are open to questions, and might conceivably have affected the results 9.

Dutch guidelines suggest a societal perspective. According to Canadian experience in some cases the sponsor (for example, pharmaceutical industry) may influence the choice of the perspective 10. Perspective depends also on the aim of the study and the exact use of its outcomes in the decision making process.
Differentiation between efficacy and effectiveness was satisfactory, as well as the application of discounting, but implementation of outcomes in terms of LYGs and QALYs was less well performed, used only in 7 studies.
Regarding reference prices, the guideline recommends the use of a list of standard costs, primarily estimates of national averages. The usage of the Dutch manual on costing for reference prices was applied in 9 studies.

The most non compliance was discovered in the area of subgroup analysis. Consequence of non applying suitable subgroup analysis may be rendering non correct results. There is big difference between population groups involved in the study regarding age, sex, medical condition etc.
The decision making process is complex and by following the guidelines it is easier to evaluate methods used and validity, and to judge about the cost and outcomes as reported in the economic evaluation 11.The use of pharmacoeconomic guidelines is not unified yet at the international level 10, 11–13. Guidelines for pharmacoeconomic research aim to enhance quality (assessment) of such studies, providing a framework of objectivity and evidence based research.
Standard and formats for reporting assure transparency of scientific pharmacoeconomic evaluation. It is important especially in issues as reimbursement of drugs, submission by pharmaceutical industries and in applying research at national levels for health care budget decisions.

Conclusion

The application of the Dutch national guidelines of recently published pharmacoeconomic studies in the Netherlands is quite satisfactory.
Main improvements must be made in areas of the subgroup analyses primarily and in further implementation of standardized and comparable health outcomes, such as LYGs and QALYs.

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Appendix 1

Guideline 2: The perspective. "*All studies must be reported from a social perspective.*"
Explanation
Pharmacoeconomic research must be conducted from a social perspective. There is a broad consensus, both nationally and internationally, that on the grounds of welfare-theory the social perspective should form the basis for pharmacoeconomic evaluation. This social perspective means that the analysis should cover all costs and benefits, irrespective of who actually bears the costs or receives the benefits. This means that costs and benefits outside the field of healthcare should also be taken into consideration.
Healthcare itself should therefore be considered as a whole (in other words, non-compartmented): additional costs for one budget section can be compensated, for example, by savings in another budget section. Pharmacoeconomic research can provide insight into such substitution effects.

Guideline 6: Indications. "*The patients for whom the drug is intended must be clearly specified. The starting points for pharmacoeconomic research are the registered indications. The subgroup analyses for patient groups, disease subtypes, degree of seriousness, presence or absence of comorbidity, etc., must all be stated. The economic evaluation must be performed on the entire study population and also on the subgroups that have been identified in the protocol on the basis of possible differences in effectiveness, costs and/or other arguments.*"
Explanation
Because a treatment can be cost-effective for some groups of patients but not for others, it is essential that a prior distinction is made in the protocol between the different subgroups. Sometimes these subgroups will already have been clearly described in the registration text. These will then be the subgroups on which clinical research has been performed and for which the efficacy-safety balance has been found to be positive. From the point of view of cost- effectiveness, the results of a pharmacoeconomic analysis may suggest that the field of application should be limited further within the registered range of indications. These results can be taken into account during the decision-making process. In the case of subgroup analyses, care must be taken that the statistical power of the analyses, i.e. the group size, is guaranteed. The precision needs to be sufficient to enable decisions to be taken regarding the subgroups.

Guideline 8: Incremental and total analysis. "*Costs and effects must be reported in the form of incremental values (i.e. as differences between two alternatives). These incremental values must be used in the pharmacoeconomic evaluation. The study must also provide insight into the total values of the costs and effects of both treatments.*"
Explanation
In an economic evaluation we are concerned with an incremental analysis: what is the difference in costs and effectiveness when intervention A is replaced by intervention B? Two treatments need to be compared: the current treatment (standard treatment, see guideline 7) is compared with the new drug. From the incremental analysis one can deduce what the (net) difference in costs and effects will be when the new treatment replaces the existing one. In order to place the outcome of the incremental analysis in a broader context, the total costs and effects also need to be reported. The inclusion of total costs and effects will, moreover, improve the ability to translate the study to, for example, (future) situations with another comparative treatment.

Guideline 9: Analysis period. "*The analysis period of the study must be such that it enables valid and reliable statements to be made. If modeled data are necessary to meet this requirement, then the model's structure and basis need to be described. The model must have a sound scientific basis at the time the study was performed.*"
Explanation
The costs and effects must be measured over the same time-span. This time span should provide sufficient opportunities for observing the most important outcomes of the intervention. The time period within which effects and costs can be anticipated depends on the treatment goal and thus on the anticipated outcome. When a decision has to be made regarding the inclusion of a new drug on the list, there is often insufficient information available about its effectiveness. To obtain this information, the drug needs to be used in practice. Because primary data usually provide insufficient insight into the value of a drug in the medium- and long-term, modeled data will often have to form an integral part of the dossier being submitted in application for inclusion on the drugs list.

Guideline 10: Efficacy versus effectiveness. "*Ideally, pharmacoeconomic studies should report on a drug's effectiveness, and not on its efficacy. Efforts should be made to collect information on the*

relevant end points in terms of morbidity and mortality. If possible, the data should be collected under realistic conditions. If no effectiveness data are available, then appropriate modeling techniques may be used to translate data from efficacy studies into what can be expected in practice (i.e. effectiveness). The model used needs have a sound scientific basis. All assumptions in such modeling techniques must be explicitly stated and evaluated with the help of a sensitivity analysis."

