

From DEPARTMENT OF CLINICAL SCIENCE,  
INTERVENTION AND TECHNOLOGY  
Karolinska Institutet, Stockholm, Sweden

**COSTS AND CONSEQUENCES IN  
PERIOPERATIVE CARE**

**ANALYTIC MODELS IN STUDIES ON  
PAIN TREATMENT AND ON  
HAEMODYNAMIC OPTIMIZATION OF  
ELDERLY PATIENTS**

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“Live as if you were to die tomorrow; learn as if you were to live forever”

Mahatma Gandhi

To Rolf



# ABSTRACT

## *Background*

Because resources are scarce in health care, costs and consequences of new interventions must be assessed to support informed policy decisions. This thesis analyses the cost-effectiveness of advanced postoperative pain treatment and perioperative haemodynamic optimization by applying decision modelling as an analytic framework.

1. Postoperative pain treatment refers to epidural analgesia and to patient-controlled intravenous analgesia. Based on the superior analgesic effect found in clinical trials, epidural analgesia is regarded as the gold standard following major surgery, but a drawback is the high failure rate (10–15%). Considering that approximately 40 000 patients are treated by epidural analgesia per year in Sweden, costs and consequences of this clinical problem are substantial.

2. Haemodynamic optimization refers to fluid protocols targeted to increase blood flow, referred to as goal-directed haemodynamic treatment. These protocols are beneficial in the perioperative care of high-risk patients, but there is lack of evidence in elderly patients. In Sweden 20 000 patients are operated on each year for proximal femoral fracture, with poor postoperative outcome. Large trials are required to assess whether any protocol of the goal-directed haemodynamic treatment is beneficial in the elderly population, in terms of outcome and health care costs. Considering the cost and complexity of such a trial, a prior cost-effectiveness analysis might be adequate to guide the initiation of such a trial.

## *Methods*

1. Epidural analgesia vs. patient-controlled intravenous analgesia:

Paper I: A decision-analytic cost-effectiveness model was developed to analyse data of a clinical database on pain treatment following major abdominal surgery.

Paper II: Postoperative intensive care costs were analysed on data from patients included in a previously published trial on postoperative pain treatment following thoracoabdominal oesophagectomy.

2. Goal-directed haemodynamic treatment vs. traditional fluid treatment in elderly patients:

Paper III: A decision-analytic cost-effectiveness model was developed, and relevant data from published trials and national registries were analysed. As the clinical outcome for elderly patients was previously unknown, reasonable estimates are applied in the model.

Paper IV: The prior cost-effectiveness analysis (Paper III) guided the initiation of a large ( $n = 460$ ) randomized clinical trial in elderly patients with proximal femoral fracture, and interim analyses of safety and efficacy were conducted ( $n = 100$ ). Given the interim efficacy data, the monetary value of further data collection was analysed by calculating the expected value of perfect information.

## *Results*

1. The epidural analgesia is not cost-effective and no saving of the postoperative costs can be achieved, given the available evidence in Swedish clinical routine (Papers I–II).

2. The goal-directed haemodynamic treatment is predicted to be cost-effective in elderly patients, based on the available evidence and on the prior estimates of clinical outcome before the initiation of the trial. The expected value of perfect information is high, indicating that collecting further data by continuing the trial is potentially worthwhile (Papers III–IV).

## *Conclusions*

1. The analyses of epidural analgesia challenge its position as the gold standard and may assist revision of clinical policy decisions on postoperative pain treatment.

2. The analyses of the goal-directed haemodynamic treatment in elderly patients using a decision-analytic cost-effectiveness model suggest the usefulness of the initiation and continuation of a large clinical trial.

## LIST OF PUBLICATIONS

- I. E Bartha, P Carlsson, S Kalman. Evaluation of costs and effects of epidural analgesia and patient-controlled intravenous analgesia after major abdominal surgery. *British Journal of Anaesthesia* 2006; 96(1): 111–7.
- II. E Bartha, Å Rudin, P Flisberg, CJ Lundberg, P Carlsson, S Kalman. Could benefits of epidural analgesia following esophagectomy be measured by perceived perioperative patient workload? *Acta Anaesthesiologica Scandinavica* 2008; 52(10): 1313–8.
- III. E Bartha, T Davidson, A Hommel, KG Thorngren, P Carlsson, S Kalman. Time for clinical research? Goal-directed hemodynamic treatment of elderly patients with proximal femoral fracture is promising from a health economic perspective. Submitted.
- IV. E Bartha, T Davidson, TH Brodtkorb, P Carlsson, S Kalman. A new approach to interim analysis of a randomized clinical trial. The value of further research on goal-directed haemodynamic therapy for elderly patients. (Trial nr. NCT01141894 [ClinicalTrials.gov](https://clinicaltrials.gov)). Manuscript.

# CONTENTS

1	Introduction.....	1
1.1	Background .....	1
1.2	Aims .....	2
1.3	Outline of the thesis .....	3
2	Health economic evaluations - overview .....	4
2.1	Basic forms of economic evaluation .....	4
2.1.1	The perspective .....	4
2.1.2	Value of consequences .....	4
2.1.3	Analytic strategies .....	4
3	The analytic framework.....	6
3.1	Cost-effectiveness analysis.....	6
3.1.1	Costs.....	6
3.1.2	The measure of effect .....	7
3.1.3	Incremental cost-effectiveness ratio.....	7
3.2	Construction of a model.....	9
3.2.1	Decision tree .....	9
3.2.2	Markov structure.....	9
3.2.3	Handling uncertainty .....	10
3.3	Estimation of the value of further research .....	11
4	Studies on postoperative pain treatment .....	14
4.1	Paper I. Evaluation of costs and effects of epidural analgesia and patient-controlled intravenous analgesia after major abdominal surgery.....	14
4.1.1	Aims .....	14
4.1.2	Methods.....	14
4.1.3	Results.....	15
4.2	Paper II: Could benefits of epidural analgesia following thoracoabdominal oesophagectomy be measured by perceived perioperative patient workload? .....	16
4.2.1	Aims .....	16
4.2.2	Methods.....	16
4.2.3	Results.....	17
4.3	Discussion of Papers I–II.....	18
4.3.1	The strengths of Papers I–II .....	18
4.3.2	The limitations of Papers I–II.....	18
4.3.3	Implications for policy decisions .....	19
5	Studies on haemodynamic optimization .....	20
5.1	Paper III. Time for clinical research? Goal-directed haemodynamic treatment of elderly patients with proximal femoral fracture is promising from a health economic perspective .....	20
5.1.1	Aims .....	20
5.1.2	Method .....	20
5.1.3	Results.....	21

