THE ROLE OF ECONOMIC EVALUATIONS IN HEALTH CARE DECISION MAKING

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Stockholm 2005
ABSTRACT

Increasing health care expenditures, a rapid introduction of new medical technologies and a need for cost containment policies in most countries during the last decades have led to a growing interest in information from economic evaluations for decision making about resource allocation in health care. Economic evaluations can provide valuable information in many types of decision making, e.g. related to the use of drugs, other health care interventions/programs and investments in new technologies or research. These are, however, currently most widely used in pricing and reimbursement decisions for new drugs, in health technology assessment and for development of guidelines for prevention and treatment.

This thesis discusses the role of economic evaluations in different types of health care decision making concerning resource allocation. Two of the studies analyse the available cost-effectiveness evidence for new drugs. The other four studies discuss and provide cost-effectiveness information to be used in the following important types of decision making situations in Sweden: reimbursement of new drugs, investments in new technology, implementation of screening programs and choices between therapies.

The publication of economic evaluations increased dramatically during the 1980’s and 1990’s. This thesis demonstrates that economic evaluations during the 1990’s were more likely to be conducted for drugs with improved effectiveness or safety as compared to those of the competitors and for drugs with high sales. Although requirements for economic evaluations for reimbursement decisions may lead to a more cost-effective use of the resources, it is important to recognise that regulations also involve a cost. Increasing requirements for cost-effectiveness in Sweden and Finland may have been associated with a delayed introduction of new drugs on the market, at least the first year after the changed regulations. However, it cannot be ruled out that the observed data might be due to chance or adaptations in the timing of new drug introductions.

This thesis discusses four types of decision making where cost-effectiveness information can be of value for the decisions. The four economic evaluations identified patient populations and indications where teriparatide treatment for osteoporosis, proton radiation for breast cancer, screening for abdominal aortic aneurysm in men and use of iodixanol in angiography may be considered cost-effective in Sweden.

Keywords: Economic evaluation, cost-effectiveness, decision making, drugs, reimbursement

II. J. Lundkvist, B. Jönsson, C. Rehnberg. The costs and benefits of increased reimbursement regulations for new drugs. *Manuscript submitted for publication*


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<table>
<thead>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>SEK</td>
<td>Swedish kronor</td>
</tr>
<tr>
<td>HEED</td>
<td>Health economic evaluations database</td>
</tr>
<tr>
<td>OTC</td>
<td>Over the counter</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality adjusted life year</td>
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<tr>
<td>LFN</td>
<td>The Swedish Pharmaceutical Benefits Board</td>
</tr>
<tr>
<td>SBU</td>
<td>The Swedish Council on Technology Assessment in Health Care</td>
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<tr>
<td>NCE</td>
<td>New chemical entity</td>
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<tr>
<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
</tr>
<tr>
<td>AAA</td>
<td>Abdominal aortic aneurysm</td>
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<td>ADR</td>
<td>Adverse drug reaction</td>
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1 BACKGROUND

Diseases have always been a threat to the well being of humans and finding treatments alleviating them has therefore been given high priority in resource allocation. The first available treatments were mainly based on removing secretions from the body, e.g. by vomiting, bleeding and diuretic methods[1]. These primitive methods were later followed by more sophisticated drug treatments. One of the first and most successful drugs through all times was the universal drug “theriac”, which was extremely popular during the era of Greek medicine[1].

These first medical treatments constituted the start of a growing interest in medical science. During a very long period of time, however, most treatments used were only palliative, not curative[1]. The most dramatic change in the treatment of diseases started in the 1940’s when the first sulfa-preparation, which could be used to treat infectious diseases, was synthesized[2]. Short thereafter, penicillin became available in large quantities, later followed by the development of several new treatments e.g. cortisones, antihypertensive treatments and psycho drugs[2].

From the beginning of the 20th century, concerns were raised about the appropriateness and safety of pharmaceutical treatments. Different laws and regulations were introduced in many countries to control the sale and marketing of new pharmaceuticals[2]. The pharmaceutical market thus became highly regulated, as compared to with many other health care services[2] [3]. The provision of health care services is controlled by regulations[3], e.g. by the registration of health care personnel, but price and quality control does usually not exist to the same extent for these services as for pharmaceutical products[2]. Regulations concerning the manufacturing and sale of pharmaceuticals in Sweden have been available since the 17th century, but one of the first regulations concerning the quality of pharmaceutical products in Sweden was introduced in 1913[3]. The regulation was later, in 1934, expanded to also include public control of the appropriateness of these products[3]. The expansion of the regulation continued and quality, safety and efficacy evolved as three basic demands for drugs.

As research and development within universities and the pharmaceutical industry increased, many new treatments became available during the second half of the 20th century[4]. These new available treatments often came at high prices, which lead to a growing concern about their increasing costs, and the possible implication of this on the access to care. Various forms of reimbursement for other health care services than drugs existed in Sweden and many other countries at this time and many countries expanded these reimbursement systems to also include drugs. In Sweden, the first reimbursement system for drugs was introduced in 1954[2]. As more treatments were developed, the expenditures for drugs increased rapidly and constituted a growing part of the total health care expenditures in many countries[5] (Figure 1.1). The increase in expenditure was caused both by an increased sales volume and increased unit prices. The unit price increases were mainly caused by the introduction of new and expensive drugs[6, 7].
Figure 1.1. Expenditures on drugs in Sweden between 1985 and 2004

Source: National Corporation of Swedish Pharmacies, 2005. In 1997, a new reimbursement system was introduced, which explains the break in the curve in 1996-1997. Real prices were calculated based on Swedish consumer price indices[8].

The increasing availability of new expensive treatments and the limited resources within the health care systems led to a growing need for prioritising. Evidence based medicine and economic evaluations evolved as tools for assisting in decisions about allocation of resources within health care. Today, the demand for an efficient use of the scarce health care resources is evident and economic evaluations are becoming an increasingly important source of information as basis for decision making concerning resource allocation in health care.

1.1 ECONOMIC EVALUATIONS

Health economics studies how, individually and collectively, we use our resources to produce health[9]. A main purpose of health economic studies is to provide information to decision makers, which can be used to achieve an efficient use of the available resources. Cost-effectiveness in the use of resources implies that they are allocated so that the total health in the population is maximised.

Economic evaluation is one part of health economics, and it is a tool for comparing costs and consequences of different interventions. Economic evaluation is currently the largest area within health economics, in terms of publications. There is a rapid increase in the number of persons trained in economic evaluations and methodological standards are developing. Guidelines for performing cost-effectiveness studies have, for example, been published by several authorities, journals and organisations[10-13]. Figure 1.2
shows the number of economic evaluations in the Health Economic Evaluations Database (HEED) and the number of studies in Medline identified in searches for “cost-effectiveness or cost-utility” in the title/abstract section of the studies[14]. The figure shows the number of published economic evaluations to have increased dramatically, at least between 1980 and 1998. The figure, however, also indicates a drop in the number of studies in HEED during the last years, but it is not clear whether this is caused by a lag in the inclusion of studies in the database or whether there has actually been a reduction in the number of published economic evaluations. The drop in publications in the last 5 years is not seen in the studies identified in Medline, but these may not solely have been economic evaluations since they were identified in searches only using keywords related to economic evaluations.

Figure 1.2. Economic evaluations in the Health Economic Evaluations Database (HEED) and Medline 1980-2004. Number of studies published each year.

1.2 ECONOMIC EVALUATIONS IN HEALTH CARE RESOURCE ALLOCATION DECISION MAKING

Health care decision making affecting the allocation of resources is performed at many levels. At the national (macro) level, decisions are usually made concerning policies or programs for the whole population in a country. Pricing and reimbursement of drugs and national policies or treatment guidelines are common examples of decision making at this level. Decisions are, however, often decentralised to the local (meso) level, e.g. for establishing local treatment guidelines. Decisions are also made at an individual (micro) level, e.g. prescription of drugs by the individual physician or when patients buy over the counter (OTC) drugs without a prescription. Most economic evaluations are undertaken with a national perspective, since data is seldom available at the local levels within countries and also because performing many different local economic evaluations would be very time-consuming and costly.

Results from cost-effectiveness analysis can guide decision makers about how to maximise the chosen outcome measure, for example survival, given the available resources. The objective of society and health care decision makers are, however, more
complex, because there are several other criteria to take into account besides maximizing the life years, the quality adjusted life years (QALYs) or whatever the chosen measure of health outcome is. This means that the results from economic evaluations provide one type of information as a basis for decision making, but there are several other types of information that also need to be considered, for example distributional aspects[15]. These other aspects can, in theory, be included in the analysis, but make it more complicated and reduce the comparability between different studies.

Economic evaluations are also used for decision making outside the health care system. Pharmaceutical companies, for example, are increasingly using health economics information during the drug development process. Economic evaluations are performed early in the development process to assist in go/no-go decisions, future price and marketing strategies, and the planning of clinical trials[16].

This thesis will mainly discuss decision making related to three types of resource allocation: concerning the use of drugs, other health care interventions/programs and investments in new technologies or research.

1.2.1 Decisions concerning the use of drugs

The drug market can be divided into three sub-markets: hospital, OTC and prescription drugs. There are important differences between these sub-markets e.g. in financing, purchasing and consumer involvement in the decision. In the hospital market, drugs are reimbursed within a global budget or a particular diagnosis related group. Individual physicians have an influence over the decisions within the overall budget constraint, but their decisions are mediated by management decisions within the hospital at different levels; clinics, divisions and hospital board. Hospitals have incentives to make a careful trade-off between costs and value. Money spent on drugs is not available for the use of other types of resources, for example staff. Consumers of OTC drugs also have incentives to take both costs and effectiveness (benefits) into account, since they pay the whole price, including potential side effects. In the prescription market, the prescribing physician is the key decision maker. Studies indicate that physicians are cost conscious only when the patient pays a significant part out of pocket[17]. The prescription market is the largest market, usually responsible for at least 75% of the total drugs sales[18].

The decision making concerning drugs may be divided into three steps. The first concerns market authorisation, the second reimbursement and the third the choice between and the adoption of the treatments by physicians and patients. The first step, concerning market authorisation, is controlled by regulatory authorities in many countries. The authorities make decisions about market authorisation, based on evidence provided by the manufacturers. Safety, efficacy and quality are now well established as three basic requirements on the new drugs in this process, while cost-effectiveness is usually not a criterion for market authorisation. In the European countries, these decisions are today often taken at a European rather than national level[4, 19].
The second step, reimbursement of drugs, is in some countries controlled by specific regulations. Prescription drugs not included in these reimbursement systems usually have limited possibilities for success in the market. Cost-effectiveness is an important criterion for inclusion in these systems. Developing new drugs is a costly process and the manufacturers often request high prices for new drugs as compared to older drugs. This requires assessments of the costs and benefits (value) by the reimbursement authorities, to make decisions about the value for money related to the price asked. Economic evaluations of drug therapies have therefore become an important factor for pricing and reimbursement decisions and many reimbursement authorities have introduced a regulatory requirement of efficiency during the last decade, i.e. cost-effectiveness, on new drugs. In 1992, Australia was the first country to demand cost-effectiveness information for drug reimbursement decisions[20]. Reimbursement authorities in many countries have followed the Australian example and more or less formal regulatory requirements for cost-effectiveness information can now be found in about 10 countries around the world[12, 13, 21-28]. The increased influence of cost-effectiveness on the pricing and reimbursement decision has made the evidence of cost-effectiveness a fourth area where pharmaceutical companies now need to provide evidence[29, 30].