Explanation

Efficacy and effectiveness are two different concepts. However, both provide insight into the effect of a drug. In the case of efficacy, the effect is examined under ideal conditions in a homogeneous group of patients, and usually whilst making use of intermediate outcomes. Effectiveness data offer a clearer picture of actual value because an effect is studied under more realistic conditions, making use of a heterogeneous group of patients, and with aspects such as therapy (non-)adherence playing a role. This information about use in common practice also provides more insight into whether the treatment aim is ultimately being achieved. Effectiveness research is thus oriented towards final outcomes, such as reduction in morbidity and mortality. The ZFR would like to have access to effectiveness data as soon as a drug is put forward for inclusion on the drugs list. However, from a practical perspective this is not usually possible. Phase 3 studies form the basis for registration and admission to the market. This research is carried out on a select group of patients using a clear treatment protocol, and tends to be done in specialized centers, for a limited period of time and without a follow up after the study has finished. These are not ideal circumstances for pharmacoeconomic research, in view of the fact that research conditions need to match the practical situation as closely as possible. The most important problem with using clinical studies for pharmacoeconomic research is the extent to which an evaluation based upon intermediate outcomes provides any meaningful information on the reduction in morbidity and mortality. For this reason, it is necessary to obtain satisfactory insight into the relationship between the intermediate outcomes and the final outcomes. In order to be able to make a statement on a drug's effectiveness, data from clinical studies can be modeled on the basis of realistic and explicit assumptions. All assumptions need to be carefully discussed and scientifically substantiated. Important variables in the study need to be examined for validity and reliability. Further studies after registration (Phase IV) will have to demonstrate the extent to which the modeling was performed responsibly.

Guideline 12: Outcomes for cost-utility analysis. "*Survival and QOL-results must be reported separately. The method for combining the two must be clearly described. The recommended method for primary analysis is to combine survival data with the QOL valuation using quality-adjusted life-years (QALYs). Utilities must be used as quality-weighting for the calculation of QALYs, measured on an interval scale, where 0 represents the state of death and 1 represents good health.*"

Explanation

The choice of one uniform outcome measure, the QALY, makes it possible to compare the results of different pharmacoeconomic studies. At the moment the QALY is internationally the most widely used and most recommended method. Primary analysis should therefore be based upon QALY's. Secondary analyses may be performed using a different outcome measure. The World Bank, for example, has proposed the disability-adjusted life-year (DALY) as an alternative to the QALY.

Guideline 15: Cost evaluation. "*Economic definitions should be used for the costs. Ideally, uniform amounts should be used for certain cost categories in order to promote the comparability and extrapolability of the results of different studies.*"

Explanation

A standard cost list will be available in mid-1999. This list must be used.

Guideline 16: Discounting for future outcomes and costs. "*Future outcomes and costs should be discounted at equal rates. The current discount rate must be applied. This discount rate must be varied in a sensitivity analysis. If other percentages are used as the basic discount rate, they need to be thoroughly substantiated.*"

Explanation

Internationally, different percentages are used as basis for discounting. At the moment the current discount rate in the Netherlands is 4%, according to the 'Cabinet's standpoint on the reconsideration of the discount rate' dated 9 January 1995. (Source: HAFIR: Textbook Financial Governmental Information and Administration, Part A 8.2, Publisher: Dutch Ministry of Finance).

Guideline 17: Reliability and validity. "*In explaining the analysis methods, all underlying assumptions must be listed, arranged and substantiated. The most important limitations of these assumptions must also be stated. A sensitivity analysis must be used to show how the results depend on the assumptions made. As a minimum, a univariate sensi-*

tivity analysis must be included. If this is insufficient, then multivariate techniques must be included. The methods used, the choice of the parameters and the range of these parameters all need to be stated and substantiated."

Explanation

Prior to presenting a definitive estimate of the costs, the effects and a costeffectiveness ratio, a number of methodological choices will have been made and a number of parameters estimated. The methodological choices concern, for example, the calculation of indirect costs, the definition of the effects and the time window. The estimates relate to aspects such as the use of healthcare facilities, unit prices and the effect parameters.

In performing sensitivity analyses, it is desirable to first formulate an upper and lower limit for each estimate; these represent the uncertainty margins. One can then examine to what extent the costs and the cost-effectiveness ratio will alter if the extreme limits are applied. If this procedure is followed for all estimates successively, it is known as a univariate sensitivity analysis. A multivariate sensitivity analysis examines the effect of simultaneous alterations in various variables, taking into account the correlation between these variables. The most advanced method attempts to create probability distributions around each parameter and repeatedly makes a new estimation for each parameter according to the distributions. Each combination of estimations results in a new estimate for the costs, effects and the costeffectiveness ratio. If this is repeated many times, a risk distribution can be presented for the results of the study.

If there are indications that a univariate sensitivity analysis is insufficient, then a multivariate analysis should be carried out. It is important to adopt the perspective of the end-users of the information as a starting point. By making use of the sensitivity analyses results, policy makers can assess how much value can be attached to the results of the economic analysis, i.e. how reliable the results are.

CONCLUSION

The aim of this doctoral thesis was to explore pharmacoeconomics and its use in the decision making process.

The larger part of the thesis was oriented toward the theoretical approach to Pharmacoeconomics and Outcomes Research, with a defined distinction between two. The literature search applied was from various sources mainly in the electronic form of web sites, or in the form of published articles, journals, books, manuals, databases and software programs, as methods in accordance to objectives that had to be met.

The topics addressed were types of pharmacoeconomic studies and techniques, types of cost and discounting. The decision making process was highlighted with relevance to statistical models. As well known pharmacoepidemiology is a fundamental principle for pharmacoeconomic research to take place, which was also presented here, finishing in software programs and modeling examples by DATA, BUGS and MCMC.

Finally pharmacoeconomic guidelines were revised. The national guidelines from The Netherlands from the CVZ database, which are applied across Europe with a few exceptions, are compared to Canada or Australia from a methodological point of view, with the implementation of new Dutch guidelines for pharmacoeconomics and outcomes research.

The practical part focused on particular conditions and the adherence to pharmacoeconomic guidelines. Each study used different data sources for given aims.

The main goal in this doctoral thesis was to demonstrate the use of pharmacoeconomy in decision making with regards to a specific clinical example. For this purpose the analysis of venous thromboembolism primary prophylaxis after hip replacement surgery in Europe was chosen. The work focused on clinical and pharmacoeconomic studies and practices. In this way pharmacoepidemiology was firstly addressed and then the application of pharmacoeconomics. Also the aim was to provide an integrated perspective on the present guidelines for clinical practice and possible use

of novel anticoagulants. The search was performed using the Pub Med database (English language), giving the European perspective for the specific European clinical practices, with pharmacoeconomic insight. The results demonstrated that during the first 10 days, low molecular heparins started preoperatively or fondaparinux commenced postoperatively are preferred over the vitamin K antagonists. Clinical results included in the new Dutch CBO evidence-based guidelines have shown that LMWHs, VKA and fondaparinux are equally effective in the extended period. Pharmacoeconomic studies indicate that fondaparinux is only cost saving in the long term; for example over a 5-year period. From the presented clinical and economic data, it is impossible to make an evidence-based statement on the best available cost-effective strategy for THR prophylaxis; all the given options are speculative. One must also realize that some of the pharmacoeconomic analyses are company driven and, thus, are only available for fondaparinux. The study recommended additional research without the use of company sponsored projects. Additionally, it noted that many economic studies focus on symptomatic DVTs only, whereas the prevention of asymptomatic events may also be expected to, eventually, lead to health gains. So, full integrative and independent economic studies are lacking and are urgently needed.