5.2	Paper IV. A new approach to interim analysis of a randomized clinical trial. The value of further research on goal-directed haemodynamic therapy for elderly patients. Trial nr (NCT01141894 ClinicalTrials.gov).....	22
5.2.1	Aim .....	23
5.2.2	Methods .....	23
5.2.3	Results .....	24
5.3	Discussion of Papers III–IV .....	25
6	Overview of the studies and implications.....	27
6.1	Methodological issues on modelling .....	27
6.2	The future implication for modelling.....	28
7	Conclusions .....	29
8	Appendix .....	30
8.1	Short-term model.....	30
8.1.1	The structure of the decision tree.....	30
8.1.2	Short-term outcome of traditional perioperative fluid treatment .....	30
8.1.3	Short-term outcome of GDHT.....	31
8.1.4	Quality of life .....	35
8.1.5	The short-term costs.....	36
8.1.6	Key assumptions in the decision tree .....	38
8.2	Long-term model .....	39
8.2.1	The Markov structure.....	39
8.2.2	Long-term postoperative outcome.....	39
8.2.3	Long-term quality of life.....	40
8.2.4	Long-term health care costs .....	40
8.2.5	Assumptions in the Markov structure.....	41
9	Swedish Summary.....	42
10	Acknowledgments.....	43
11	References .....	45



## LIST OF ABBREVIATIONS

ASA	Five-category physical status classification adopted by the American Society of Anaesthesiologists
CER	Cost-effectiveness ratio
CI	Confidence interval
EDA	Epidural analgesia
EQ-5D	Questionnaire for a descriptive system of health-related quality of life states consisting of five dimensions
EVPI	Expected value of perfect information
EVPII	Expected value of partial perfect information
GDHT	Goal-directed haemodynamic treatment
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
PCEA	Patient-controlled epidural analgesia
PCIA	Patient-controlled intravenous analgesia
PCU	Postoperative care unit
QALY	Quality-adjusted life-year
QALY weight	Index value attached to a health state measured by EQ-5D
RCT	Randomized clinical trial
RR	Relative risk
VAS	Visual analogue scale



# 1 INTRODUCTION

At the clinical level decisions to adopt new interventions are usually assisted by evidence-based *efficacy*, that is, how these interventions *can ideally work*. Often there is a lack of knowledge as to clinical *effectiveness*, that is, how these new interventions *actually work* in the clinical routine care and also whether it is reasonable to strain the clinical budget with additional costs. Clinicians are important actors in adoption decisions and in such positions two types of barriers may be experienced: i) the first prevents the adoption of new interventions with a high grade of evidence-based efficacy<sup>i</sup> ii) the second prevents revision of previously adopted interventions when new evidence comes up. I initiated this thesis based on my clinical awareness of these barriers, which is grounded in the understanding of two separated issues:

1. Beside evidence of efficacy, analyses of costs and consequences are also needed to influence the adoption procedure.
2. For the revision of already adopted treatments a dynamic framework is required to update the evidence with new findings.

Such assessments are the key features of health economic evaluations. This thesis is devoted to applying established analytic frameworks in health economics to assess two common interventions in perioperative medicine.

## 1.1 BACKGROUND

During the past decade the number of operations involving the cardiovascular, intrathoracic, and gastrointestinal organs has doubled from approximately 80 000 to 160 000 per year.<sup>i</sup> During the same period the inpatient health care costs have increased by 30 per cent, the number of patients over 65 years increased representing 13.5 per cent in 2007.<sup>ii</sup> At the same time the number of hospital beds and the length of hospital stay have decreased. In 2007 the mean length of hospital stay was 6.1 days. These changes require adoption of new strategies in perioperative care to accelerate postoperative recovery by minimizing the physiological disturbances associated with surgical trauma and anaesthesia. New approaches to preoperative assessment using new biomarkers or exercise testing<sup>2,3</sup>, new approaches to fluid treatment using new monitoring technologies<sup>4,5</sup>, and advanced recovery and pain treatment programs have been proposed and partially implemented. However, resources in health care are scarce, and not all new opportunities can be introduced. Therefore, it is necessary to identify treatment strategies that offer the greatest patient benefits in relation to costs. Such assessments are the objectives of health economic evaluations. Health economic evaluations provide an analytic framework to compare alternative interventions in terms of costs and consequences. The alternative interventions are the range of options that could be used to increase the population's health. Costs refer to the value of health care resources used. Consequences represent clinical effects, including changes in patients' health. Health economic evaluations aim to assist the decision-making process on the use of new treatment strategies to maximize health in the population, given the limited resources in health care. Such analyses are a part of a prioritization process in health care according to Swedish law.<sup>iii</sup>

The increased use of economic evaluation in health care decisions has induced a rationale of strict analytic frameworks; one of them is decision analytic modelling.

This thesis applies decision analytic models to analyse the costs and consequences of two common interventions within anaesthesia care: postoperative pain treatment and perioperative haemodynamic optimization. Common features of both treatments are that they involve a large

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<sup>i</sup> <http://www.socialstyrelsen.se/statistik/statistikdatabas>.

<sup>ii</sup> <http://www.socialstyrelsen.se/publikationer2009/2009-126-72>.

<sup>iii</sup> <http://www.riksdagen.se/webbnav/index.aspx?nid=3911&bet=1982:763>.

number of patients; they may influence the postoperative outcome, patient's postoperative health, and the length of hospital stay.