Australia has the longest experience of using economic evaluations for pricing and reimbursement decision making, and a few studies have evaluated the consequences of the cost-effectiveness requirement in the Australian reimbursement system. An analysis of the applications submitted to the reimbursement authority between 1994 and 1997 demonstrated that 127 of the 326 applications submitted contained significant flaws[31]. Some other studies have discussed positive and negative experiences of the Australian reimbursement system[32, 33]. An increased dialogue between the authorities and the pharmaceutical industry has been one of the main positive consequences of the new regulation, but the industry has also experienced several problems, e.g. increased costs and time for producing the economic evaluations, and difficulties in finding appropriate data for the studies.

The choice and adoption of the treatments by physicians and patients are usually not regulated, but are influenced by many factors, e.g. opinions from institutions, formula lists and other recommendations[34, 35]. Economic evaluations have an influence on these decisions, but the magnitude of this influence is not known[34].

1.2.2 Decisions concerning the use of other health care interventions/programs

There are many other health care interventions/programs for which decisions must be made about how they should be used. This group of decisions includes a wide range of interventions, e.g. surgical interventions, screening programs, vaccination programs, information campaigns etc, and also a wide range of decision makers. The decisions concerning the use of health care interventions/programs other than drugs are not as regulated as those concerning drugs. There is usually no regulatory authority controlling the price, quality or cost-effectiveness of these interventions/programs. Their adoption is therefore only dependent on the decisions by the decision makers responsible for providing the funding. However, these decisions are increasingly based
on formal evaluations of the interventions/programs, including evaluations of the cost-effectiveness.

1.2.3 Decisions concerning investments in new technologies or research
The decisions concerning investments in new technology or research are usually not controlled by any regulations: They are influenced by assessments of the potential benefits and cost-effectiveness of the investments, but data is usually scarce about the consequences of new technologies/research projects. The decisions are made by a wide range of decision makers at different levels in the health care system.

1.3 HURDLES AGAINST USING INFORMATION FROM ECONOMIC EVALUATIONS
Pricing and reimbursement of new drug therapies is the area where economic evaluations have been most widely used so far. The use of economic evaluations in other types of health care decision making is less clear and may be lower than desired[36-38] and therefore it is important to discuss how this may increase. One interesting type of studies is therefore those identifying hurdles discouraging decision makers from using cost-effectiveness information. Some questionnaire and interview studies have been performed, mainly in the US and the UK[39] to assess this question. The results from these studies highlight some aspects that are important for the use of economic evaluations in decision making. The quality of the study and the methodology used constitute a major concern for many decision makers. Lack of transparency, particularly in modelling studies, is also a common concern. Some decision makers are not comfortable with the use of QALYs as an outcome measure in economic evaluations. Other aspects that may discourage the use of economic evaluations are lack of knowledge about health economics among decision makers, limited or inflexible health care budgets and uncertainty of the generalisability of the results to decision makers’ context.

1.4 HEALTH CARE DECISION MAKING IN SWEDEN
The Swedish health care system is a regional system, divided into 21 county councils and regions responsible for delivering health care within their respective geographical area. The county councils and the Ministry of Health and Social Affairs (Socialdepartementet) formulate the basic objectives and policies of Swedish health care[3]. The main role of the central government is to overview the health care system and ensure that the objectives are reached. The health care system is divided into three levels: primary care, county care and regional care. Primary care consists of local health care centres and private general practitioners. The county-level hospitals deal with all kinds of illnesses, while complicated illnesses and injuries are dealt with at hospitals at the regional level. County councils are grouped into six health care regions.

From October 1 2002 the decisions about reimbursement for prescription drugs in Sweden are made by the newly created Pharmaceutical Benefits Board (LFN)[28]. They decide on reimbursements of drugs and the decisions are based on different
criteria, one of which is cost-effectiveness. Thus, this means that Sweden has a regulated mechanism for reimbursement decisions, where cost-effectiveness and economic evaluations play a key role. Economic evaluations, however, played a role for decisions about pricing and reimbursement even before LFN, as both the National Social Insurance Board (Riksförsäkringsverket), and before that Apoteksbolaget, used economic evaluations as information for their pricing and reimbursement decisions[40]. LFN, the reimbursement agency, does not control the co-payments for patients and the budget for drugs. The first is decided by the government (Ministry of Health), and the latter by negotiations between the government and the county councils. The fact that a drug is reimbursed does not mean that there is an open budget for prescription. Drug formula committees at the county councils have a strong influence on which drugs are prescribed, through the recommendations they issue.

Another institution which has played a significant role for introducing cost-effectiveness and economic evaluations into the Swedish health care system is the Swedish Council on Technology Assessment in Health Care (SBU)[41]. SBU was established in 1988, with the aim of providing guidelines for evidence-based medicine to the county councils and the medical community. SBU performs assessments on a project basis with teams of clinical and scientific experts. It does not conduct original research and the assessments typically include systematic reviews of available research findings. The topics selected for assessments are generally topics of major importance for public health and quality of life. The results are reported in three types of publications, yellow, white or alert reports.

The budget restrictions at local levels, e.g. primary care centres, hospitals etc, have a strong influence on local decision making. Although cost-effectiveness is considered an important criterion for choosing therapies, limited budgets may in some cases make it difficult to introduce new expensive treatments in practice. Even if a new treatment is cost-effective in a social perspective, there may be a problem in reallocating resources from less cost-effective interventions. It is easier to do the reallocations in a growing economy, where the additional resources available could be directed towards the most cost-effective interventions. When reallocations should be undertaken together with cost-containment programs, there is a risk that the introduction may be delayed, if specific funds may not be earmarked for the new technologies. The costs for reimbursed drugs in Sweden were financed by the central government until 1997, when the responsibility for drug costs was in 1997 decentralised to the county councils. The decentralisation process was an attempt at increasing the cost awareness of the county councils, thereby reducing the increasing drug expenditures and to providing incentives for a rational use of drugs in relation to other health care resources. The transfer of responsibility for drug budgets thus gave the county councils opportunities to decide locally on the allocation of resources between drug budgets, hospital care, primary care etc.

Table 1.1 summarizes the decision makers and regulations currently associated with four types of health care decision making in Sweden. Decisions concerning the authorisation and reimbursement of drugs are regulated by the Medical Products Agency and the reimbursement authority (LFN), but the final decision concerning drug use, the adoption of treatments by physicians and patients, is not regulated. The
decision by the physicians to use a drug is, however, partly regulated because physicians can generally not prescribe drugs not authorised by the Medical Products Agency and they cannot prescribe drugs with reimbursement that are not approved by the reimbursement authority.

Decisions concerning the use of other health care interventions/programs and investments in new technology/research are not regulated in Sweden. These decisions are made at national or regional levels, depending on the type of decision. These decisions are influenced by evaluations made by, for example, SBU or The National Board of Health and Welfare. The role of cost-effectiveness information is, however, unclear and varies substantially between different types of decisions.

Table 1.1 Decision makers and regulations in Swedish health care decision making

<table>
<thead>
<tr>
<th>Decision</th>
<th>Use of reimbursed outpatient drugs</th>
<th>Use of inpatient hospital drugs</th>
<th>Use of other health care interventions</th>
<th>Investments in new technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulation</td>
<td>Drug authorisation, reimbursement approval</td>
<td>Drug authorisation</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Regulator</td>
<td>Medical Products Agency, Pharmaceutical Benefits Board</td>
<td>Medical Products Agency</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Influencer</td>
<td>Drug formula committees, SBU, The National Board of Health and Welfare, etc.</td>
<td>Drug formula committees, SBU, The National Board of Health and Welfare, etc.</td>
<td>SBU, The National Board of Health and Welfare, etc.</td>
<td>Few</td>
</tr>
<tr>
<td>Decision maker</td>
<td>Prescribing physicians, individual patients</td>
<td>Prescribing physicians, individual patients</td>
<td>Ministry of Health, County Councils, hospitals, hospital departments etc.</td>
<td>Ministry of Health, County Councils, hospitals, etc.</td>
</tr>
</tbody>
</table>

The most important decision makers for the adoption of drugs and other interventions in Sweden are prescribing physicians and hospitals. The most important influencer for decisions concerning drugs in Sweden is probably the drug formula committees, while the SBU is probably the most important influencer for other interventions. However, it is difficult to measure the influence, and there is a general lack of information about the impact of the significant investments in resources for drug formula committees, SBU, guidelines and priorities by National Board of Health and Welfare, etc. The most important decision makers and influencers for investments in new technology or research in Sweden are even more difficult to identify, however.

1.5 A SURVEY TO SWEDISH DECISION MAKERS

We sent a questionnaire to health care decision makers in Sweden during the spring of 2004. The study was part of a European study of the use of economic evaluations in
decision making[36, 42]. The questionnaire contained 12 questions about how economic evaluations influence medical and health care funding decision making[42]. The questionnaire was answered by physicians, local drug formula committee members and county council administrators. In total, 35 persons answered the questionnaire.

The results agreed well with findings in previous European studies[36-38]. Clinical data was considered to be the most important source of information for the decision making by physicians and formula committee members, while health economics data was most important for county council administrators. The information from economic evaluations was in most cases obtained from scientific meetings and reports, followed by colleagues and scientific journals.

The sponsorship of studies by the pharmaceutical industry was the most important factor that discouraged the use of economic evaluations in their decision making. Other important factors were: economic studies make too many assumptions, savings/costs in economic studies are anticipated and not real, difficulties in moving resources from one sector (budget) to another and ethical considerations. Easier access to studies, outcome measures that are clinically relevant and widely accepted, more flexibility in health care budgets and more comparability of studies were the most important factors that could encourage a greater use of the results of economic evaluations. Most of the respondents thought that economic/cost considerations should play a larger role in the future and all thought that it will play a larger role in the future.

The conclusion of the survey is that there seems to be a high interest in economic evaluations among the Swedish health care decision makers, but health economics and quality of life data are currently not so often taken into account in the actual decision making. However, most of the respondents agreed that economic evaluations will play a larger role in decision making in the future; the potential use is much greater than the actual use. The knowledge about health economics and the methods for economic evaluation is rather low, and most of the respondents thought that more education and training in the concepts and techniques used in such studies would be useful for closing the gap between the actual and potential use of such studies for future decision making.

### 1.6 AN ECONOMIC PERSPECTIVE ON REGULATIONS FOR COST-EFFECTIVENESS INFORMATION

The pharmaceutical market is highly regulated, in particular decisions related to market authorisation and reimbursement. However, the economic consequences associated with these regulations have received much less attention than the costs and benefits of the use of individual drugs. Therefore, it is interesting to further discuss the impact of regulations, in terms of costs and benefits, from an economic perspective[43].