The final consideration was the study that investigated the application of the Dutch national guidelines, from 1999, to pharmacoeconomic studies in the Netherlands. The review concerned all Dutch pharmacoeconomic studies published in English during 2003–2004, using Medline and Embase databases as a source. Nine methodological guidelines were selected for investigation with respect to their application to pharmacoeconomic studies. The results of this study were: From the 56 studies utilized, only 13 studies satisfied the inclusion criteria. An appropriate time period for analysis was applied in all studies (100%), as well as an incremental analysis. The sensitivity analysis was present in 11 studies (85%). In 10 from 13 studies (77%) following three criteria were taken into account: societal perspective, discounting (of costs, benefits and health gains), and efficacy versus effectiveness distinction. LYGs or QALYs as effectiveness expression were used in 7 (54%) and reference prices in 9 studies (69%). Adequate subgroup analyses were presented in only 5 studies (38%). It was

recommended that main changes are needed in areas of suitable subgroup analysis and utilization of the preferred outcomes life-years gained (LYGs) or quality-adjusted life years (QALYs).

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ABBREVIATIONS

AC	Acceptability Curve
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
ATB	Antibiotic
BUGS	Bayesian inference Using Gibbs Sampling
CBA	Cost Benefit Analysis
CBO	The Dutch Institute for Health Care Improvement
CEA	Cost Effectiveness Analysis
CEAC	Cost Effectiveness Acceptability Curve
CEP	Cost Effectiveness Plane
CER	Cost Effectiveness Ratio
CI	Confidence Interval
CMA	Cost Minimization Analysis
COI	Cost Of Illness
CrI	Credibility Intervals
CUA	Cost Utility Analysis
CVZ	College Voor Zorgverzekeringen (Health Care Insurance Board)
DATA	Decision Analysis by TreeAge
EBM	Evidence Based Medicine
EMEA	European Agency for the evaluation of Medicinal Products
FDA	Food and Drug Administration
GP	General Practitioner
ICER	Incremental Cost Effectiveness Ratio
LYG	Life Year Gained
MCMC	Markov Chain Monte Carlo
NICE	The National Institute for Clinical Excellence
QALY	Quality Adjusted Life Year
RCT	Randomized Clinical Trial
WTP	Willingness to Pay

SUMMARY

PHARMACOECONOMICS IN DECISION MAKING

INTRODUCTION

Current trends indicate that costs for health care are increasing in most European countries. New agents are expensive and therefore increase the cost of drugs in society and health care costs in general. Health economics play an important role in health policy makers' attempts to introduce more efficiency into the organization of health care, financing and resource allocation since budgets are limited. Pharmacoeconomic analyses signify relevance of assessment, registration and reimbursement of drugs. The science of pharmacoeconomics presents analytic methods to answer such question in economic terms. Pharmacoeconomics, as a term present in literature since 1986, has been defined as "the description of the costs of drug therapy to health care systems and society". Pharmacoeconomic research involves the evaluation of pharmaceutical products and services, the measuring of its costs in form of given resources, and the outcomes which result at clinical, economic or at societal level.

AIM OF THESIS

Theoretical part

The first objective of this thesis is to explore pharmacoeconomics as a science and its application with methods and models.

The second objective of this thesis is to focus on Dutch pharmacoeconomic guidelines both from 1999, compared to Australia or Canada, and actualized guidelines from 2006.

Practical part

The main and the third objective of this thesis is to analyze a specific example and its pharmacoeconomic evaluation. Venous thromboembolism primary prevention after total hip replacement surgery in Europe, from clinical and pharmacoeconomic point of view, was presented

Last objective of this thesis is to evaluate the use of the methodological national guidelines, from 1999, and their adherence to published literature in The Netherlands.

THEORETICAL PART

Pharmacoeconomics and Outcomes Research

Pharmacoeconomics is a collection of techniques used in evaluation not only of pharmacotherapy, in which it is a point of interest, but also in evaluating surgical procedures, medical devices or clinical services. It is important to distinguish between outcomes research and pharmacoeconomy. Outcomes Research is the process that evaluates different therapies or drug regimens in order to measure the extent to which a goal of therapy or desirable outcome can be reached. Outcomes are economic, clinical, and humanistic.

This part of the thesis involves description pharmacoeconomics, types of pharmacoeconomic studies: prospective, retrospective and model, and analyses used in pharmacoeconomic research as CMA, CBA, CEA and CUA.

It is also important to identify different types of cost which are defined as direct or indirect, medical or non-medical, fixed or variable, with implementation of CER where cost elements that can have dramatic effect on resulting CER.

Discounting is a regular procedure throughout all economic analyses. The reason for converting future dollars into today's dollars is based on an assumption that a dollar in the future is worth less than dollar today. Rationale behind this is that the costs of goods or services will continue to rise in future due to inflation. For example, for The Netherlands, discount rates of 4% for money and 1.5% for health were estimated in the Dutch context and implemented from 2006.

In decision making, pharmacoeconomics is used by government in the evaluation of medical intervention and is regular practice in many European countries. CEA and CUA are tools in priority setting in health care, and are implemented in reimbursement procedure or in recommendations for clinical guidelines. For example in The Netherlands the threshold is given for cost-effectiveness of €20,000 per LYG and in the US up to $100,000 per LYG or QALY. The correct measure of cost-effectiveness is the ICER of a treatment relative to less expensive options. This is because usually more than one treatment is available for a given condition. CEP is used to explain ICER with its four quadrants.

Use of different statistical models in reading CEA is crucial for valid evaluation. It is straightforward to calculate confidence intervals for each of the cost and effect differences, ΔC and ΔE, using standard methods, and these intervals can also be plotted on the CEP. Estimation of uncertainty by the point estimates (means) from the effect and cost distributions provide the best estimate of the treatment and cost effects and should be used in the primary analysis. There have been many proposed solutions to the problem of estimating confidence limits for the ICER. However, a general consensus has emerged in support of two main approaches: the parametric method introduced by Fieller half a century ago and the nonparametric approach of bootstrapping, both of which have been described in relation to CEA. A better solution is AC because it presents much more information on uncertainty than do the CIs of the first two methods.