### 1. Treatment of postoperative pain

In Sweden approximately 40 000 patients per year undergo major abdominal surgery. The most commonly used pain treatment strategies are epidural infusion of a mixture of local anaesthetics and opiates with or without patient control (EDA/PCEA) and patient-controlled administration of intravenous opiates (PCIA). Consensus is found concerning the superior analgesic effect of EDA over PCIA,<sup>6</sup> but not concerning the influence on postoperative complications<sup>7-10</sup> or on the length of hospital stay.<sup>11-19</sup> It is also unclear whether the better analgesic effect is clinically meaningful or can be translated into patient-oriented outcome.<sup>20</sup> EDA<sup>1</sup> is regarded as the gold standard for routine postoperative pain treatment following major abdominal surgery, based on the superior analgesia in efficacy trials. The low success rates (75–85%) in clinical practice<sup>21-24</sup> and the insufficient evidence of patient-oriented<sup>20</sup> and clinical<sup>10</sup> outcomes should challenge this position.

### 2. Perioperative haemodynamic optimization

The rationale of haemodynamic optimization is to increase the global blood flow in critical situations to prevent organ failure. It covers various treatment protocols that are referred to as goal-directed haemodynamic treatment (GDHT). The GDHT can be guided by a variety of haemodynamic parameters such as blood flow in the aorta,<sup>25</sup> oxygen delivery,<sup>26</sup> stroke volume,<sup>27</sup> central venous pressure,<sup>28</sup> central venous oxygen saturation,<sup>29</sup> pulse pressure,<sup>30</sup> and stroke volume variation.<sup>31</sup> In high-risk patients the GDHT can influence the postoperative outcome,<sup>4,5,32-39</sup> but there is scarce evidence in elderly patients with proximal femoral fracture. In this thesis the GDHT refers to an approach described by Shoemaker<sup>40</sup> that is targeted by goal values of haemodynamic parameters (oxygen delivery  $>600 \text{ ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ , cardiac index  $>4.5 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ). The GDHT is unproven in clinical practice in elderly patients. Controlled clinical trials are required to also address health economic aspects; if results favour the GDHT, the adoption decision could have implications for approximately 20 000 treatments per year in Sweden.

## 1.2 AIMS

The specific aims in this thesis are:

1. To analyse the costs and effects of postoperative epidural and patient-controlled intravenous analgesia following major abdominal surgery in routine clinical care (Paper I).
2. To determine the influence of postoperative patient-controlled epidural and intravenous analgesia on the perceived nursing workload transformed into postoperative costs on the Intensive Care Unit following thoracoabdominal oesophagectomy (Paper II).
3. To establish a prior estimation of cost-effectiveness of goal-directed haemodynamic treatment of elderly patients with proximal femoral fracture to guide the initiation of a randomized clinical trial (RCT) with the same objective (Paper III).
4. To evaluate the monetary value of further data collection, given the interim efficacy data of the initiated RCT on GDHT of elderly patients with proximal femoral fracture by calculating the expected value of perfect information (Paper IV).

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<sup>i</sup> In the thesis the term EDA is used as the abbreviation of epidural analgesia, irrespective of whether it is delivered by fixed rate pump or by patient-controlled pump, with one exception: EDA and PCEA are distinguished in the chapter in which Papers I–II are presented.

### **1.3 OUTLINE OF THE THESIS**

Chapter 3 provides a brief introduction to health economic evaluations, including analytic strategies. Chapter 4 presents the analytic framework used in the studies. Chapter 5 includes the studies on postoperative pain treatment, and Chapter 6 the studies on haemodynamic optimization. Chapter 7 contains the implications of modelling and the conclusions. The Appendix provides further relevant details on the modelling of GDHT, on the data collection (search of literature and registries), measures of outcomes (postoperative morbidity, mortality, health-related quality of life, long-term survival), and data incorporation that could not be included in the papers because of the limited space available in the journals.

## **2 HEALTH ECONOMIC EVALUATIONS - OVERVIEW**

As noted above, health economic evaluation compares costs and consequences of alternative treatment options. Such comparisons are required for policy decisions in a publicly funded health care system to ensure that the available health care resources are used to maximize the health of the population.

### **2.1 BASIC FORMS OF ECONOMIC EVALUATION**

The basic forms of health economic evaluation are defined by the applied perspectives, the way consequences are valued, and the analytic strategy used. In all forms of health economic evaluations at least two alternatives are compared with each other, the intervention and the comparator (which is often standard treatment).

#### **2.1.1 The perspective**

Two perspectives are common in health economic evaluations. One is the societal perspective, which involves all relevant costs and consequences. Besides health care costs, changes in the patient's or family's productivity and the use of family resources affecting the work or leisure activities are also considered. The second is the health care perspective, which considers only health care costs and health outcomes strictly associated with the treatment. In the present thesis a health care perspective is taken.<sup>41</sup>

#### **2.1.2 Value of consequences**

There are four different types of economic evaluation, depending on which type of consequence is used.<sup>41</sup>

1. Cost-effectiveness analysis: costs are related to a single common effect, for example, a gain in life-years, or pain-free or angina-free days. When the common effect is expressed by a generic measure of health (quality of life), it provides a possible comparison between interventions in health conditions with different clinical outcomes.
2. Cost-utility analysis: the outcome is converted into a preference-based outcome measure. Normally quality-adjusted life-years (QALYs) are used, which combine the health-related quality of life of a health state with the duration of that health state. It can be considered as special case of cost-effectiveness analysis and the two terms are often used interchangeably.
3. Cost-benefit analysis: the outcome is converted to monetary value; for example, reduced length of hospital stay is converted into hospital costs.
4. Cost-minimization analysis: this type of economic evaluation searches for the least costly alternative when the size of the effects is similar.