Increasing costs in the health care system and a desire to have an efficient use of the scarce resources have increased the use of cost-effectiveness information in health care decision making. The potential benefit of increased requirements for evidence from economic evaluations is that more information about the cost-effectiveness of individual technologies will increase the probability of using cost-effective alternatives, which may lead to more health for society, given what is spent on health care. It is,
however, important to recognise that like, most regulations, the increasing requirements for economic evaluations, as also involve costs. The most obvious costs are the expenditures on research for the producers to obtain the cost-effectiveness information and the costs for the decision makers for evaluating the information. Another potential cost, or foregone benefit, for producers, patients and society is delayed market entry and uptake of new drugs, which may occur if new cost-effective treatments are not introduced, or delayed, due to a lack of cost-effectiveness information. The delay may be caused by increased time for the manufacturers to obtain the information or by increased time for the decision makers to evaluate the information and make a decision. This potential delay would mean lost revenues for the producer and delayed access to effective treatments for the patients. Thus, as with all regulatory information, there is a trade-off between the costs and benefits of regulatory requirements for economic evaluations as a basis for decision making, and therefore, finding the right balance between them is an important question. A cost-benefit analysis of the requirements for economic evaluations in the ordinary way is, however, difficult to make since the costs and benefits are not easily quantified.

It may be possible to estimate the costs of producing and evaluating cost-effectiveness information, since these costs mostly involve the costs of health economics research and the costs for the evaluating authority. In Sweden, the costs for running the reimbursement authority (LFN) during the year 2004 were about €5.8 million[44]. During this year, there were during this year 39 applications for reimbursement of new drugs, which means that the costs per new drug may be estimated at about €150 000 (including costs for all decisions concerning a drug, e.g. various strengths, price changes etc). The costs for the pharmaceutical company for producing the application and the required information are more difficult to assess, but they are probably somewhat higher than the costs for the reimbursement authority. For the costs of producing and evaluating the cost-effectiveness information, it may be plausible to assume that the marginal cost increase slightly as the requirements for economic evaluations increases, since it is more difficult and costly to obtain detailed data for cost-effectiveness analysis, e.g. as local data collection may be necessary.

The costs of a delayed market entry are more difficult to quantify. The first question to address is if an increased requirement leads to delayed market entry. If it does, it will lead to both lost revenues for the producer and lost benefits for patients. How this is affected by changes in the requirements for economic evaluations is, however, difficult to assess. In this discussion, we will assume that this cost is rather proportional to the requirements.

The benefits of having better information to make decisions leading to a more efficient use of resources are also very difficult to quantify. One potential way of getting some information about this is to study the cost-effectiveness of technologies available in health care today, and estimate the resources spent on adopted technologies not considered cost-effective and the forgone benefits of cost-effective technologies that are not used. For this cost, it may be most reasonable to assume that the marginal benefit of an inefficient use of resources is decreasing as the requirements for economic evaluations increase, e.g. because we can expect that we first have cost-effectiveness
information for technologies with the greatest impact on the budget and the patients’ health.

**Figure 1.3 Costs and benefits of regulatory requirements for economic evaluations**

Figure 1.3 describes the different costs and benefits associated with the requirements for cost-effectiveness evidence. From a theoretical point of view, we want to find the point where the costs of requiring economic evaluations exceed the benefits. From a public policy view, however, it is more important to analyse if we are to the left or right of this point, i.e. to know whether we should increase or decrease the requirements for cost-effectiveness information before we start using a new technology. Our knowledge of the marginal costs and benefits of requiring economic evaluations is very limited, however. We can, however, at least be certain that it is a waste of resources to require cost-effectiveness information, if the information does not influence decision making and resource allocation.

Regulations provide strong incentives for the actors involved and are therefore effective ways of controlling a decision making process. It is, however, important to evaluate the costs and benefits of new or changed regulations, in order to find the optimal level of the regulations. The costs and benefits associated with regulations are, however, often difficult to estimate. The costs of obtaining cost-effectiveness information constitute a minor part of the total costs for developing a new treatment, and usually are considerably lower than the costs of obtaining clinical evidence from clinical trials. The potential costs of a delayed market entry may therefore be the most important cost of regulations related to evidence of cost-effectiveness.
2 AIMS OF THE THESIS

This thesis discusses the role of evidence from economic evaluations in different types of health care decision-making situations. A first aim of the thesis is to analyse the available cost-effectiveness evidence for new drugs and its use in pricing and reimbursement decisions. A second aim is to discuss and provide cost-effectiveness information to be used in the following four important types of decision-making situations in Sweden:

- Pricing and reimbursement of new drugs
- Investments in new technology
- Implementation of general screening programs
- Choices between therapies and establishment of treatment guidelines
3 MATERIALS AND METHODS

3.1 MATERIALS

The thesis is based on two main types of studies. Papers I-II assess the amount of cost-effectiveness evidence, and how the increasing requirements for such evidence have affected the introduction of new drugs on the market. These two studies are based on databases of drugs containing new chemical entities (NCE). Papers III-VI present economic evaluations of different health care interventions/programs. Two clinical trials, which have been used as main sources of data for papers III and VI, are further discussed below.

3.1.1 NCE databases

Drugs with NCE contain chemical entities not previously used in any drug formulation. A database with all new NCE drugs approved by the Medical Products Agency in Sweden between 1987 and 2000 was used in paper I. Additional information about the therapeutic value of the drugs, sales statistics and therapeutic classes were collected and included in the database. Information about authorisation years and therapeutic classes were obtained from the Medical Products Agency in Sweden and sales statistics were obtained from the National Corporation of Swedish Pharmacies[45]. Information about the innovative therapeutic value was obtained from a previously published study[46] and unpublished data from the authors of that study.

Paper II analyses another set of NCE drugs, approved by the regulatory authorities in Sweden or Finland between 1995 and 2003. Information about authorisation dates, reimbursement dates, size of manufacturing companies, requirements for economic evaluations by reimbursement authorities, therapeutic class, therapeutic value and sales statistics were obtained and included in the database.

3.1.2 Clinical trial of teriparatide

A randomised double-blind placebo-controlled trial was undertaken by Neer et al to assess the anti-fracture efficacy of addition of teriparatide (parathyroid hormone) to calcium and vitamin-D[47]. The trial included 1637 postmenopausal women with prior vertebral fractures receiving 20 or 40 microgram of teriparatide or placebo, subcutaneously administered by the women daily. Vertebral radiographs were obtained at base-line and at the end of the study. The results showed that new vertebral fractures occurred in 14% of the women in the placebo group and in 5% and 4% of the women in the 20-microgram and 40-microgram teriparatide groups, respectively. As compared to placebo, the 20-microgram and 40-microgram doses of teriparatide increased the bone mineral density by 9% and 13% in the lumbar spine and by 3% and 6% in the femoral neck. Teriparatide reduced the risk of vertebral fracture by 65% and non-vertebral fragility fracture by 53%.
3.1.3 The NEPHRIC study

The NEPHRIC study was a randomised, double-blind, multicentre study comparing the two contrast media iodixanol and iohexol, in subjects with a combination of impaired renal function and diabetes mellitus undergoing angiography[48]. 135 subjects in 17 centres in Denmark, France, Germany, Spain and Sweden were enrolled in the study. The main objective was to compare the effects of the two contrast media on renal function. The primary endpoint was to investigate the nephrotoxicity measured as maximum peak increase in serum creatinine to day two or three after the examination compared to baseline. The two randomised groups, receiving iodixanol or iohexol, were comparable with regard to demographics and other baseline characteristics, as were the radiography procedures undertaken. The analysis showed a significant difference in the main endpoint between the two contrast groups, with the iodixanol group having a lower peak increase on average. In addition to several measures related to serum creatinine, the rate of adverse events was a secondary endpoint.

3.2 METHODS

Papers I and II analyse the cost-effectiveness evidence for new drugs. Regression models are used to explore the relations between variables and test hypotheses set up in the studies.

Papers III-VI present cost-effectiveness information to be used in different types of decision making. Each study presents a different decision making situation and illustrates the issues related to the various situations. The cost-effectiveness analyses also demonstrate how different methods of economic evaluations can be used, depending on the question studied and the available data. The four evaluations are performed in a Swedish setting.

3.2.1 Methods of economic evaluations

A health economic evaluation may be defined as a comparison of two or more courses of action in terms of both their costs and health consequences (effectiveness)[49]. The health consequences of a health care intervention can, for example, be its effectiveness in curing, relieving or preventing a disease. The incremental cost-effectiveness ratio (ICER), which is often calculated when comparing two interventions in an economic evaluation, is defined as:

\[
ICER = \frac{\Delta C}{\Delta E} = \frac{C_1 - C_0}{E_1 - E_0}
\]

where \(\Delta C\) is the difference in total costs between the two interventions, and \(\Delta E\) is the difference in effectiveness.

An economic evaluation can be performed from different perspectives. This means that only costs and health consequences affecting the adopted perspective of the analysis are included. A societal perspective is often undertaken in economic evaluations, and means that all costs and consequences are included. However, there may be rationales for also choosing a partial perspective, e.g. the health care, the work place or the patient.
3.2.2 Costs
Costs in economic evaluations are often divided into direct and indirect ones. Direct costs are costs directly linked to the treatment, detection, prevention or care of an illness, and these are often further separated into medical cost, occurring in the health care sector, and non-medical costs occurring in other sectors. Indirect costs are costs resulting as a consequence of an illness, death or treatment of an illness. Indirect costs can be separated into time costs and production loss.

When an intervention prolongs the life of a patient, he or she will be able to consume or produce goods for a longer period of time. This means that the patient may incur future costs, or benefits, that would not have been incurred without the intervention[50]. In economic evaluations, future costs for health care which occur as a consequence of increased survival have traditionally often been included in analyses, while future costs not related to the disease have not. It has been argued that all future costs in added years of life, including those unrelated to the disease, should be included in economic evaluations using a societal perspective, to achieve an optimal use of society’s resources[50].

3.2.3 Effectiveness (health consequences)
The effectiveness of an intervention can be measured in several different ways, and the method of measuring the effectiveness in an economic evaluation defines the type of evaluation. There are four major types of evaluations[49]:
- Cost-minimisation analysis
- Cost-effectiveness analysis
- Cost-utility analysis
- Cost-benefit analysis

Cost-minimisation analysis
Cost-minimisation analysis only compares the costs of the interventions without taking the health consequences into account. Thereby it implicitly assumes the health consequences of the compared interventions to be equal. The results from a cost-minimisation analysis imply that the least costly alternative is the most cost-effective one and should be used. However, the interpretation of results from a cost-minimisation analysis may not be so simple, since exclusion of the health consequences from an economic evaluation may lead to difficulties in fully assessing the uncertainty of the cost-effectiveness[51].

Cost-effectiveness analysis
Cost-effectiveness analysis measures the health consequences in non-monetary units on a one-dimensional scale. This can, for example, be the number of life years, mmHg, the number of adverse events avoided etc. The choice of clinical outcome measure in cost-effectiveness analyses is important, since only one measure is chosen to represent all clinical effects of the interventions. There are four main types of results from a cost-effectiveness analysis, which can be illustrated in the cost-effectiveness plane (figure
3.1). If one intervention is more costly and less effective (B in figure 3.1.), it is apparently not cost-effective, and we can say that it is dominated by the other alternative. Naturally, we will have the same situation if one intervention is less costly and more effective (D in figure 3.1.). If one intervention is more costly and more effective (A in figure 3.1.), or less costly and less effective (C in figure 3.1.), it is more complex. In these cases, there is a trade-off between costs and effects, and we must establish the value of an additional unit of effectiveness to say that one intervention is cost-effective. The dotted line in the figure illustrates the willingness-to-pay for one additional unit of effect, and the space to the lower right of the dotted line represents cost-effective results.