Epidemiology is complementary to the economics; it encompasses rubrics ranging from health services research to Pharmacoepidemiology, Outcomes research and Clinical epidemiology. Epidemiology describes the distribution of diseases and exposures in populations and draws conclusions regarding association between the exposures and diseases. The ideal clinical trial is that it is randomized and double-blinded. Randomized clinical trials (RCT) compare the effectiveness of one or more interventions with a control. Validity of the study is an important step in evaluating RCT, determining whether the study results (i.e., the effect) are really due to drug under study (i.e., the cause) or due to some other cause or factor present among the study participants who received the treatment. All evaluations aim to have research which is under the guidelines of EBM. A meta-analysis is the extraction of data from each individual study. The calculation of a result for the given study (the 'point estimate')as well an estimate of the chance variation expected from previous studies (the 'confidence interval'), allow us to decide whether it is appropriate to calculate a pooled average result across studies and, if so, calculate and present such a result. The results of meta-analyses are often presented in a forest plot.

Sensitivity analyses provide reviewers with an approach to testing how robust the results of the review are, relative to key decisions and assumptions that were made in the process of conducting a review with frequentist versus Bayesian approach.

Modeling in pharmacoeconomic research is crucial nowadays. There are two types of models, Markov model and MCMC. The software programs available can be found on web sites and freely downloaded as the BUGS project is flexible software concerned with the Bayesian analysis of complex statistical models using MCMC methods. Decision trees by DATA are a simple way to structure problems of decision making with uncertainty. It transforms decision analysis from a potentially tedious exercise into an easily applied and highly visual means of organizing the decision making process, analyzing the problem at hand, and communicating both the structure of the problem and the basis for decision reached.

In The Netherlands, in 1999, the guidelines for pharmacoeconomic research were presented. Since January 2005, the Ministry of Health in the Netherlands implemented the use of pharmacoeconomics as a supplementary aspect in the evaluation for drug reimbursement. This policy was already in practice for many years in other countries, such as the UK, Australia and Canada. Initially there were 19 recommendations with some of a methodological nature (# 2, 6, 8, 9, 10, 12, 15, 16, 17) and some merely of a procedural nature. Currently, methodological and procedural ones are being separated in distinct booklets. The new guidelines were assessed on 1st April 2006 and are only 11.

PRACTICAL PART

Thromboprophylaxis in total hip-replacement surgery in Europe: acenocoumarol, fondaparinux, dabigatran and rivaroxban

This paper reviews the clinical and pharmacoeconomic studies that have been conducted within Europe for patients undergoing elective hip-replacement surgery. Additionally, a perspective on the possible future clinical use of new agents in orthopedic surgery, such as dabigatran and BAY 59–7939 (rivaroxban) was offered. LMWH are standard therapy for patients requiring thromboprophylaxis and, therefore, we compare these with the other agents: vitamin K antagonists, fondaparinux and the direct oral inhibitors (thrombin or factor Xa inhibitors). The majority of evidence on cost–effectiveness and efficacy is

available for the LMWHs and fondaparinux. The major limitation in clinical use is that they require parenteral administration. Only fondaparinux has undergone an extensive pharmacoeconomic evaluation. The direct thrombin inhibitors and direct factor Xa inhibitors are possibly the drugs of the future. However it must be borne in mind that they are still in Phase III clinical trials and, therefore, their safety and efficacy profile is not completely understood. Thus the pharmacoeconomic aspects are also unclear.

In Europe, by the year 2020, the demand for THR is expected to increase by 25–50% compared with current incidence, primarily owing to aging of the population.

Methods: In this review, we searched the Pub Med database (English language) for clinical trials using any of the following agents after hip-replacement surgery: acenocoumarol, fondaparinux and direct oral inhibitors. Given the European perspective of our analysis, such trials had to also be relevant for the specific European clinical practices, in particular with respect to the timing of LMWH and fondaparinux (this did, for example, imply that the European Pentasaccharide Hip Elective Surgery Study (EPHESUS) would be included, whereas the North American-based PENTATHLON 2000 study was not). Additionally, literature was searched for combinations of all previously mentioned agents with any of the following key words: pharmacoeconomics, economy, economic studies, hip replacement and cost. Additional references from the bibliographies from the selected papers were also considered. LMWH was primarily considered the comparator drug since it is standard treatment for preventing DVT.

Results: Studies have shown that during the first 10 days, low molecular heparins started preoperatively or fondaparinux commenced postoperatively are preferred over the vitamin K antagonists. Clinical results included in the new Dutch CBO evidence-based guidelines have shown that LMWHs, VKA and fondaparinux are equally effective in the extended period. Pharmacoeconomic studies indicate that fondaparinux is only cost saving in the long term; for example over a 5-year period. Fondaparinux appears more cost effective than LMWH 40 mg, once daily commenced preoperatively, but appears to be less cost effective then LMWH 30 mg twice daily commenced postoperatively.

Expert opinion and future recommendations: Direct oral inhibitors are possibly the drugs of the future and, although ximelagatran was withdrawn from the market owing to safety concerns (liver enzyme elevation), the next generation of oral agents (still in Phase

III trials) appear promising. One of the most interesting new compounds is dabigatran, which has been proven effective; liver enzyme elevation has not been observed to the same extent as ximelagatran and, therefore, there is a strong possibility that it could be used routinely in clinical practice to prevent DVT following major orthopedic surgery.

Key issues: The demand for total hip replacement (THR) is increasing owing to a growing number of elderly people in Europe and it remains a costly intervention for the health care budget; Low-molecular weight heparins (LMWHs) started preoperatively or fondaparinux commenced postoperatively are clinically preferred over the vitamin K antagonists (VKAs) if used during the first 10 days after surgery; Current clinical guidelines in THR thromboprophylaxis state that LMWHs, VKAs and fondaparinux are equally effective if used for extended periods (10–42 days); Fondaparinux is only cost saving compared with LMWH in the long term (> 5 years); Orally administered direct thrombin and factor Xa inhibitors are promising drugs for the future.

In: Future Drugs section on Expert Review of Pharmacoeconomics & Outcomes research. February 2007, Vol. 7, No. 1, Pages 49-58.