#### **2.1.3 Analytic strategies**

The analytic strategies are defined by the methods of data collection and analysis. Data can be collected from a single clinical trial, or alternatively, drawn from different data sources using analytic models; these strategies can be combined.<sup>41</sup> The key feature of data collection is to identify relevant, unbiased data with high precision.<sup>42</sup>

### 2.1.3.1 *Clinical trials for health economic evaluation*

Randomized clinical trials generally provide the most unbiased evidence on outcomes, and have a high degree of internal validity, but they may have a low degree of external validity for some of the reasons given below. Use of the clinical trial as a *single data source* has several drawbacks.<sup>41</sup>

1. Clinical trials are designed to find evidence of short-term efficacy rather than safety and effectiveness, and may lack precision with respect to clinical endpoints occurring rarely (side or adverse effects) that are relevant for policy decision on a population basis.
2. The majority of trials that are designed to explore intermediate or surrogate outcomes do not assess relevant health outcomes and are too small to detect differences in mortality and morbidity. The intermediate or surrogate outcomes have to be ‘translated’ into morbidity, mortality, and health outcome by epidemiologic data, if any exists.
3. The follow-up of clinical trials is, as a rule, shorter than is required for health economic evaluations, as many health conditions and treatments require a lifelong perspective.
4. The cost estimates of interest in a clinical trial may be biased, because part of the costs is protocol-driven rather than attributable to the therapy.
5. The estimated sample size of efficacy trials is usually lower than is required for evidence of cost-effectiveness; that may lead to ethical financial considerations as to whether the trial should be continued, if evidence of efficacy is reached.

### 2.1.3.2 *Decision analytic modelling*

As noted above, the use of a single clinical trial for economic evaluation is not always possible because of the limited number of observations, short follow-up, and failure to collect relevant outcome data required for a health economic evaluation. Therefore, data have to be drawn from several data sources, if relevant policy issues are to be highlighted.<sup>42</sup> An analytic framework, a model, provides a network between ranges of data sources, using mathematical relationships. The data incorporated in the model are called parameters. The parameters are estimated or defined, depending on which kinds of data are available. In the early assessment of a technology, sampled variables are not available and the parameters may be estimated by experts, based on empirical or theoretical knowledge.<sup>41</sup> When sampled variables are available, the parameters may be defined by means of these. Such models are *deterministic models*, because point estimates are used (mean values or expert estimates). Another option is to define the parameters by probability distributions that characterize the uncertainty of the sampled variables; in this case the model is *probabilistic*.<sup>42</sup> The probabilistic models address two separate key decisions. One is the decision to choose between alternative interventions based on costs and health outcomes, and the other is the decision as to whether further information is needed to decrease the uncertainty of this decision. This analysis is done by the estimation of the value of further research.

### 3 THE ANALYTIC FRAMEWORK

In this thesis cost-effectiveness<sup>1</sup> is analysed. The analytic strategy is modelling; deterministic model analysis was used in Papers I–III and probabilistic analysis in Paper IV (Table 1). Paper II represents a cost-minimization analysis where modelling and data collection alongside a clinical trial are combined.

**Table 1.** Summary of the form of economic evaluation and the analytic strategies used in the papers

<b>Economic evaluation</b>	<b>Paper I</b>	<b>Paper II</b>	<b>Paper III</b>	<b>Paper IV</b>
Form	Cost-effectiveness	Cost-minimization	Cost-effectiveness	Expected value of perfect information*
Analytic strategy	Deterministic model	Deterministic model and clinical trial	Deterministic model	Probabilistic model

\* The expected value of perfect information is based on the cost-effectiveness analysis.

This chapter presents the principles of cost-effectiveness analysis and the analytic methods used.

1. Cost-effectiveness analysis (Papers I–III)
2. Construction of decision analytic models (Papers I–IV)
  - a. Deterministic model (Papers I–III)
  - b. Probabilistic model (Paper IV)
3. Estimation of the value of further research by calculating the expected value of perfect information (Paper IV)

#### 3.1 COST-EFFECTIVENESS ANALYSIS

As noted previously, cost-effectiveness analysis is one form of health economic evaluation.

##### 3.1.1 Costs

Costs in this thesis refer to resources used in the health care. The cost analysis has the following steps. First, the relevant range of cost items is identified, then the use of resources is quantified (measured or estimated), and finally, the evaluation by monetary terms, that is, by assignment of prices.

###### 3.1.1.1 Cost items

The cost items in this thesis include costs of personal care, technical equipment; medical devices, drugs, and hospital stay (postoperative care unit, intensive care unit, and general ward).

###### 3.1.1.2 Quantification of the resources used

For the procedures of postoperative pain treatment (Papers I–II) and of haemodynamic optimization (Papers III and IV) the time devoted to the particular activities, and the number of medical devices and quantity of drugs used were measured in the clinical practice. The length

<sup>1</sup> In this thesis the term cost-effectiveness analysis is used also when quality-adjusted life-years are used as outcome measure.



of stay on the intensive care unit (Paper II) and on the general ward (Papers III and IV) was measured by individual data collection alongside clinical trials. In Paper II nursing workload on the intensive care unit (ICU) was measured by nursing scores alongside a clinical trial.

### 3.1.1.3 *How prices were assigned*

The price per hour per person was obtained from the hospital Accounting Department; the prices of technical equipment, medical devices, and drugs were obtained from the hospital pharmacy and Accounting Department. The price per hospital bed-days and per nursing score was established by the hospital Accounting Department.

## 3.1.2 The measure of effect

In cost-effectiveness analysis both clinical measures and measures of health can be used.<sup>41</sup>

### 3.1.2.1 *Number of pain-free days*

In the cost-effectiveness analysis of postoperative pain treatment (Paper I) the number of pain-free days was used as the primary clinical outcome. The pain was measured as pain intensity on a visual analogue scale (VAS 1–100 mm), both at rest and during activity throughout a whole day. The measure of effect was 3 if the patient had 3 pain-free days, 2 in the case of 2 pain-free days, 1 in the case of 1 pain-free day, and 0 if the patient did not experience VAS  $\leq 30$  at all.