**Figure 3.1. The cost-effectiveness plane**

Cost-consequence analysis measures the health consequences in more than one non-monetary unit, without combining them into one summary effectiveness measure. This type of analysis can be used when an intervention has several important effects that cannot be combined into one single health outcome measure. The analysis can be seen as a special case of cost-effectiveness analysis, or rather several cost-effectiveness analyses combined into one, because several cost-effectiveness ratios can be calculated in a cost-consequence analysis.

**Cost-utility analysis**

Cost-utility analysis measures the health consequences based on preferences. QALYs are used as clinical outcome measure, and takes both the quality and quantity of life into account[52]. Quality of life is measured as utility, and is expressed as values on a cardinal scale between 0 (death) and 1 (full health). QALYs are calculated by multiplying utility with the life expectancy, or more precisely calculating the integral of the utility over the life time. There are two main methods for estimating utility weights for different health states which have appropriate theoretical foundations: standard gamble and time-trade-off. Both these methods are based on peoples’ preferences and their willingness to trade between quality and quantity of life.

The main advantage of cost-utility analysis is the single summary measure of the health consequences, which is assumed to take all consequences of an intervention into account. This also means that the cost-effectiveness of different interventions can be compared across diseases, which simplifies prioritising and resource allocation between
various health care areas. The interpretation of the results from a cost-utility analysis is similar to the cost-effectiveness analysis, where the value of one additional unit of effectiveness (QALY) needs to be established.

**Cost-benefit analysis**

Cost-benefit analysis measures the health consequences in monetary units. The net benefit is calculated by summarising all costs of the interventions. The main problem with this type of analysis is the valuation of the health consequences in monetary terms. A common way of estimating the value of a change in health is the contingent valuation method, which assesses the patient’s or the general population’s willingness-to-pay for a health improvement (or the willingness-to-accept for a health reduction). The benefit measure in a cost-benefit analysis should reflect society’s value of the health consequences, and since benefit is measured in monetary terms, it can be directly compared with the costs. If the benefits are greater than costs, i.e. the net benefit is positive, the intervention should be implemented.

**3.2.4 Uncertainty in economic evaluations**

Assessment of the uncertainty of economic evaluations is important to inform the decision makers about the precision of the results[53]. Economic evaluations often contain data from a range of sources. Lack of appropriate data, particularly on long-term consequences, is often a problem, in particular for new technologies. A common solution is to base an economic evaluation on data from a randomised clinical trial and extrapolate the consequences after the follow-up time in the trial using epidemiological data. Combining data from different sources may, however, introduce uncertainties, since the different data may not be obtained from the same type of patients or environment.

A common way of assessing the uncertainty of an analysis is to perform simple sensitivity analysis[54]. This means that one or several variables are varied and the effect of the variation on the result is assessed. This can provide valuable information about parameters in the analysis having large or small effects on the results. The advantage of simple sensitivity analyses is that they are simple to perform and understand, the disadvantage is that the information gained about the joint uncertainty of all parameters in the analysis is limited. A threshold analysis assesses the range within which a parameter can vary without changing the conclusion from the results.

Different methods for assessing the uncertainty of the cost-effectiveness ratio and calculating confidence intervals have been proposed, e.g. confidence ellipses, angular transformation and Fieller’s theorem[54-56]. Another method for assessing the uncertainty is the Bootstrap method[57], which resamples data to give an empirical estimate of the distribution of the results. Defining the confidence interval around a cost-effectiveness ratio using these methods may, however, be problematic, e.g. if the interval stretches over several quadrants of the cost-effectiveness plane. The net benefit method is an alternative way of assessing the uncertainty surrounding the mean cost-effectiveness ratio, which avoids some statistical problems related to the incremental cost-effectiveness ratio and therefore implies several advantages[58]. One of these
advantages is that standard statistical methods can be used to estimate the confidence-interval and for hypothesis testing. The net benefit is defined as the incremental effect multiplied with the price society is willing to pay per unit of effectiveness (\( \lambda \)), minus the incremental cost:

Net benefit (\( \lambda \)) = \( \lambda \) * \( \Delta E \) - \( \Delta C \)

Probabilistic sensitivity analysis is a method often used in modelling and allows for examining the effects of joint uncertainty of several variables. Distributions are assigned to the variables in the model and a large number of sets of values from the specified distributions are produced. The sets of values generate a distribution of the results, which can be used to assess the uncertainty. One way of illustrating the uncertainty surrounding the estimate of the cost-effectiveness ratio, which is linked to the probabilistic analysis, is to produce cost-effectiveness acceptability curves. An acceptability curve shows the proportion of estimates of the incremental cost-effectiveness ratios that falls below different values of willingness-to-pay for one unit of health effect[59] (figure 3.2). For a given significance level (p value), the curve gives information at what values of \( \lambda \) the intervention can be considered cost-effective. By applying probabilistic sensitivity analysis, an acceptability curve can be derived using data from clinical trials, or alternatively, the distribution of the ratio can be directly obtained from an observed sample of subjects.

Figure 3.2 Illustration of an acceptability curve

![Acceptability Curve](image)

\[ 1 - P \text{ value} \]

Willingness to pay (\( \lambda \))

3.2.5 Transferability and generalisability

There is a trend towards an international evaluation of the safety, efficacy and quality of new drugs. Assessment and market authorisation of new drugs in Europe, for example, are often made by the European Medicines Agency rather than by national agencies[19]. Clinical trials today are mostly multinational and their results are often considered to be transferable across countries, although it is well known that the health consequences of treatments may vary between populations. The generalisability and transferability of results from economic evaluations are more questionable because differences in health care systems, treatment traditions, demography, epidemiology, price level etc. lead to a large variation in resource use and costs between different populations[60]. It has, for example, been shown that the cost-effectiveness of drugs
varies between countries in Western Europe and that it is difficult to find systematic variations between the results from the various countries[61]. Performing country-specific economic evaluations based on a multinational clinical trial is a common approach in the assessment of the cost-effectiveness of new drug treatments, and it is therefore important to discuss the methods used in this type of evaluations[62]. If we look at the three main types of data used in economic evaluations; clinical effectiveness, resource use and unit costs, we see that the clinical efficacies (effectiveness) of treatments are often considered to be transferable. Unit costs are usually not considered to be transferable, while resource use sometimes is[61].

Another level of generalisability is the validity of results from clinical trials in a real-world setting. The design of clinical trials often introduces treatment patterns and behaviours differing from those in a situation outside the trial. The patients’ motivation also differs, which influences the compliance and hence the consequences of the treatment.

3.2.6 Decision rules for economic evaluations

The decision rules for economic evaluations were briefly described above in the presentation of the various types of evaluations. The most common situation is when increased effectiveness must be valued against a higher cost. In this case, the decision will mainly depend on the cost-effectiveness, the value of an additional unit of effectiveness and the available budgets[63, 64].

If the budget is fixed, the goal for the decision maker is to obtain as much health as possible for the available budget. In this case, the decision maker should, after the exclusion of dominated alternatives, start by implementing the technology with the lowest ICER, irrespective of type of technology, disease etc. Then, the decision maker should continue and implement the technology with the second, third etc lowest ICER, as long as there are remaining budget resources.

If we have a flexible budget, with no upper limit of the amount of resources we can spend, the approach should be somewhat different. In this case, the decision should be based on the value for a unit of effectiveness. This means that a maximum value for a unit of effectiveness must be established and the decision maker should implement technologies with ICER below the established threshold[37]. The threshold approach for choosing therapies is the most commonly adopted, mainly because cost-effectiveness information is not available for all interventions used in health care. The levels of the cost-effectiveness threshold are therefore widely debated. Currently, there is no established threshold, but there are indications of the value of an additional life year of QALY in different countries [65]. Analyses of decisions issued by, for example, the National Institute of Clinical Excellence in Britain show that a strong case is needed to support a technology with a cost-effectiveness ratio above £30 000 per QALY gained (about €47 700)[10, 65]. Another source of information for the value of a QALY is Swedish investments in road safety. Based on this, a value of about €66 000 per QALY has been calculated for the year 2001[66, 67].
3.2.7 Modelling in economic evaluation

Three of the studies (papers III-V) in this thesis are based on modelling, which is a commonly used tool in economic evaluations. The main basis for the need for modelling is that the time frames of clinical studies are often too short to capture all relevant consequences of an intervention. Economic evaluations are also often based on a combination of information from different sources and, in these cases, modelling can provide a convenient way of combining this data.

Markov models are a certain type of state-transition simulation models often used in economic evolutions. These models define different states based on, for example, specific events or definitions of the health status of the patient. The states are mutually exclusive and collectively exhaustive, which means that patients must be in one, and only one, of the states at all times. Another important assumption of the Markov model is that the probability of future events only depend on the current state of the patient is in, and not on the history of prior events[68, 69].

Monte Carlo simulation is a method sometimes used in modelling. There are two types of Monte-Carlo simulations; first-order and second-order simulations. In a first-order simulation it is possible to retain memory of previous events by evaluating one patient at a time. This can be useful when, for example, costs and effects depend on the occurrence of, or the time since, previous events. By evaluating one patient at a time, there will be random variation in individual outcomes, which means that a number of iterations must be carried out to achieve a stable result. Second-order Monte-Carlo simulations take the uncertainty in the underlying parameters into account by allowing them to vary over a given range with a given distribution[68, 70].

3.2.8 Regression analysis

Papers I and II use multiple linear regression models to analyse the influence of various variables on the amount of evidence of cost-effectiveness and the time lag between market authorisation and reimbursement. The generic form of a linear regression model is[71]:

\[ Y_i = \beta_1 x_{i1} + \beta_2 x_{i2} + \ldots + \beta_k x_{ik} + \epsilon_i \]

where \( y \) is the dependent or explained variable, and \( x_{i1}, \ldots, x_{ik} \) are the independent or explanatory variables. Parameters \( \beta_1, \ldots, \beta_k \) are the coefficients for the explanatory variables, indicating how they are related to the explained variable. The term \( \epsilon \) is a random disturbance. The disturbance will occur because the regression model cannot perfectly predict the dependent variable.
The results from the six studies will be used to discuss the role of economic evaluations in health care decision making, with the focus on the following health care decision making situations in Sweden:

**Pricing and reimbursement of new drugs:**
Paper I and II analyse the availability of cost-effectiveness evidence for new drugs and its use in pricing and reimbursement decisions. Paper III presents an example of an economic evaluation that was used in a decision about the pricing and reimbursement of a new drug treatment, teriparatide, in the treatment of osteoporosis in postmenopausal women.

**Investments in new technology or research:**
Paper IV presents an example of an economic evaluation used as a basis for a decision about investment in a new type of radiation treatment for cancer.