Application of national guidelines to pharmacoeconomic research in the Netherlands

Objective: This study investigates the application of the Dutch national guidelines to pharmacoeconomic studies in the Netherlands.

Methods: In 1999, Dutch Health Care Insurance Board presented Dutch guidelines for pharmacoeconomic research. The review covers all Dutch pharmacoeconomic studies that were published in English during 2003–2004. The databases used were MEDLINE and EMBASE. The search used the terms ''cost (-) effectiveness'', ''pharmaco (-) economic(s)'' and ''(the) Netherlands''. The formal inclusion criteria for this review were that studies should be: pharmacoeconomic evaluations; cost-effectiveness or a cost-utility analysis; original research; and that full text reports would be available. Nine methodological guidelines were selected for investigation with respect to their application to pharmacoeconomic studies. Each pharmacoeconomic study was reviewed by minimum of two reviewers for objectivity and correctness of results.

Results: From 56 studies identified only 13 studies satisfied the inclusion criteria.

An appropriate time period for analysis was applied in all studies (100%), as well as an incremental analysis. Sensitivity analysis was present in 11 studies (85%). In 10 from 13 studies (77%) following three criteria were taken into account: societal perspective, discounting (of costs, benefits and health gains), and efficacy versus effectiveness distinction. LYGs or QALYs as effectiveness expression were used in 7 (54%) and reference prices in 9 studies (69%). Adequate subgroup analyses were presented in only 5 studies (38%).

Conclusions: It was found in this review that the application of some of the Dutch guidelines for pharmacoeconomic research to pharmacoeconomic studies were favorable. Main changes are needed in areas of suitable subgroup analysis and utilization of the preferred outcomes life-years gained (LYGs) or quality-adjusted life years (QALYs).

Key words: guidelines, application of guidelines, pharmacoeconomics, The Netherlands.

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CONCLUSION

The aim of this doctoral thesis was to explore pharmacoeconomics and its use in decision making process. The topics addressed were types of pharmacoeconomic studies and techniques, types of cost and discounting. Decision making process was pointed out with relevance to statistical models. Pharmacoepidemiology is a fundamental principle for pharmacoeconomic research to take place, which was also presented here. Also finishing in software programs and modeling examples by DATA, BUGS and MCMC were included here.

The main goal in this doctoral thesis was to show using a specific clinical example, the use of pharmacoeconomy in decision making, as described in the practical section of the thesis. The example of THR was chosen due to increased future need for it as well as the added cost for society secondary to an aging population in Europe. From the presented clinical and economic data, it is impossible to make evidence-based statement on the best available cost-effective strategy for THR prophylaxis; all the given options are speculative. In the final part, research of pharmacoeconomic guidelines was focused on Dutch guidelines from 1999, but herein new guidelines are presented in this thesis.

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"It's what you have always wanted to accomplish. Everyone, when they are young, knows what their destiny is. At that point in their lives, everything is clear and everything is possible. They are not afraid to dream, and to yearn for everything they would like to see happen to them in their lives. But, as time passes, a mysterious force begins to convince them that it will be impossible for them to realize their destiny. It's a force that appears to be negative, but actually shows you how to realize your destiny. It prepares your spirit and your will, because there is one great truth on this planet: whoever you are, or whatever it is that you do, when you really want something, it's because that desire originated in the in the soul of the universe. It's your mission on earth. Yes, or even search for treasure. The Soul of the World is nourished by people's happiness. And also by unhappiness, envy and jealousy. To realize one's destiny is a person's only real obligation. All things are one. And, when you want something, all the universe conspires in helping you to achieve it."

"The Alchemist" Paulo Coelho

"To je ono sto si oduvijek zeljela da ostvaris. Svako, kada je mlad, zna sta je njegova sudbina. U tom trenutku zivota, sve je jasno, i sve je moguce. Ne boje se da sanjaju, i da jako prizeljkuju za svim sto bi zeljeli da im se dogodi u njihovim zivotima. Ali, kako vrijeme prolazi, misteriozna sila pocinje da ih nagovara da ce za njih biti nemoguce da ispune svoju sudbinu. To je sila koja izgleda negativna, ali u stvarnosti ti pokazuje kako ostvariti svoju sudbinu. Priprema tvoju dusu i tvoju volju, zato sto je jedna velika istina na ovoj planeti: ko god da si, ili sta god da radis, kada stvarno nesto zelis, to je zato sto ta zelja izvire iz duse svemira. To je tvoja misija na zemlji. Da, i kada si u potrazi za blagom. Dusa Svijeta je hranjena ljudskom srecom. A isto nesrecom, zavisti i ljubomorom. Ostvarenje sudbine je jedina prava obaveza osobe. Sve stvari su jedno. I, kada nesto zelis, citav svemir se ujedini da ti pomogne da to ostvaris."

"Alhemicar" Paulo Coelho

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- Total hip replacement (THR);
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- Acenocoumarol, fondaparinux, dabigatran & rivaroxban;
- **Clinical guidelines** in THR;
- **Pharmacoeconomic guidelines** for pharmacoeconomic research;
- Application of pharmacoeconomic guidelines;
- **New pharmacoeconomic guidelines** versus previous version.

Research Interests:

- Anticoagulant therapy and VTE (venous thromboembolism) prevention in elderly after hip replacement, due to increasing number of elderly population in Europe and higher demand for treatment.
- Pharmacoeconomic guidelines as a tool in controlling expenditures on health care and enhance economically rational drug use and reimbursement procedure.

Publications and poster presentations

1) **Natasa Ivanovic, MSc**, Maarten Beinema, MD, Jacoubs RBJ Brouwers, PhD, Mark Naunton, PhD, and Maarten J Postma, PhD.

Thromboprophylaxis in total hip-replacement surgery in Europe: Acenocoumarol, Fondaparinux, Dabigatran & Rivaroxban,

Future Drugs Ltd. (Expert Review of Pharmacoeconomics and Outcomes Research) [Special Reports] Feb.2007; 7(1), 49-58.

2) **Natasa Ivanovic MSc**, Tatiana Foltanova PharmDr, Jana Davidova MSc, Lenka Praznovcova PhD. and Maarten J Postma PhD.

Application of national guidelines to pharmacoeconomic research in the Netherlands,

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3) Pharm Dr. Josef Suchopar, Lenka Praznovcova PhD, **Natasa Ivanovic MSc**, **Ciclesonid,**

Remedia, 15.March.2005; p. 307-10.