### 3.1.2.2 *Quality-adjusted life-years*

In the studies on haemodynamic optimization (Papers III and IV) quality-adjusted life-years are used as health outcome. The advantage of QALYs is that comparisons of cost-effectiveness can be made across disease areas. In the Appendix a detailed description of QALYs is given. The QALY combines the quality and quantity of life in a single measure. QALYs are calculated by quality adjustment weights (QALY weights), where 0 represents dead and 1.0 represents full health, multiplied by the time spent in the actual health state.

## 3.1.3 Incremental cost-effectiveness ratio

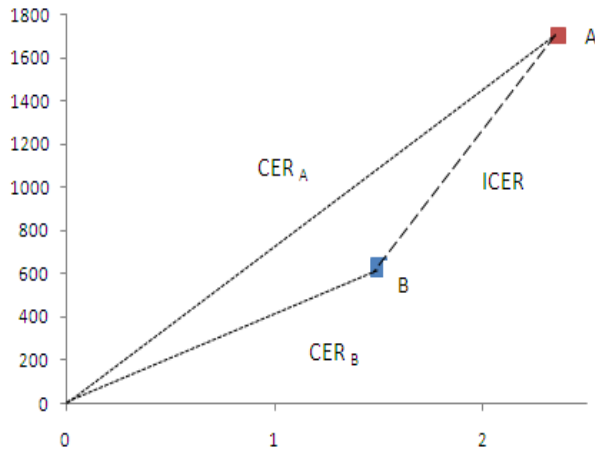
The result of the cost-effectiveness analysis is expressed as the incremental cost-effectiveness ratio (Papers I and III). First the cost-effectiveness ratio (CER) is calculated, that is, the mean cost of reaching a particular outcome.

$$CER = \frac{Cost}{Effect}$$

When a decision has to be made whether to replace a treatment with a more expensive and more effective treatment, an estimate of the additional resources needed to obtain the additional effect is expressed as the incremental cost-effectiveness ratio (ICER):

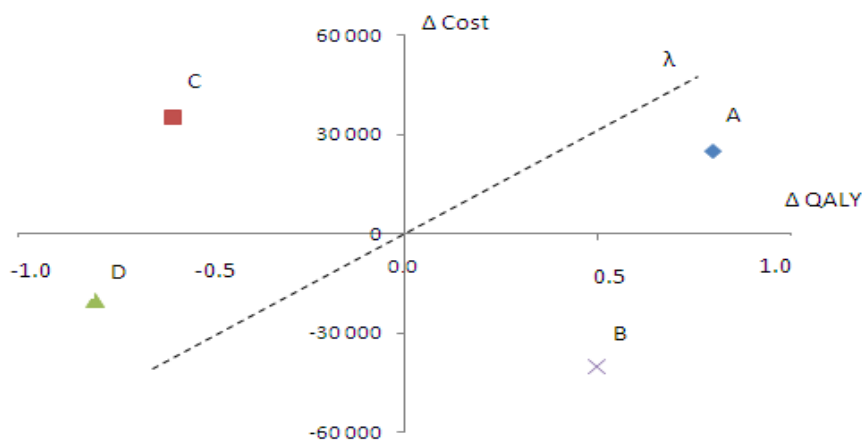
$$ICER = \frac{(Cost_A - Cost_B)}{(Effect_A - Effect_B)} = \frac{\Delta C}{\Delta E}$$

where  $\Delta C$  is the difference between costs and  $\Delta E$  is the difference between effects of two alternatives (A and B). The interpretation of the ICER is demonstrated in Fig. 1.



**Fig. 1.** Illustration of cost-effectiveness ratio (CER) and incremental cost-effectiveness ratio (ICER). The slopes of the dotted lines from origin represent the CERs of treatments A and B and the slope of the dotted line between A and B is the ICER. This is the estimate of the additional resources that would have to be used to obtain the additional effect.

In Fig. 2 the cost-effectiveness plane is illustrated, where the incremental costs (vertical axis) are plotted against the incremental effects (horizontal axis) of four hypothetical treatments (A to D) when compared to relevant alternatives. Treatment B is dominant; it is less costly and better than the comparator (negative  $\Delta C$ , positive  $\Delta E$ ), and ICER calculation is not required. Treatment C is more costly and less effective (negative  $\Delta C$  and  $\Delta E$ ); it is not cost-effective. For treatments A and D the ICER calculation is needed, and it has to be related to the threshold value that society is willing to pay per one additional year with full health, denoted  $\lambda$  (the slope of the dotted line, also called the cost-effectiveness threshold). In Sweden there is no fixed value or official range of willingness to pay; Paper IV refers to a cost range of €20 000–50 000. The treatments below the dotted line are cost-effective, while those above and to the left of the line are cost-ineffective (Treatments C and D).