**Implementation of general screening programs:**
Paper V presents an example of an economic evaluation aimed at assessing if, and how, a screening program for abdominal aortic aneurysm (AAA) in men could be implemented.

**Choices between therapies and the establishment of treatment guidelines:**
Paper VI presents an example of an economic evaluation used to assess whether the more costly drug iodixanol, which has a lower risk of contrast-induced nephropathy than iohexol, should be used for patients at high risk of these adverse events.
4.1 PRICING AND REIMBURSEMENT OF NEW DRUGS

4.1.1 Cost-effectiveness of new drugs (paper I)

The number of published economic evaluations has increased dramatically during the last decade\[72\], but the number of studies performed for different drugs and in different therapeutic areas varies. Although the impact of this cost-effectiveness information in decision making is unclear, it is interesting to analyse how the evidence of cost-effectiveness was distributed among the new drugs introduced during the last years and also when the evidence was available. The objective of this study was to analyse the amount of cost-effectiveness evidence for new drugs introduced on the Swedish market between 1987 and 2000, by systematically reviewing the published evidence of cost-effectiveness of these new drugs.

The study assessed the published evidence of cost-effectiveness for 442 new chemical entities (NCE). Information about published studies for the NCE drugs was obtained from the Health Economic Evaluations Database\[14\].

Two hypotheses were tested using linear regression models. The first concerns factors related to the amount of cost-effectiveness evidence. The hypothesis assumed that drugs with improved effectiveness or safety (high therapeutic benefit) would have more published evidence of cost-effectiveness than those with low therapeutic benefit. The second hypothesis concern the relation between the sale of the NCE drugs and the evidence of cost-effectiveness. The hypothesis assumed that drugs with a large sale would have more evidence of cost-effectiveness than drugs with a low sale.

The analyses showed that for many drugs, there was no published study on their cost-effectiveness. The classification of the drugs by the amount of evidence of cost-effectiveness placed 51 drugs in group 1 (much evidence), 84 in group 2 (some evidence) and 307 in group 3 (little evidence). Most studies (about 55% of all articles) were published about 1 to 5 years after the authorisation year and very few articles were published before or during the authorisation year.

The regression analyses indicated that drugs with improved effectiveness or safety as compared to other marketed drugs were more likely to have more evidence of cost-effectiveness than drugs in the other two therapeutic benefit groups. This supports the hypothesis that new and more effective or safe drugs in competitive therapeutic submarkets would more often be studied as it is interesting for both producers and health care financers to provide evidence that the premium price that is asked for these drugs can be motivated by the added clinical benefits in relation to their competitors.

The analyses also demonstrated that drugs with a low sale were less likely to have evidence of cost-effectiveness than those with a high sale. In other words, this indicates that drugs with high sale were more often evaluated in published studies, which thus supports the hypothesis that it is most important to have cost-effectiveness information for drugs with a large (expected) sale. The causality is, however, not known, which means that the results may also indicate that more evidence of cost-effectiveness could lead to increased sales.
4.1.2 Costs and benefits of reimbursement regulations (paper II)

Safety, efficacy and quality are now well established as three basic requirements, or hurdles, for the market authorisation of drugs. The new requirements for cost-effectiveness information for reimbursement, pricing and formula decisions in many countries have, however, made this a fourth hurdle for full market access. The benefit of information on the cost-effectiveness is an increased probability of a cost-effective use of the drug budgets. It is, however, important to recognise that the increasing requirements for economic evaluations, in the same way as all regulations, also involve costs. A delayed diffusion of drugs to consumers may potentially be one important cost of an increased requirement of cost-effectiveness information for reimbursement decisions.

The objective of this study was to analyse the time lag between drug approval and reimbursement for NCE drugs in Sweden and Finland, and to assess factors associated with this time lag.

The study was based on a sample of NCE drugs, approved and reimbursed in Sweden or Finland between January 1995 and April 2003. Data on approval dates, reimbursement dates, size of manufacturing companies, requirements for economic evaluations by reimbursement authorities, therapeutic value and sale statistics were collected for the drugs. A hypothesis, assuming that the lag between approval and reimbursement is affected by the introduction of regulatory requirements for cost-effectiveness information for reimbursement decisions, was tested using a linear regression model.

138 of the 242 drugs included in the analyses were reimbursed in Sweden and 104 in Finland. The total mean lag time from market authorisation to reimbursement decision was 175 days, and the mean lag times in Sweden and Finland were 114 and 256 days, respectively. Regression analysis demonstrated that drugs with a low sale and drugs from large manufacturers were associated with longer and shorter lag times, respectively. The results also demonstrated that authorisation during the first year after the introduction of the requirement for cost-effectiveness information was associated with an increased lag time.

The results indicated that increasing the regulations for reimbursement by introducing requirements for cost-effectiveness information may be associated with an increased time lag between approval and reimbursement, at least in the first year after the introduction of the new requirements. Although the conclusions from this study must be considered as very tentative, it is important to further discuss the costs and benefits of an increased regulation for reimbursement, to find the optimal regulatory requirements. It is also important that the required cost-effectiveness information really influences the actual decision making and thereby leading to a more efficient use of the resources, otherwise there will be no benefit from increasing the regulatory requirements of cost-effectiveness information.
4.1.3 Cost-effectiveness of teriparatide (paper III)

Osteoporosis is a disease mainly affecting elderly women. Besides the negative impact on survival and quality of life of the individual, it is also a costly disease for society. Effective treatments for osteoporosis are available, but the disease is still a problem for many patients. Some patients continue to fracture, despite treatment, or are unable to tolerate the available drugs. Therefore, there is a place in the treatment armamentarium for new agents with proven efficacy.

Teriparatide (parathyroid hormone) is a new treatment for osteoporosis and has in clinical trials been found to reduce the risk of vertebral and non-vertebral fractures in postmenopausal women[47]. The drug was recently approved by the authorities and applications for reimbursement have been submitted to several countries. To make a decision about the price and reimbursement of this new drug, information about its cost-effectiveness is needed. The objective of this study was therefore to analyse the cost-effectiveness of teriparatide in the treatment of osteoporosis in postmenopausal women from a societal perspective in Sweden.

A simulation model was developed to analyse the long-term consequences in patients treated with calcium and vitamin D with or without the addition of teriparatide. The model was partly based on previous models used in economic evaluations of osteoporosis treatments[73, 74], but a new development within the present model was the incorporation of fracture risks and mortality rates that were dependent on both the age of the patients and the time since previous fractures. The structural change was made in line with recent epidemiological evidence, indicating that fractures have an impact on mortality and the risk of new fractures, and that this risk is highest immediately post-fracture[75, 76]. Patients in the base case model were at the risk of clinical vertebral, hip and wrist fractures. Total accumulated life time costs and QALYs were the main outcome measures.

The results demonstrated that the cost-effectiveness of the treatment, compared with no teriparatide treatment, was better if the treatment was started early after a previous fracture. The cost per QALY gained for treatment of a population of 69-year olds with a T-score at femoral neck of -3 was in the base case estimated at between €20 000 and €64 000, for patients with a previous vertebral fracture recently or a long time ago, respectively. The cost per QALY gained was increased to between €38 000 and €80 000 if costs in added years of life were included in the analysis. The results also demonstrated that the cost per QALY gained was lower if women with lower bone mineral density were treated. Figure 4.1 shows the cost per QALY gained for treatment of women with a recent vertebral fracture and different bone mineral densities.
Implications for decision making

The results of this study indicate that the incremental cost per QALY gained for adding teriparatide treatment may be within society’s willingness-to-pay for patients with low bone mineral density and a recent vertebral fracture.
4.2 INVESTMENTS IN NEW TECHNOLOGY OR RESEARCH

4.2.1 Cost-effectiveness of proton radiation therapy (paper IV)

Proton beam radiation therapy offers clinical advantages as compared to traditional radiation therapy with photons or electrons for many cancer patients[77, 78]. The benefits are mainly the result of a more favourable dose distribution of the radiation. The treatment costs are, however, higher with proton radiation than with conventional radiation, mainly due to large investment costs for building a proton therapy facility. The investment cost for a proton radiation facility has been estimated to about €60 million, with a facility lifetime of about 30 years. Therefore, it is important to evaluate whether the medical benefits of proton therapy are sufficiently enough to motivate the higher costs. The major problem when evaluating proton therapy is the limited number of clinical studies available.

Breast cancer is a potential target for proton therapy, in particular for patients with left-sided breast cancer[79]. The effect on the tumour may be the same with protons as with conventional radiation, but the dose in sensitive tissues in the heart and the lung may be considerably reduced, so that very low toxicity can be expected to develop later [79-82]. The objective of this study was to assess the cost-effectiveness of proton therapy as compared with conventional radiation from a societal perspective in Swedish breast cancer patients.

Two hypothetical cohorts of 55-year old women with left-sided breast cancer, receiving proton or conventional radiation therapy, were compared in the base case analysis. A Markov cohort simulation model was developed to estimate the costs and effects of the two therapies. A review of the literature was conducted to estimate parameters in the model[81, 83-87]. The patients in the model were at risk of death, cardiac and pulmonary adverse events related to the cancer disease and the radiation therapy.

The study found a cost per QALY gained of €67,000 for the base case analysis of an average breast cancer patient (€92,000 if costs in added years of life were included in the analysis). The cost per QALY gained was, however, considerably lower if a population at high-risk of developing cardiac diseases was treated (figure 4.2). The cost-effectiveness is thus dependent on the possibility of selecting appropriate risk groups as targets for the therapy.
Figure 4.2. Effects of the risk of cardiac diseases on the cost-effectiveness (€/QALY)

Implications for decision making

Proton therapy is today only available in a limited number of places around the world. The investment costs for a proton therapy facility are large and information about the potential clinical advantages and cost-effectiveness of the therapy is important for future decisions about investments in new facilities. Although the analyses presented here were based on somewhat uncertain data, the result is still an indication of the cost-effectiveness of proton therapy, which supports new investments in this new technology in Sweden. However, it is estimated that a proton facility can treat about 1000 patients per year, and therefore it is also necessary to identify additional patient populations where the use of proton therapy can be expected to be cost-effective. When a facility is available, it is important to follow up with well designed studies to verify the model calculations and optimise the use of the facility.
4.3 IMPLEMENTATION OF GENERAL SCREENING PROGRAMS

4.3.1 Cost-effectiveness of screening for abdominal aortic aneurysm (paper V)

AAA is a common disease, particularly among elderly men, in whom the prevalence is 4-7% [88-96]. Rupture of AAA is associated with high mortality, causing about 1% of all fatalities in men over 60 years of age [97]. Most patients with ruptured AAA die before they come to surgery and the overall mortality is about 80%, compared to a reported mortality during elective surgery of 0-9% [90, 96-112]. Due to this difference in outcome, early detection by screening has been advocated [113-117]. However, a screening program for AAA would be associated with substantial costs, and the objective of this study was therefore to analyse the cost-effectiveness of screening for AAA from a societal perspective in Sweden.