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1. New pharmacoeconomic guidelines.
2. Expenditures on medication in developed European countries.
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1. **ISPOR 9th Annual European Congress**

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PHP25 EXPENDITURES ON DRUGS IN DEVELOPED EUROPEAN COUNTRIES

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(19-23 May 2007 Crystal Gateway Marriott)

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PHP29 REGULATION OF DRUG EXPENDITURES IN EUROPEAN COUNTRIES

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- **Statistical Considerations in Economic Evaluations**, by Lieven Annemans PhD, ISPOR 10th Annual International Meeting, Washington DC, US 2005.
- **Elements of Pharmaceutical Pricing**, by Lorne Baskin Pharm.D, ISPOR 10th Annual International Meeting, Washington DC, US 2005.
- **Bayesian Analyses Applications**, by Bryan Luce, PhD, ISPOR 11th Annual International Meeting, Philadelphia, US 2006.
- **Bayesian Overview**, by Bryan Luce, PhD, ISPOR 11th Annual International Meeting, Philadelphia, US 2006.
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- **WHO**, World Health Organization Conference on Drug Policy, Bratislava, Slovak Republic 7-9 November 2004 and 6-8 December 2007.
- **ICORD,** International Conference on Rare Diseases and Orphan Drugs, the 1st conference, Stockholm, Sweden 2005.
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3) **Ciclesonid,** Remedia, 15.March.2005; p. 307-10.

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- **Pharmacotherapy**, by Prof. Jacoubs RBJ Brouwers PhD., Clinical Pharmacist, Rijks University of Groningen, the Netherlands 2005.
- **Pharmacoeconomics for Decision Makers**, by Peter Neumann ScD, ISPOR 10th Annual International Meeting, Washington DC, US 2005.
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- **ISPOR**, 10th Annual International Meeting, Washington DC, US 2005 and 11th Annual International Meeting, Philadelphia, US 2006.
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SOUHRN

FARMAKOEKONOMIKA ROZHODOVACÍHO PROCESU

ÚVOD

Dnešní trendy ukazují, že náklady zdravotní péče ve většině zemí Evropy narůstají.

Nové léky jsou drahé, a proto narůstají výdaje na léky ve společnosti a zároveň celkové náklady ve zdravotnictví. Ekonomie zdravotnictví hraje důležitou roli ve snaze činitelů odpovědných za zdravotní politiku o zvýšení efektivity v organizaci zdravotní péče, financování a přidělování zdrojů, v době, kdy jsou rozpočty limitovány. Farmakoekonomické analýzy poslouží k určení významu výběru, registrace a úhrad léčiv.

Farmakoenkonomická věda presentuje analytické metody, které odpoví na tyto otázky v ekonomických termínech. Farmakoekonomie jako termín se nachází v literatuře od roku 1986, a je definován jako „ popis výdajů lékové terapie pro systém zdravotní péče a společnost".

Farmakoekonomický výzkum zahrnuje hodnocení farmaceutických produktů a služeb, měření jejich nákladů ve formě vydaných zdrojů a výsledků na klinické, ekonomické a sociální úrovni.

CÍL PRÁCE

TEORETICKÁ ČÁST

Prvním cílem této práce je prozkoumat farmakoekonomiku jako vědu a její využití pomocí metod a modelů.

Druhým cílem je zaměření se na holandské farmakoekonomické guidelines od 1999 v porovnání s Austrálií a Kanadou a aktualizace guidelines od roku 2006.

PRAKTICKÁ ČÁST

Třetím a hlavním cílem této práce je analýza specifického příkladu a jeho farmakoekonomické hodnocení. Je zde uvedena primární prevence venózní tromboembolie po chirurgické totální endoproteze kyčle v Evropě, z hlediska klinického a ekonomického. Posledním cílem této práce je hodnocení využití metodologických národních guidelines od roku 1999 a jejich dodržování v publikované literatuře v Nizozemsku.

TEORETICKÁ ČÁST

Farmakoekonomika a Outcomes Research

Farmakoekonomie je soubor metod používaných k hodnocení ne pouze farmakoterapie, ve které je ohnisko zájmu, ale také k hodnocení chirurgických postupů, zdravotnických prostředků nebo klinických služeb. Je důležité rozlišovat mezi Outcomes Research a farmakoekonomií. Outcomes Research je proces, který hodnotí různé terapie nebo lékové režimy v pořadí tak, aby měřil šíři, ve které by mohl být dosažený cíl terapie nebo žádaný výsledek. Výsledky jsou ekonomické, klinické a humanistické.

Tato část práce zahrnuje deskripci farmakoekonomie a dále typy farmakoekonomických studií: prospektivní, retrospektivní a modelová, a analýzy používané ve farmakoekonomickém výzkumu jako CMA, CBA, CEA a CUA.

Je rovněž důležité identifikovat různé typy nákladů, které jsou definovány jako přímé a nepřímé, zdravotnické a nezdravotnické, fixní a variabilní, s CER implementací kde nákladové prvky mohou mít pozoruhodný efekt na výsledek CER.

Diskontování je regulérní postup vyskytující se ve všech ekonomických analýzách. Důvod pro přepočet budoucích dolarů na dnešní dolary je založen na předpokladu, že dolar v budoucnosti bude mít menší hodnotu než dnešní. Logicky z toho vyplývá, že náklady na zboží a služby budou stoupat v budoucnu v souvislosti s inflací. Například pro Nizozemí jsou poměry diskontování odhadovány na 4% pro finanční prostředky a 1,5% pro zdraví v holandském kontextu a implementovány od roku 2006.

Farmakoekonomie je v rozhodovacím procesu používaná vládou v hodnocení zdravotnických intervencí a je regulérní praxí v mnoha Evropských zemích.

CEA a CUA jsou nástroje v prioritním nastavení ve zdravotní péči, a jsou implementovány v úhradovém procesu nebo v doporučeních pro klinické guidelines. Například v Nizozemí je práh pro efektivnost nákladů 20 000 € na 1 LYG a v USA až do 100 000 $ na 1 LYG nebo 1 QALY.

Správné měření nákladové efektivity je ICER léčby v poměru k méně drahým možnostem. Důvodem toho je, že pro dané podmínky většinou existuje více než jedna možná léčba. CEP s jeho 4 kvadranty je používán k vysvětlení ICER.