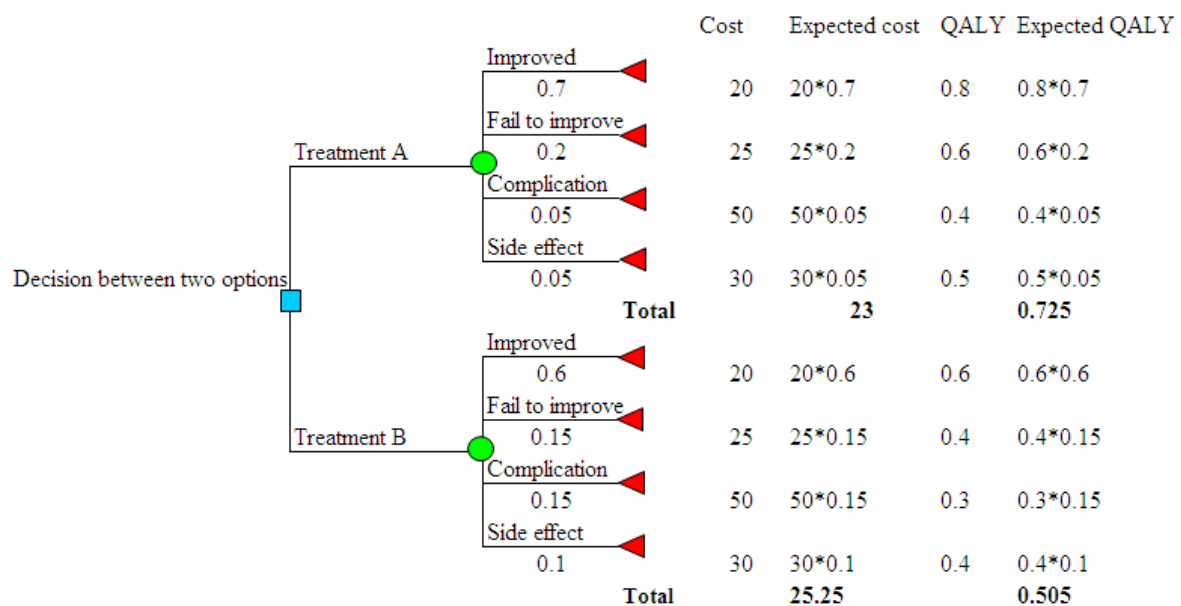
**Fig. 2.** Illustration of the cost-effectiveness plane with the threshold value of what the society is willing to pay for one additional year with full health ( $\lambda$ , the slope of the dotted line).

### 3.2 CONSTRUCTION OF A MODEL

The purpose of modelling is to illustrate the course of events following a decision between alternative options. Two types of models are used in this thesis, the decision tree and the Markov structure.<sup>42</sup> The development of a model requires specification of the decision problem, definition of the model structure, of the time horizon, and the boundaries of the model, and identification of the available evidence. These steps are detailed in Papers I–III, and further details on Papers III–IV are given in the Appendix. Below a brief description and examples of the model structures are given.

#### 3.2.1 Decision tree

A decision tree is constructed in all Papers (Fig. 3). It starts with the decision represented by a rectangle between the two alternatives followed by a circle (a chance node) where alternative events are possible; these are illustrated by branches coming out from chance node, representing the clinical pathways. At the ends of the branches are end nodes (triangles) representing outcomes. The pathways are mutually exclusive and are characterized by the probabilities; the sum of probabilities following each node is 1.0. Each pathway is associated with health care costs and an outcome. The expected costs and effects are based on the summation of pathway values weighted by the pathway probabilities. The calculation is illustrated in Fig. 3.

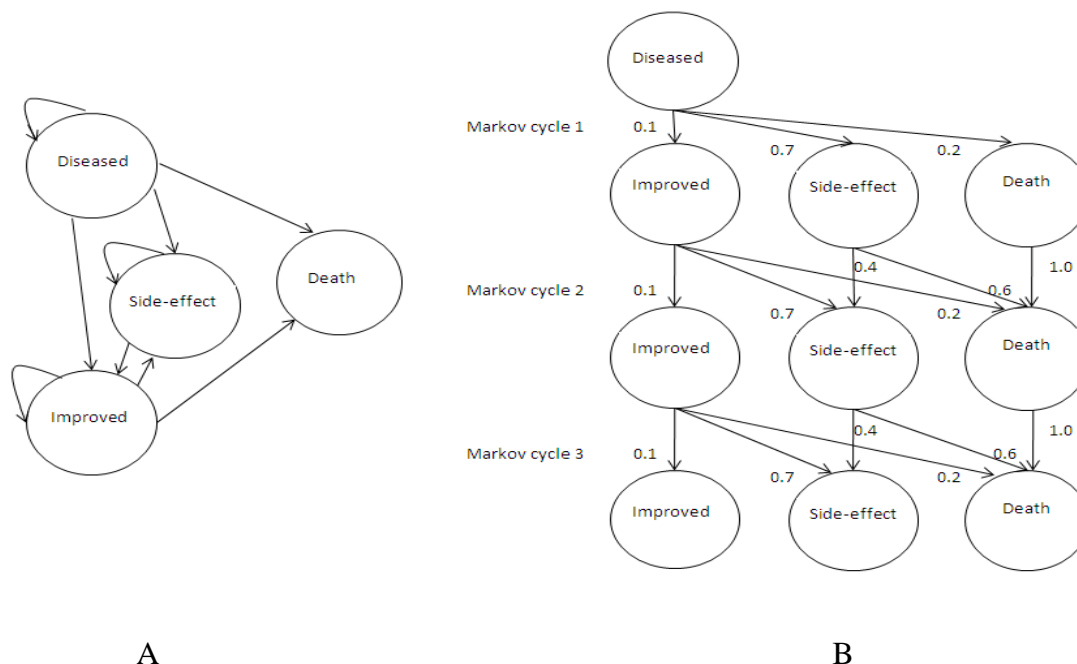


**Fig. 3.** Example of a decision tree. The values in this decision tree are only to demonstrate how the costs and effects are calculated.

#### 3.2.2 Markov structure

The Markov structure is used in Papers III–IV. A simple form is illustrated in Fig 4A. It allows more complexity and a longer time horizon compared with the decision tree. In Papers III–IV a 10-year period was used; such a long simulation by a decision tree would require a large number of branches, which is difficult to handle and visualize. The circles in the Markov structure

represent health states associated with clinical outcomes. The arrows show possible transitions through the model during a Markov cycle and are characterized by probabilities.



**Fig. 4. A.** Illustration of a Markov structure.

**B:** The principle of how to apply the probabilities in each Markov cycle.

As with the decision tree, the likelihood of each consequence is expressed as a probability and each consequence has a cost (C) and a health outcome/effect (E). These are allocated in the model where they occur. How the probabilities are used in a Markov structure is illustrated in Fig. 4B. During intervals of equal length (referred to as the Markov cycle) the individuals make transitions from one health state to another by the determined probability of transition. The cycles can be repeatedly applied and the expected costs and outcomes are accumulated at the end of the simulation.