Two hypothetical groups of people were compared: one group invited to ultrasound screening and another not invited. The accumulated costs and life years were the main outcome measures and were assessed using a Markov cohort simulation model. A systematic review of the literature was conducted to estimate parameters in the model. The base case analysis assumed a strategy where 65 year-old Swedish men were invited once for screening. Other screening strategies with different assumptions of the age of the screened population, risk profiles [118] and the introduction of re-screening were also analysed.

The cost per life year gained was in the base case estimated at €8 197 (€27 000 if costs in added years of life were included in the analysis). The invited population had a 50% reduction in AAA related death, corresponding to 4 deaths per 1000 individuals, as compared to the non-invited population. Table 4.1 shows the results for some of the different screening strategies.

Table 4.1. Results from analyses of different screening strategies in men, per person

<table>
<thead>
<tr>
<th>Screening strategy</th>
<th>Cost difference per person (€)*</th>
<th>Difference in life years per person*</th>
<th>Cost per life year gained (€)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-year-old siblings</td>
<td>463.8</td>
<td>0.068</td>
<td>6856</td>
</tr>
<tr>
<td>65-year-olds with angina or claudication</td>
<td>254.5</td>
<td>0.031</td>
<td>8133</td>
</tr>
<tr>
<td>65-year-old smokers</td>
<td>241.3</td>
<td>0.029</td>
<td>8370</td>
</tr>
<tr>
<td>60-year-olds with re-screening after 5 years</td>
<td>229.5</td>
<td>0.025</td>
<td>9116</td>
</tr>
<tr>
<td>60-year-olds with re-screening after 10 years</td>
<td>219.6</td>
<td>0.023</td>
<td>9523</td>
</tr>
<tr>
<td>65-year-olds with re-screening after 5 years</td>
<td>218.0</td>
<td>0.023</td>
<td>9349</td>
</tr>
<tr>
<td>65-year-olds (base case)</td>
<td>164.0</td>
<td>0.020</td>
<td>8197</td>
</tr>
<tr>
<td>60-year-olds</td>
<td>154.5</td>
<td>0.018</td>
<td>8687</td>
</tr>
<tr>
<td>70-year-olds</td>
<td>156.1</td>
<td>0.014</td>
<td>11022</td>
</tr>
</tbody>
</table>

* Invitation to screening versus no invitation to screening
The study demonstrated that the incremental cost per life year gained for screening all 65-year-old men for AAA was lower than what is generally considered cost-effective, and that the cost per life year gained was similar to that for screening risk groups. The assessment of different screening strategies indicated that screening 60-year-olds with re-screening after 5 years resulted in the largest benefit in terms of life years gained, with a low additional cost per life year gained.

Implications for decision making

The results indicate that screening for AAA may be cost-effective and that a general screening program could provide health benefits for society at an acceptable cost. The results further indicate that screening 60-year-olds with re-screening after 5 years may be preferred strategy.
4.4 CHOICES BETWEEN THERAPIES AND ESTABLISHMENT OF TREATMENT GUIDELINES

4.4.1 Cost-effectiveness of iodixanol (paper VI)

Acute renal failure is a costly and medically important complication of the use of iodine-based radiological contrast media, particularly in high-risk subjects[119-121]. Iodixanol, an isosmolar contrast medium, and iohexol, a low-osmolar contrast medium, have different adverse event profiles. Iodixanol has been shown to have a lower risk of nephrotoxic effects[48, 122], but has a higher price than iohexol, which means that the clinical benefit should be related to the added drug cost to decide for which patients the safer drug should be used.

The NEPHRIC study compared iodixanol to iohexol in subjects with a combination of impaired renal function and diabetes mellitus undergoing angiography[48]. The objective of this study was to analyse the cost-effectiveness of iodixanol compared to iohexol, from a hospital perspective, in subjects undergoing angiography in Sweden, Germany and France, based on the results from the NEPHRIC study.

The main outcome measures used in the study were costs and the number of adverse drug reactions (ADRs) related to the contrast medium, since the main difference between the two contrast media was assumed to be found in the adverse event profile. Effectiveness data and some resource use data were obtained from the clinical study, while additional resource use data was retrospectively collected from hospital records.

Seven serious ADRs occurred in the iohexol group (0.109 ADRs per subject) and two non-serious ADRs occurred in the iodixanol group (0.033 ADRs per subject). The average total hospital costs in the iodixanol and iohexol groups were €1978 and €2467, €1519 and €2092, and €1754 and €2147, using Swedish, German and French unit prices respectively. The mean costs of treating ADRs per subject in the iodixanol and iohexol groups were calculated at €1.8 and €373, €0.5 and €399, €0.4 and €445, using Swedish German and French unit prices. Table 4.2 shows some of the cost results.

<p>| Table 4.2. Cost results from bootstrap samples (Swedish unit prices, in €) |
|---------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Mean difference</th>
<th>2.5% and 97.5% percentiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast medium</td>
<td>8.5</td>
<td>-7.6</td>
</tr>
<tr>
<td>Medication</td>
<td>-3.3</td>
<td>-10.8</td>
</tr>
<tr>
<td>Hospital days</td>
<td>-257.0</td>
<td>-587.7</td>
</tr>
<tr>
<td>Procedures</td>
<td>-239.5</td>
<td>-872.3</td>
</tr>
<tr>
<td>Total hospital cost</td>
<td>-486.5</td>
<td>-1277.9</td>
</tr>
</tbody>
</table>

Iodixanol had both a lower mean cost and better mean effect than iohexol (i.e. dominated iohexol). The non-parametric bootstrap method, which was used to estimate the uncertainty of the mean costs and effects, showed that iodixanol dominated iohexol in 91%, 71% and 92% of the samples, using Swedish, German and French unit prices.
Implications for decision making

The results from the analysis indicate that iodixanol to be cost-effective as compared to iohexol for subjects with impaired renal function and diabetes mellitus undergoing angiography. Although the study was based on a rather small patient sample, the results suggest that the safer iodixanol should be the drug of choice for these high-risk patients.
The increasing availability and costs of new effective health technologies, in combination with the need for cost containment policies, stresses the importance of an efficient use of the scarce resources in health care. The role of economic evaluations in decision making varies substantially between different types of decisions. Table 5.1 presents the main types of decisions discussed in this thesis, and the formal (i.e. based on regulations) and informal (i.e. not based on regulations) use of economic evaluations in decisions related to them in Sweden.

### Table 5.1 Regulated (formal) and unregulated (informal) use of economic evaluations in Swedish health care decision making

<table>
<thead>
<tr>
<th>Decision</th>
<th>Use of reimbursed outpatient drugs</th>
<th>Use of inpatient hospital drugs</th>
<th>Use of other health care interventions</th>
<th>Investments in new technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discussed in paper</td>
<td>I, II and III</td>
<td>VI</td>
<td>V</td>
<td>IV</td>
</tr>
<tr>
<td>Formal/informal use of economic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>evaluations</td>
<td>Formal regulatory requirement for</td>
<td>No formal use, some informal</td>
<td>No formal use, some informal use</td>
<td>No formal use, some informal use</td>
</tr>
<tr>
<td></td>
<td>reimbursement decisions, informal</td>
<td>use</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>use for choices between therapies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Availability cost-effectiveness</td>
<td>Large</td>
<td>Large</td>
<td>Small</td>
<td>Very small</td>
</tr>
<tr>
<td>information</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 5.1 ECONOMIC EVALUATIONS IN DIFFERENT TYPES OF DECISIONS

**Decisions about drug treatments**

In the early 1990’s, Australia was the first country to require economic evaluations for reimbursement decisions. Many countries have followed the Australian example and the use of economic evaluations in the pricing and reimbursement of drugs is now well established in Sweden and many other countries. This thesis showed that the amount of published cost-effectiveness evidence for new drugs introduced between 1987 and 2000 varied substantially between different drugs. Drugs with improved effectiveness or safety compared to the competitors and drugs with a high sale were more likely to have evidence of cost-effectiveness. One problem identified in the study was that published studies were usually only available several years after the introduction of the drug.

Paper III assessed the cost-effectiveness of teriparatide, a new treatment against osteoporosis. The study aimed at providing information as a basis for pricing and reimbursement decision. As seen in paper I, published studies are usually available with a long time lag. Reimbursement decisions at market authorisation must therefore be supported by new, unpublished studies, directly related to this decision. The fact that an
economic evaluation is therefore available earlier for use by decision makers, not only the reimbursement agency, is one of the benefits of the regulation.

Economic evaluations of new drugs for pricing and reimbursement decisions are often hampered by lack of data, because the new drugs have usually not yet been extensively evaluated. This type of economic evaluations is therefore typically based on phase III clinical trials, which was also the case in the evaluation of teriparatide. Using clinical trial data is, however, surrounded by uncertainties, mainly due to the experimental design of the clinical trials and the short follow-up times. Models extrapolating the result from the clinical trials are therefore widely used to assess the cost-effectiveness of new treatments and a model was also used in the evaluation of teriparatide.

Although requirements for economic evaluations for reimbursement decisions can lead to a more cost-effective use of the resources, it is also important to recognise that regulations also involve costs. This thesis demonstrated that there are considerable time lags between the approval and the reimbursement for new drugs in Sweden and Finland. The analysis indicated that increasing the regulations for reimbursement by introducing requirements for cost-effectiveness information may be associated with an increased time lag between approval and reimbursement, at least during the first year after the introduction of the new requirement. This may indicate that there was a period of adaptation to the new regulatory requirements where the manufacturers needed additional time to produce the new information required by the authorities, or that the authorities needed additional time to evaluate the submitted evaluations. No statistically significant relation was found in the second or following years after introduction of the requirement, which might indicate that the manufacturers had then adapted to the new requirements. More studies on this issue are, however, needed before any conclusion can be made.

Reimbursement of a drug is only one of the decisions required before a drug is prescribed. The prescribing physicians usually have a number of reimbursed drugs between which to choose. Paper VI evaluated two contrast media used during angiographic procedures. The two drugs have different adverse event profile and the study aimed at identifying a patient population where the higher costs for the safer drug could be motivated. The two contrast media are only used in hospitals, which mean that the reimbursement of these drugs is not a relevant factor for the choice between them. However, the choice will have budgetary consequences for the hospital. These costs can only be accommodated if savings are made on other activities in the hospital, if the hospital budget is increased or if the hospital will run a deficit which will be covered in one way or another in subsequent periods. The way the hospital is reimbursed; global budget, per diem, diagnosis related group or procedure payment, or fee for service (per item payment), as well as internal payment mechanisms between radiology and other departments, may affect the rate of acceptance of the intervention.

The two contrast media evaluated in paper VI had been available for several years before the study was conducted. Economic evaluations of treatments already on the market may have the advantage of access to more data, particularly on long-term consequences. Long-term data was not included in the evaluation in paper VI, however, because the main consequences were expected to occur shortly after the procedures.
Studies conducted after a drug has been launched may also provide information about the costs and consequences in real clinical practice, which may differ substantially from those observed in a clinical trial.

Decisions about other health care interventions/programs

The role of economic evaluations in decisions concerning other types of health care interventions or programs than drug therapies is less clear in most countries. Usually there is no regulated role of economic evaluations in these decision making processes, but the decisions are influenced by various forms of evaluations, including economic evaluations.