Použití různých statistických modelů v interpretaci CEA je rozhodující pro validní hodnocení. Je přímý k výpočtům konfidenčních intervalů pro každý z nákladových a efektivních rozdílů, ΔC a ΔE, s použitím standardních metod, a tyto intervaly mohou být

založeny na CEP. Odhady nejistoty k bodu odhadů (průměr) od efektivních a nákladových distribucí poskytují nejlepší odhad léčby a nákladových efektivit a měl by být použit v primární analýze. Bylo navrženo mnoho řešení problému odhadu konfidenčních limitů pro ICER. Nicméně na základě všeobecného koncensu se využívají především dva hlavní přístupy: parametrová metoda představena Feillerem před půl stoletím a neparametrický přístup bootstrapping, oba byly popsány v souvislosti s CEA. Lepší řešení je AC, protože představuje mnohem více informací nejistoty než CI prvních dvou metod.

Epidemiologie je doplňková k ekonomii; zahrnuje rubriky v rozsahu od zdravotnických služeb do farmakoepidemiologie, Outcomes Research a klinickou epidemiologii. Epidemiologie popisuje výskyt nemocí a expozice v populacích a ukazuje závěry s ohledem na vztah mezi expozicemi a nemocemi.

Ideální klinická studie je randomizovaná a dvojitě zaslepená. Randomizované klinické studie (RCT) porovnávají efektivitu jedné nebo více intervencí s kontrolní. Validita studie je důležitým krokem v hodnocení RCT, determinuje, zda jsou výsledky studie (např. efekt) opravdu důsledkem působení léku ve studii (např. příčina), nebo důsledkem některé jiné příčiny či faktorů přítomných u účastníků, kteří obdrželi léčbu. Všechna hodnocení jsou směřována k tomu, aby měla výzkum podle EMB guidnelines. Meta – analýza je extrakce dat z každé individuální studie. Kalkulace výsledku pro danou studii („bod odhadu") a také odhad náhody varianty očekávané na základě předešlé studie („konfidenční interval"), nám umožňuje rozhodnout, zdali je vhodné vypočítat společný výsledný průměr na základě studie, a pokud ano, vypočteme a presentujeme tento výsledek. Výsledky meta – analýz jsou často presentovány ve forest plotu.

Analýzy citlivosti poskytují hodnotitelům s přístupem k testování informaci, jak přesvědčivé jsou výsledky review, vzhledem ke klíčovým rozhodnutím a předpokladům, které byly zjištěny v průběhu vedení review s frequentist versus Bayesian přístupu.

Modelování farmakoekonomického výzkumu je v dnešní době velmi významné. Existují dva modely: Markovův model a MCMC. Softwarové programy jsou k dispozici na webových stránkách a jsou zdarma ke stažení jako BUGS projekt, což je flexibilní software týkající se Bayesian analýzy komplexních statických modelů a používá MCMC metody. Rozhodovací stromy v DATA jsou jednoduchá cesta ke strukturním problémům v rozhodovacím procesu s nejistotou. Převádějí rozhodovací analýzu z potenciálně obtížného použití na lehce aplikovatelnou a vysoce vizuálně vnímanou strukturu rozhodovacího procesu, analýzováním problému přímo a komunikaci struktury problému a základny pro dosažené rozhodnutí.

V Nizozemí v roce 1999 byly představeny guidelines pro farmakoekonomický výzkum. Od ledna 2005 ministerstvo zdravotnictví v Nizozemí inplementuje používání farmakoekonomie jako doplňujícího aspektu v hodnocení pro lékové úhrady. Tato politika byla již v praxi po mnoho let v jiných zemích jako je VB, Austrálie a Kanada.

Z počátku bylo 19 doporučení, z nichž některá byla metodologické povahy (# 2, 6, 8, 9, 10, 12, 15, 16, 17) a některá pouze procedurální. Současně jsou metodologické a procedurální rozdělené v různých brožurách. Nové guidelines byly hodnoceny 1. dubna 2006 a je jich pouze 11.

PRAKTICKÁ ČÁST

Tromboprofylaxe v chirurgii totální endoprotézy kyčle v Evropě: acenokumarol, fondaparinux, dabigatran a rivaroxban.

Tento článek hodnotí klinické a farmakoekonomické studie, které byly vedeny na území Evropy pro pacienty podstupující volitelnou chirurgickou totální endoprotézu kyčle (THR).

Dodatečně byl nabídnut pohled na možnost budoucího klinického využití nových léčiv v ortopedické chirurgii, jako dabigatran a BAY 59–7939 (rivaroxban). LMWH jsou standardní terapií pro pacienty požadujících tromboprofylaxi, a proto jsme porovnali tyto s dalšími léčivy: antagonisty vitamínu K, fondaparinuxem a přímými orálními inhibitory (thrombinu nebo inhbitory faktoru Xa). Většina dokladů o cost - effectiveness a efficacy je k dispozici pro LMWHs a fondaparinux. Největší omezení v jejich klinickém využití je nutnost jejich parenterálního podání. Pouze fondaparinux podstoupil extensivní farmakoekonomické hodnocení. Přímé inhibitory thrombinu a faktoru Xa jsou snad léky budoucnosti. Nicméně je nutno mít na paměti, že jsou stále ve Fázi III klinického zkoumání, a proto jejich profil bezpečnosti a účinnosti není kompletní. Proto také farmakoekonomické aspekty zůstávají nejasné.

V Evropě do roku 2020 se očekává nárůst požadavků na THR od 25 – 50% v porovnání se současnou incidencí, a to především následkem stárnutí populace.

Metodika: V této review, jsme provedli průzkum Pub Med databáze (v anglickém jazyce) pro klinické studie s použitím následujících léčiv po chirurgické náhradě kyčle: acenokumarol, fondaparinux a přímé orální inhibitory. S ohledem na evropské hledisko naší analýzy, tyto pokusy musí být také relevantní pro specifické evropské klinické praxe,

jednotlivě s ohledem na načasování LMWH a fondaparinuxu (z toho vychází předpoklad, že studie European Pentasaccharide Hip Elective Surgery Study (EPHESUS) měla být zahrnuta, kdežto severoamerický PENTATHLON 2000 zahrnut nebyl. Dodatečně byly v literatuře vyhledány kombinace všech předešlých léčiv s některým z následujících klíčových slov: farmakoekonomie, ekonomie, ekonomické studie, endoprotéza kyčle a náklady. Dodatečné reference z bibliografií vybraných článků byly též brány v úvahu. LMWH byly primárně považovány jako porovnávací lék protože jsou standardní léčbou pro prevenci DVT.