In deterministic analyses point estimates are used (mean values or other estimates), and in probabilistic analyses probability distributions are defined in both model structures.

### 3.2.3 Handling uncertainty

All cost-effectiveness analyses are associated with uncertainty, as costs and effects can never be predicted with complete precision. Paper II is a combined analysis using both model and collected individual data alongside a clinical trial. The uncertainty of costs is handled by t-test. In Papers I and III the term *data uncertainty* is used; such uncertainty is handled by sensitivity analyses in order to investigate the influence of these parameters on the results (Papers I and III). The steps of the sensitivity analysis are i) to identify the most relevant uncertain parameters and ii) to specify a plausible range of the parameters that are tested. One-way sensitivity analyses are used, that is when the estimates of each uncertain parameter of interest are varied one at a time. The data uncertainty has different sources. First, in early cost-effectiveness analyses of unproven new interventions with lack of clinical data, estimates based on empirical or theoretical knowledge can be used (Paper III). Second, imprecise data may be available, as for example, when price lists are used as estimates of the hospital costs (Papers I and III). Third, methodological controversy may be incorporated into the model; one example is the use of pain intensity at rest as outcome; it can be discussed whether the most valid

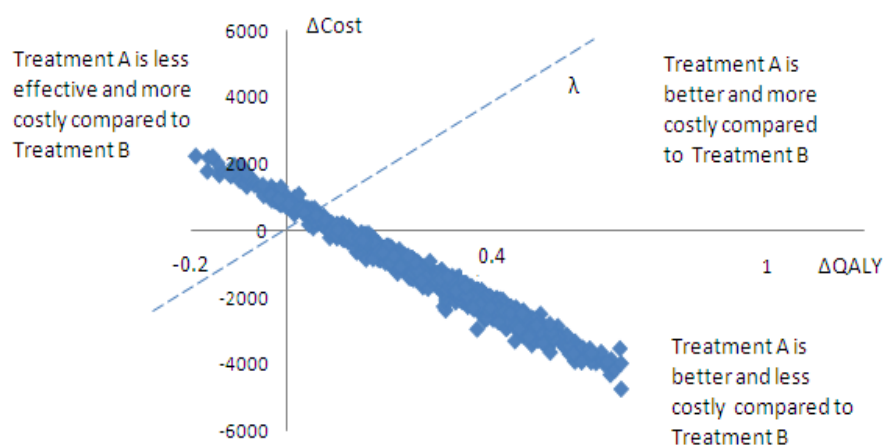
measure of pain is obtained at rest or during activity (Paper I). Last, the input parameters may characterize specific clinical settings and the generalizability of the results may be explored by adjusting these parameters (Paper I).

The term *data uncertainty* has to be distinguished from term *parameter uncertainty*, used in Paper IV. The term *parameter uncertainty* in modelling is related to the definite value that can be known with a certain precision for a particular population, and where more precision can be achieved by increasing the number of observations. It does not cover heterogeneity and variability. The heterogeneity relates to differences between patients that can be explained by age, sex, or comorbidity. Variability is the natural variation between individuals, even if they have the same observed characteristics, and it cannot be reduced by increasing the number of observations.

The parameter uncertainty is defined by probability distributions according to recommendations.<sup>42</sup> Beta distribution is constrained on the interval 0–1 and is appropriate to define the distribution of QALY weights. Dirichlet distribution is a multivariate generalization of beta distribution and is used to define the uncertainty of mutually exclusive events, which means that the sum of probabilities is always 1.0. It is used for the transition probabilities. Gamma distribution is constrained on the interval 0 to positive infinity and is used to represent the uncertainty of cost data that are usually highly skewed. Lognormal distributions are appropriate to define the relative risk, because the relative risk is made up of ratios and the most natural way to handle the ratios is to transform these into a log form.

### **3.3 ESTIMATION OF THE VALUE OF FURTHER RESEARCH**

The probabilistic model is a suitable framework to handle the uncertainty, as the input parameters are characterized by appropriate probability distributions. For the analysis a Monte Carlo simulation is used where the values of the input parameters are randomly drawn from the defined probability distributions 1000 times, generating 1000 estimates of costs and health outcomes in terms of QALYs (Paper IV). In Fig. 5 simulated incremental costs and effects in QALYs are illustrated when Treatment A is compared to B. The uncertainty of input parameters is propagated into output uncertainty. For the majority of the simulations Treatment A is better and less costly (lower right quadrant). If Treatment A were adopted, this decision would be uncertain because of the risk of taking ‘wrong decision’. The ‘wrong decision’ is the upper left quadrant in Fig. 5 and also those values in the upper right quadrant that are above the dotted line ( $\lambda$ ) representing the cost-effectiveness threshold. The decision uncertainty is determined by the combined uncertainty of the model inputs. The probability of a wrong decision is quantified and the consequences of ‘making a wrong decision’ are expressed as a monetary value.



**Fig. 5.** The difference of costs ( $\Delta\text{Costs} = \text{Cost}_A - \text{Cost}_B$ ) are plotted against the difference of effects ( $\Delta\text{QALY} = \text{QALY}_A - \text{QALY}_B$ ). For most of the model outputs Treatment A is better and less costly (lower right quadrant), for some it is better and more costly (upper right quadrant), and for others it is less effective and more costly compared to Treatment B (upper left quadrant). The slope of dotted line is the cost-effectiveness threshold.

### 3.3.1.1 Calculation of the net benefit and incremental net benefit

For each of the 1000 simulations the net benefit (NB) is calculated by:

$$\text{NB} = \lambda * E - C$$

Where  $\lambda$  is the cost-effectiveness threshold; E is the effect (measured by QALYs), and C is the cost of the treatment.

The monetary value of making the ‘correct decision’ between Treatments A and B is calculated by the incremental net benefit (INB) using the following equation:

$$\text{INB} = \lambda * (\text{Effect}_A - \text{Effect}_B) - (\text{Cost}_A - \text{Cost}_B) = \lambda * \Delta E - \Delta C$$

When the value of INB is  $>0$ , Treatment A is the ‘correct decision’.