Paper V evaluated screening for AAA in men. The introduction of screening programs for diseases is an example of a decision related to other health care technologies than drugs. Early diagnosis of a disease by screening can increase the possibility to cure or slow the progression of the disease, and can therefore be of great benefit for the patients. Evaluations of the consequences of early diagnosis of diseases may have the advantage of better access to data than evaluations of new treatments. AAA and surgical treatment of the disease have been studied for many years and a fairly large amount of studies have investigated the incidence of the disease and the outcome of the surgical intervention, both in clinical trials and real world settings. This increased the validity of the study, although there was still uncertain data, e.g. about the quality of life of AAA patients.

We can note that historically, preventive programs including screening have been evaluated in terms of costs and benefits to a greater extent than treatments. A typical example is cancer, where the majority of published health economic studies concern screening rather than treatment[14]. The explanation for this may be that screening involves interventions for individuals who do not yet have the disease, which means that there is no objective and observable need for intervention. It is also obvious that there is a choice between using resources for prevention or treatment; screening programs involve the use of medical resources, for example physicians, with an obvious opportunity cost in the production of health.

Decisions about investments in new technology or research

The influence of economic evaluations in decisions concerning investments in new technologies or research projects varies substantially. These types of decisions are usually based on less evidence about clinical effectiveness than decisions concerning existing health technologies, because the limited experiences of new technologies make it difficult to estimate their consequences of them. A new technology, in particular if it involves large investments, is also often expected to be used for many years. This means that the costs of the investment must be distributed over a long time period, which increases the uncertainty. The life expectancy of the technology and the potential introduction of alternative interventions may be difficult to foresee, which also complicates the assessment of the cost-effectiveness. All these uncertainties were encountered in paper IV, which evaluated a new type of radiation therapy for cancer. The investment cost for a facility to deliver proton radiation was estimated at about €60 million and was expected to have a life time of about 30 years. The treatment of many
types of cancers may change substantially during this time, which means that the benefit of the proton therapy as compared to other alternatives may change during. Investments in research involve yet another uncertainty, since a clinical benefit of individual research projects may be difficult to establish.

**Similarities and difference between different types of decision making**

There are many similarities between the three different types of decisions discussed in the thesis, but there are large differences in the role of economic evaluations between them. The rational for using cost-effectiveness information as one of the bases for the different types of decision making is similar, and the methods used to evaluate the cost-effectiveness of the different drugs, interventions and investment are also the same. However, if we compare the actors and incentives involved in the decision making, we see a distinct difference between decisions concerning drugs and decisions concerning other interventions, programs or investments. The supplier of cost-effectiveness information for drugs is usually the pharmaceutical industry, while the suppliers of cost-effectiveness information for other interventions, programs or investments are usually researchers within the health care system or universities, or in some cases manufacturers of the technologies. The resources, as well as the incentives, to produce cost-effectiveness information differ substantially between the pharmaceutical industry and the researchers with the health care system or universities, which affects the availability of cost-effectiveness information.

The influence of cost-effectiveness information on pricing and reimbursement decisions is also well established, which thus provides strong incentives for the industry to produce this information and for decision makers to take it into account in their decisions. The influence of cost-effectiveness information in decisions concerning other interventions, programs or investments is less clear and there usually exists no specified criteria for these decisions, which leads to weak incentives to produce the information and to take the information into account in the decisions. There may be stronger incentives than cost-effectiveness for taking budget restrictions, demands from individual or groups of patients, or potential political gains or losses into account even though the health care law states that this criterion should govern all decisions about resource allocation in Swedish health care, not only the use of drugs[123, 124].

The decisions to introduce a screening program or invest in a new treatment facility generally require administrative decisions with explicit allocation of additional resources to implement the program or investment. Such administrative decisions, at least if they involve large costs, are often associated with a formal evaluation and decision making process. This is not the case for the everyday choice between drug treatments made by physicians.

### 5.2 METHODS AND DATA IN ECONOMIC EVALUATIONS

Two of the four evaluations in the thesis (papers III and IV) may be defined as cost-utility analysis, since QALYs was the main outcome measure in the analyses. QALYs are (by many) the preferred outcome measure and are recommended by the reimbursement authority (LFN) in Sweden. Using QALYs and including the quality of
life aspects in addition to quantity of life would also have been desired in the evaluation of screening for AAA (paper V), since it is plausible that the disease may affect the quality of life of the patients. However, there was very limited data on this and estimates of the potential effect of including quality of life aspects were included as a secondary analysis. The evaluation of iodixanol (paper VI) used the number of ADRs as the outcome measure of the cost-effectiveness analysis. This type of measure was chosen since the most important clinical difference between the two drugs was found in the number of adverse reactions. The drugs were not expected to affect mortality and quality of life data was not available.

Three of the evaluations were based on models. The main purpose of using models is to extrapolate results from clinical trials. This was important in papers III-V because the evaluated technologies in these three studies had long-term consequences not captured in time frames of clinical trials. No model was used in paper VI for it was assumed that the most important consequences of the two drugs would occur within a few days.

Papers III-V were performed from a societal perspective, which means that all costs should be included in the analysis. The inclusion of future costs in added years of life, i.e. the incorporation of the economical consequences of a change in the mortality of the population, is debated. Inclusion of these costs is recommended by the Swedish reimbursement authority (LFN), but not by others[10, 28]. However, there are strong principle arguments for including these costs in an analysis with the purpose of assessing cost-effectiveness from a social perspective. The arguments against including these costs are usually distributional, for example between younger and older patients. The inclusion of future costs in added years of life had a fairly large impact on the results in papers III-V. The reason for this is that all three studies were performed in elderly populations where a reduction in mortality was an important benefit evaluated technology. Analyses were also performed from a more restricted cost concept excluding these costs. The drugs evaluated in paper VI were not assumed to affect mortality and future costs in added years of life were therefore not relevant in that study.

5.3 WAYS OF INCREASING THE ROLE OF ECONOMIC EVALUATIONS IN DECISION MAKING

The role of economic evaluations in different types of health care decision making varies, and seems to be small for some types of decisions. Therefore, it is important to assess the barriers of using economic evaluations and encourage wider use of this information. Some important aspects that may influence the use of economic evaluation can be identified:

5.3.1 Time

It is very important that the economic evaluations are timely, i.e. that the information is available at the time of the decision. This issue is well illustrated in the pricing and reimbursement decisions for drugs, where this information is now often is required before the drugs can gain full market access. The thesis showed that little cost-effectiveness evidence was published before or early after the approval of NCE drugs between 1987 and 2000. This may be less of a problem in the future, as the requirement
for economic evaluations in pricing and reimbursement decision is increasing. However, this requires that these studies are made publicly available as soon as possible. But early economic evaluations are also often limited by lack of data. This is well illustrated by two of the studies in the thesis, the evaluations of teriparatide (paper III) and proton radiation (paper IV). Teriparatide is a new treatment and there is limited data on the consequences, particularly in the long term and in relation to other active treatments. The same situation is seen for the evaluation of proton radiation, where little comparative data, relevant for an economic evaluation, exists. However, despite the limited data, information about the cost-effectiveness is still important for the decision making, since the decision makers need to decide on the price and reimbursement of teriparatide and whether investments in a new facility for proton radiation should be made. We have also seen that it is possible to undertake economic evaluations with statistical measures of uncertainty included, which makes it possible to also get information on the degree of uncertainty in the results. Because data is scarce and these early evaluations are therefore surrounded by a high degree of uncertainty, it is important to reassess the cost-effectiveness as more data becomes available. The validity of results from economic evaluations is also changing over time, as costs, health care systems, relevant comparators etc are changing, which stresses the need for reassessments of the long-term costs and effects in real clinical practice. The simulations may give important information on the design of the clinical studies that should follow when the technology is available.

5.3.2 Study design and quality
The quality, or internal validity, of the evaluations is, of course, a basic requirement for the credibility of the analyses and for using them as a basis for decision making. As the field of health economics and economic evaluations has grown, the knowledge of both conducting and evaluating studies has increased. Methodological standards have been developed, which simplifies the assessment of the quality of the studies. Transparency in the methodology and data used are important factors for simplifying the assessment of the evaluations. An important aspect of the design and quality of an analysis is the data used. Lack of data is, as discussed above, a common problem for economic evaluations, at least those of new technologies. Clinical trials designed to detect differences in clinical parameters often have too small sample sizes to detect differences in resource use. This problem is illustrated in the evaluation of iodixanol (paper VI), where resource use data was collected for subjects included in a clinical trial designed to detect a difference in nephrotoxicity. Analyses of the total costs in the two treatment groups were not expected to result in any statistical significant difference, due to a large variance in the resource use and a rather small sample size. An alternative method for comparing costs was therefore also performed in this study, where only costs deemed related to the adverse events of the treatments were included.

Another aspect related to the study design is the choice of comparison alternative. The alternative should be a relevant comparator and is, in some guidelines, defined as the best or most commonly used alternative. Comparisons with the best alternatives are, however, sometimes complicated by the lack of comparative data. This is illustrated in the evaluation of teriparatide (paper III), where the best alternative would probably be other active treatments, e.g. bisphosphonates. The available clinical trial data only compared the addition of teriparatide to calcium and vitamin D treatment with calcium...
and vitamin D only, and the relative efficacies of teriparatide and other treatments are therefore unclear. In this case, there is a trade-off between the relevant comparator and reliable data. In the case of teriparatide, we also performed a comparison with bisphosphonates for the reimbursement authorities, but we considered this data as too uncertain to be publishable. The results from the comparison with bisphosphonates illustrated the uncertainty in the relative efficacies, since there were large variations in the cost-effectiveness ratios obtained, depending on the assumptions made.

5.3.3 Generalisability

The generalisability, or the external validity, of the evaluations is also an important issue, since there are large variations between different patient populations in the consequences of a treatment. The transferability of results from economic evaluations between countries is a common problem, since specific local data for economic evaluations is often unavailable. The validity of studies performed in other countries or settings than the decision makers own context is therefore an important question. Other forms of generalisability are the validity of results from clinical trials in real clinical practice and in other patient populations than those included in the clinical trials.

All economic evaluations presented in the thesis are based on data from several countries. Most clinical trials are multinational and a sub analysis of patients from individual countries rarely gives sample sizes sufficiently large to give reliable estimates. One solution to this problem, which is illustrated in the evaluation of iodixanol (paper VI), is to assume clinical effectiveness and resource use to be similar across countries, while unit costs are not. The evaluation of iodixanol was also performed using unit costs for Germany and France, since these countries were the main contributors of patients in the clinical trial. Another solution, used in the other three evaluations in the thesis is to only use risk reductions of a treatment from internationally based studies, and then apply this to locally derived risks, costs etc.