Výsledky: Studie ukázaly, že v průběhu prvních 10 dnů, nízkomolekulární hepariny podány předoperačně nebo fondaparinux zahájený pooperačně jsou preferovány před antagonisty vitaminu K. Klinické výsledky zahrnuté v nové holandské CBO evidence-based guidelines ukázaly že LMWHs, VKA a fondaparinux jsou stejně účinné v prodlouženém období. Farmakoekonomické studie ukazují, že fondaparinux pouze vykazuje úsporu nákladů v dlouhodobém časovém intervalu (například v období přes 5 let). Fondaparinux se zdá mnohem účinnější než LMWH 40 mg, jednou denně podávaný předoperačně, ale ukazuje se méně účinný než LMWH 30 mg dvakrát denně podávaný postoperačně.

Odborný posudek a budoucí doporučení: Přímé orální inhibitory jsou pravděpodobné léky budoucnosti a třebaže ximelagatran byl stažený z trhu v důsledku bezpečnosti (zvýšení jaterních enzymů), příští generace orálních léčiv (stále ve Fázi III) vypadají slibně. Jedna z nejzajímavých nových sloučenin je dabigatran, u něhož byla prokázána účinnost; zvýšení jaterních enzymů nebylo pozorováno ve stejné výši jako u ximelagatranu, a proto je zde silná možnost, že bude používán rutinně v klinické praxi k prevenci DVT následujících ortopedické chirurgické zákroky.

Klíčové otázky: Požadavek na totální endoprotézu kyčle (THR) stoupá následkem zvyšujícího se počtu starší populace v Evropě a zůstává nákladná intervence pro rozpočet zdravotní péče; Nízkomolekulární hepariny (LMWHs) podané předoperačně nebo fondaparinux se zahájením podávání pooperačně jsou klinicky preferovány v porovnání s antagonisty vitaminu K (VKAs) pokud byly používány v průběhu prvních 10 dnů po operaci. Současné klinické guidelines v THR tromboprofylaxi uvádějí, že LMWHs, VKAs a fondaparinux jsou stejně účinné při použití v prodloužených periodách (10 – 42 dnů); Fondaparinux pouze vykazuje úsporu nákladů v porovnání s LMWH v používání v delším časovém intervalu (> 5 roků); Orálně podávané přímé inhibitory thrombinu a faktoru Xa jsou slibné léky budoucnosti.

In: Future Drugs section on Expert Review of Pharmacoeconomics & Outcomes research. February 2007, Vol. 7, No. 1, Pages 49-58.

Aplikace národních guidelines do farmakoekonomického výzkumu v Nizozemí

Cíl: Tato studie zkoumá aplikaci holandských národních guidelines do farmakoekonomických studií v Nizozemí.

Metodika: V roce 1999, holandský výbor pojištění zdravotní péče (Dutch Health Care Insurance Board) uvedlo holandské guidelines pro farmakoekonomický výzkum. Review pokrývá všechny holandské farmakoekonomické studie, které byly publikovány v anglickém jazyce v průběhu 2003 – 2004. Byly použity databáze MEDLINE a EMBASE. Průzkum používal termíny „cost (-) effectiveness" , ''pharmaco (-) economic(s)'' a ''(the) Netherlands''. Formální zahrnující kritéria pro tuto review byly studie které měly být: farmakoekonomická hodnocení; cost-effectiveness nebo cost-utility analýzy; přičemž fulltexty měly být dostupné. Devět metodologických guidelines bylo vybráno pro výzkum s ohledem na jejich aplikaci do farmakoekonomických studií. Každá farmakoekonomická studie byla zhodnocena minimálně dvěma posuzovateli, aby byla zachována objektivita a správnost výsledků.

Výsledky: Z 56 studií bylo vybráno pouze těch 13 studií, které uspokojovaly zahrnující kritéria. Vhodná časová perioda pro analýzu byla aplikována ve všech studiích (100%), a také jako inkrementální analýza. Studie citlivosti byla přítomná v 11 studiích (85%). V 10 z 13 studií (77%) následující tři kritéria byla vzata v úvahu: společenský pohled, diskontování (nákladů, benefitů a zdravotních zisků), a efficacy versus effectiveness rozlišení. LYGs nebo QALYs jakožto ukazatele effectivity byly použity v 7 (54%) a referenční ceny v 9 studiích (69%). Adekvátní podskupinové analýzy byly uvedeny v pouze 5 studiích (38%).

Závěry: V této review bylo zjištěno, že aplikace některých holandských guidelines z farmakoekonomického výzkumu do farmakoeknomických studií bylo příznivé. Hlavní změny jsou potřebné v oblastech vhodných poskupinových analýz a utilizace preferovaných výsledků roky života získané (LYGs) nebo roky života o standardní kvalitě (QALYs).

Klíčová slova: guidelines, application of guidelines, pharmacoeconomics, The Netherlands.

In: Farmakoekonomika a lieková politika, ročník 3, 2007, číslo 1.

(Pharmacoeconomics and Drug Policy, year 3, 2007, No. 1, Pages 33-40).

ZÁVĚR

Cílem této doktorské práce byl výzkum farmakoekonomie a jejího použití v rozhodovacím procesu. Náměty, které mě oslovily, byly typy farmakoekonomických studií a technik, typy nákladů a diskontování. Bylo poukázáno na rozhodovací proces s poukázáním na důlezitost statistických modelů. Farmakoepidemiologie je fundamentální princip pro farmakoekonomický výzkum, který zde byl také prezentován. Bylo zde také zahrnuto dokončení softwarových programů a modelování příkladů pomocí DATA, BUGS a MCMC.

Hlavním cílem doktorské práce bylo ukázat používání specifických klinických příkladů, použití farmakoekonomie v rozhodovacím procesu, jak je popsáno v praktické části práce. Příklad THR byl vybrán v důsledku zvyšující se její potřeby v budoucnosti a také v důsledku zvýšení dodatečných nákladů pro společnost sekundárně vzniklé v důsledku stárnutí populace v Evropě. Z představených klinických a ekonomických dat je nemožné vytvořit evidence-based rozhodnutí na nejlepší dosažitelnou cost-effective strategii v THR profylaxi; všechny uvedené možnosti jsou spekulativní. V poslední části byl výzkum farmakoekonomických guidelines zaměřený na holandské guidelines od roku 1999, ale v této práci jsou také uvedeny nové guidelines.