The evaluation of iodixanol reported a cost-effective result for the high risk population included in the clinical trial. This result might not have been surprising, considering the difference in adverse events and the rather small difference in drug costs between treatments. The results may, however, not be generalised to other patients than those included in the NEPHRIC trial. From a decision making perspective it might therefore have been more interesting to identify the threshold risk of adverse events where iodixanol could no longer be considered cost-effective as compared to iohexol. However, the data from the clinical trial did not allow for such an analysis, and this issue therefore needs to be explored in future studies. Although it is important that the decisions are evidenced based, it is also important to assess the value of the information obtained from research. There is a cost of research for obtaining the cost-effectiveness information, and it is therefore important to compare this cost with the value of the obtained information. The results from the economic evaluation of iodixanol were anticipated. Therefore, it may be argued that the resources spent on performing the evaluation could have been allocated elsewhere since the results did not provide valuable information. However, when an evaluation is valuable to perform is difficult to know, since in most cases, it is very difficult to foresee the results of an evaluation.
5.3.4 Diffusion of information

Access to economic evaluations is, of course, a necessity for the decision makers to be able to use the information in their decisions. Developing publicly available databases with economic evaluations is one way of increasing the access of the information. A fast publication process is also important to provide the decision makers with timely evaluations that have been assessed in a peer review process.

Access to the information is not enough, however. Lack of sufficient knowledge to interpret the economic evaluations has also been raised as a problem by some decision makers. Increased training in the methods of economic evaluations could therefore be valuable. Decisions concerning other interventions and programs than drugs are often made by many different decision makers at various levels in the health care system. This means that there may not be sufficient knowledge of the methods of economic evaluations among all of these decision makers, which may explain the limited influence in some of these decisions. A more centralised decision making process also for decisions concerning other interventions and programs than drugs might therefore also encourage a larger influence of economic evaluations. It is also important that methods and results from economic evaluations are presented clearly to simplify the interpretation[15].

5.3.5 Regulations and incentives

Two important factors for the influence of economic evaluations are the regulations and incentives for the actors within health care to provide and use this information. The provision of cost-effectiveness information for new drugs by the pharmaceutical manufacturers and the use of the information in reimbursement decisions are controlled by regulations in many countries, which thereby gives strong incentives for the manufacturers and the decision makers. There would, however, still be strong incentives for the manufacturers to provide cost-effectiveness information even without regulations as long as the information influences the reimbursement decisions. The regulatory requirements and the incentives to provide cost-effectiveness evidence have led to a large increase in the availability of cost-effectiveness information for drugs. The strong incentives for the pharmaceutical manufacturers to provide the information have, however, also led to a potential problem with biased information (discussed in a separate section below). The incentives for physicians to take cost-effectiveness criteria into account in the choices of treatments are less clear[125], as are the incentives for using the information in the allocation of other health care resources than drugs. There are often more incentives for cost containment than cost-effective use of the resources. More incentives for both producing cost-effectiveness information and using this information in the resource allocation need to be provided to increase the influence of economic evaluations.

One problem may be that decision makers are responsible for part of the health care system and there are small incentives for them to consider consequences outside their responsibilities. This may influence the role of economic evaluations in their decisions, since a common benefit of increasing the costs in one part of the health care system is a reduction in the costs of other parts of society.
5.3.6 Availability of budget resources

All four evaluated technologies in the thesis were to be found cost-effective in some patient populations. However, all four technologies were also priced higher than the comparators. This means that more budget resources are needed to follow the results from the analyses and implement the technologies, or the use of other interventions must be reduced. New effective technologies are usually more costly than existing ones, because we expect society to be willing to pay for the additional effect. Adopting new effective technologies will improve the health of the population, but this will also require additional health care resources. Using a threshold approach to decide if an intervention should be implemented, i.e. to implement all intervention with an incremental cost-effectiveness ratio below the established threshold, assumes that the health care system is based on a flexible budget. However, it may be argued that the health care budgets are fixed. This means that resources must be re-allocated from other parts of the health care system to implement a new intervention. This introduces uncertainties about the true alternative costs for the resources used to implement the new technology[126]. How resources in society should be allocated and how the cost for health care should be financed are therefore important issues which need to be discussed alongside the discussion of society’s willingness-to-pay for additional health.

The consequences of many health care interventions are a shift in resource use. A common example, illustrated in papers III and VI, is drug treatments reducing the need for other health care services. This means that an additional drug costs leads to reduced costs in other parts of the health care system. Therefore, it is important that the budget allocation within health care is flexible so that resources can be moved between sectors. Difficulties in moving budget resources between sectors have been stressed by decision makers as a hurdle against using economic evaluations as a basis for decision making[127].

5.3.7 Sponsorship of studies

The sponsorship of economic evaluations has also been raised as a hurdle for not using this information in decision making. It is very common that pharmaceutical companies perform or sponsor economic evaluations. This is understandable since the decision makers require this information from the pharmaceutical companies, e.g. for reimbursement decisions. Two of the evaluations in the thesis were sponsored by pharmaceutical companies (paper III and VI) and one by a “non-profit” group with an interest in the evaluated technology (paper IV). Potential bias due to a desire from the sponsor to obtain a certain result, or the avoidance of publication of negative results, is an important issue. It should be recognised, however, that the same bias may occur even if it is not a company sponsored study, because all researchers may potentially have a desire to obtain a certain result. The issue is also not limited to economic evaluation; the same problem is found in all medical research areas. Increasing knowledge of economic evaluations and the development of methodological guidelines are important ways of reducing the risk of publishing biased studies. The development of the good clinical practice guidelines for clinical trials has lead to a common quality standard for these studies, and similar standards may be expected to be developed for economic evaluations. The most important way of limiting the publication of biased studies may, however, be the review process. It is important that methods and data for
economic evaluations, as well as clinical studies, are transparent and clearly described. It is also important that the review process is of high quality so that studies that are unreliable in some way are detected. The issue of publication bias, i.e. avoidance of publishing negative results, may be more difficult to come around. The publication of results from clinical trials is often easier to follow since these studies need to be approved by medical authorities, ethical boards etc before they are initiated. This is not the case for most economic evaluations, however. Publishing information that an intervention is not cost-effective is important, at least for interventions already used in clinical practice, since this informs the decision makers that the intervention should not be used (unless other, more important, criteria support the use of the intervention).

Another difference between clinical trials and economic evaluations is that many economic evaluations are set up with the purpose of identifying patient populations where a treatment is cost-effective. This may, at least partly, explain why most economic evaluations report positive results, i.e. that the evaluated treatment is found cost-effective. All four evaluations in the thesis found the evaluated technologies to be cost-effective, but three of them aimed at identifying patient populations where the treatment would be cost-effective. The results from these studies might very well also be seen as negative since, for example, the evaluation of teriparatide also indicated that the treatment would not be cost-effective for the average osteoporotic women.

5.4 IMPACT IN DECISION MAKING

The four evaluations presented in the thesis were all conducted with the direct purpose of being bases for different types of decision making in Sweden.

The economic evaluation of teriparatide (paper III) was performed for a decision about pricing and reimbursement. A preliminary decision was issued by the reimbursement authority (LFN) in Sweden in December 2003[28]. The drug was approved with restrictions and the benefits board required additional data from the manufacturer to prolong the reimbursement after two years. The approved indications for the treatment closely followed the results from the economic evaluation presented in the thesis.

The evaluation of proton radiation (paper IV) was aimed at providing information for a decision about investment in a new proton radiation facility in Sweden. The main alternative for this investment will be to organize and finance it through the seven county councils in Sweden with university hospitals. The final decision about this investment will, according to current plans, be made at the end of 2005 or during first half of 2006, and the impact of the economic evaluation is therefore currently unknown.

The evaluation of screening for AAA (paper V) was performed as a basis for deciding if a general screening program should be introduced and also how such a program should be designed. The introduction of these types of screening programs may be made at local or national levels. An evaluation from SBU in Sweden in 2003 concluded that there was strong evidence that screening for AAA in men reduces mortality, but there was limited evidence of the cost-effectiveness of the method in Sweden[128]. Our study has provided additional evidence of the cost-effectiveness, and the introduction of
screening programs is currently being planned in some counties, e.g. in Uppsala. No final decision about introducing this type of screening in Sweden has, however, yet been taken, which means that the impact of the economic evaluation is not known.

The evaluation of iodixanol (paper VI) provided information for the choice between this drug and iohexol for patients with impaired renal function and diabetes mellitus undergoing angiography. These decision are made in every day practice, so it is more difficult to assess the impact of the economic evaluation. Moreover, the results from the economic evaluation were anticipated considering the differences in the adverse event rate and the marginal price difference. Figure 5.1 shows the sale statistics for iodixanol and iohexol in Sweden, and the publication of the clinical study and the presentation of the economic evaluation at a scientific congress (the economic evaluation was published in 2005) are marketed in the figure.

Figure 5.1 Sale statistics for iodixanol and iohexol in Sweden

There is a clear increase in the sale of iodixanol after the publication of the clinical study. However, the number of patients in Sweden undergoing angiography and having impaired renal function in combination with diabetes mellitus probably is probably rather limited, which may indicate that the use of iodixanol has also increased in patient populations not included in the clinical and economic evaluations.
6 CONCLUSIONS

Economic evaluations can provide valuable information as a basis for many types of decision making concerning resource allocation in health care, although they are currently most widely used in pricing and reimbursement decisions for new drugs. The publication of economic evaluations increased dramatically during the 1980’s and 1990’s. This thesis has demonstrated that economic evaluations during the 1990’s were more likely to be conducted for drugs with improved effectiveness or safety as compared to those of the competitors and for drugs with high sale. Although requirements for economic evaluations for reimbursement decisions can lead to a more cost-effective use of the resources, it is important to recognise that regulations also involve a cost. The thesis indicated that the increasing requirements for cost-effectiveness in Sweden and Finland may have been associated with a delayed introduction of new drugs on the market, at least in the first year after the changed regulations. More studies on this issue are, however, needed before any conclusion can be made.

The thesis also discussed four types of decision making where cost-effectiveness information can be a valuable basis for the decisions. The four economic evaluations identified patient populations where teriparatide treatment for osteoporosis, proton radiation for breast cancer, screening for AAA in men and use of iodixanol in angiography may be considered cost-effective in Sweden.
I would like to express my sincere gratitude to the following people:

Clas Rehnberg, main supervisor, for your contribution to this thesis and guidance during my time as PhD student.

Bengt Jönsson, co-supervisor, for sharing your outstanding knowledge and experience in the field of health economics

Peter Aspelin, co-supervisor, for sharing your scientific and medical knowledge

Anders Wanhainen, co-author, for a fruitful and interesting collaboration

Mattias Ekman, Susanne Rehn Ericsson, Ulf Isacsson, Olof Johnell, Cyrus Cooper, David Sykes, David Bergqvist, Martin Björek, Pierre Aubry, Sven-Göran Fransson, Ruth Strasser and Roland Willenbrock, co-authors, for valuable collaborations and contributions to the studies of this thesis

The National Corporation of Swedish Pharmacies and The Pharmaceutical Benefits Boards in Sweden and Finland, for providing data for papers I and II.

The federation of County Councils, The National Centre for Priority Setting in Health Care, Amersham Health, Lilly Europe, Uppsala University, Swedish University Hospitals and the Swedish Cancer Society for financial support to the studies in this thesis

Linus, friend and colleague, for introducing me to this field and sharing your extraordinary knowledge

Friends and colleagues at Stockholm Health Economics, for contributing to an inspiring work place and for sharing great moments both during and after work

All other friends for the great moments outside work

And, finally, Emma for being you and Ella for brightening my days with your “vift-vift”
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41. The Swedish Council on Technology Assessment in health Care (SBU). 