### 3.3.1.2 Calculation of the expected value of perfect information

The principles of the expected value of perfect information (EVPI) calculation are illustrated by the first five values of net benefits of a Monte Carlo simulation for Treatments A and B (Table 2, columns 2 and 3). Based on the mean results, the ‘correct overall decision’ is to choose Treatment A, has the highest *mean NB* (€7000 vs. €6520). The *mean incremental NB* (column 4) is the benefit if Treatment A is chosen instead of Treatment B (€480). However, this decision is ‘wrong’ in simulations 2 and 5, where Treatment B should be preferred. If perfect information were available, the net benefits for each simulation would be known and the wrong decision could be avoided. The improved values of NB given perfect information are averaged (€7120, column 5) and the gained benefit of the perfect decisions (€120, column 6) is the EVPI. The EVPI is the mean net benefit given the perfect information (column 5) minus the mean net benefit of the preferred treatment given the current information (column 2).

**Table 2.** Example from the Monte Carlo simulation illustrating the net benefit, incremental net benefit, net benefit with perfect information and gained benefit with perfect information (the expected value of perfect information, EVPI) for treatments A and B

Column 1	2	3	4	5	6
Simulation	Net benefit of Treatment		Incremental net benefit A vs. B	Net benefit with perfect information	Gained net benefit with perfect information
	A	B			
1	7000	6000	1000	7000	0
2	6000	6500	-500	6500	500
3	7800	6800	1000	7800	0
4	7600	6600	1000	7600	0
5	6600	6700	-100	6700	100
Mean	7000	6520	480	7120	120
	<b>MAX mean NB A vs. B</b>			<b>MEAN max NB A vs. B</b>	<b>EVPI Column 5–Column 2</b>

The mean net benefit for both strategies is calculated by the model using the 1000 simulated values of costs and outcomes. The maximum values of net benefit are taken from each simulation and the mean value of these is calculated (Table 2; column 5: net benefit with perfect information).

$$EVPI = \text{MEAN max NB (A vs. B)} - \text{MAX mean NB (A vs. B)}$$

The MEAN max NB (A vs. B) is the situation of perfect information, column 5. The MAX mean NB (A vs. B) is the situation with the given current ‘imperfect’ information, column 2. The EVPI provides the value of perfect information for each time as a whole when a decision has to be made for an individual patient. However the EVPI is available also to inform the management of all future patients, or of a certain population who stand to benefit from additional information over the expected lifetime of the treatment. Therefore, the so-called effective population has to be estimated, that is, the number of patients facing this decision uncertainty during a chosen time period (applying also a discount rate). The population EVPI is calculated by multiplying the EVPI by the effective population:

$$\text{Population EVPI} = EVPI_{\text{patient}} * \text{Effective population}$$

The EVPI can be interpreted as the maximum monetary value of further research.

## 4 STUDIES ON POSTOPERATIVE PAIN TREATMENT

This chapter introduces the first two studies, which are an application of deterministic analytic modelling that represents the early phase of learning in health economic evaluation. The methods and results are presented separately, followed by a merged discussion and conclusion. Full details on model structure, data identification, and data incorporation are found in the two papers (Papers I and II), and further details on Paper I in a published report.<sup>1</sup>

### 4.1 PAPER I. EVALUATION OF COSTS AND EFFECTS OF EPIDURAL ANALGESIA AND PATIENT-CONTROLLED INTRAVENOUS ANALGESIA AFTER MAJOR ABDOMINAL SURGERY

Good postoperative pain treatment is a mandatory component of adequate postoperative care, particularly if accelerated recovery is an aim.<sup>43-45</sup> The postoperative epidural analgesia (EDA) and patient-controlled intravenous analgesia (PCIA) were introduced in 1997 for major abdominal surgery at the University Hospital in Linköping (Sweden) and a local database was started for quality control. The first assessment of the effectiveness of EDA (1997–1999) confirmed the failure rate found by others.<sup>21-23</sup> For 10 per cent of patients the epidural analgesia was unexpectedly discontinued because of technical problems, minor side effects, or insufficient pain relief. This clinical problem affects a large number of patients treated for postoperative pain in Sweden.

#### 4.1.1 Aims

The primary aim is to analyse the cost-effectiveness of epidural analgesia compared with patient-controlled intravenous analgesia. A secondary aim is to assist the clinical choice between these two options, as according to the guidelines of the Swedish Society of Anaesthesiology, both methods are established alternatives following major surgery.

#### 4.1.2 Methods

A decision analytic model on cost-effectiveness was developed to illustrate the clinical pathways for comparing EDA and PCIA. The cost-effectiveness is expressed by the incremental cost-effectiveness ratio, as outlined in Chapter 3.2. All costs were in 2005 prices and were converted to euros using the exchange rate 1 euro = 9 SEK. The model was programmed and analyzed using Microsoft Excel (Microsoft Corporation 1985–2001, version 10.0.6856.0).

The main data source was a local register of 644 consecutive patients treated with EDA (n = 602) or PCIA (n = 42) following major abdominal surgery. The compared alternative strategies were thoracic epidural analgesia (ropivacaine 2 mg ml<sup>-1</sup> with morphine 0.03 mg ml<sup>-1</sup> by a constant volume pressure infuser at a rate of 5.5 ml/h) and patient-controlled intravenous analgesia (morphine 5 mg ml<sup>-1</sup> by individually programmed pump). In the actual clinical settings the length of postoperative observation on the postoperative care unit/intensive care unit (PCU/ICU) was 12 hours for EDA and 3–4 hours for PCIA.

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<sup>1</sup> Postoperativ smärtlindring - till vilket pris? En hälsoekonomisk modellanalys av två smärtlindringmetoder. CMT rapport 2006:1: <http://iu.diva-portal.org/smash/record.jsf?searchId=1&pid=diva2:254680>.



The structure of the decision tree is shown in detail in Fig.2 (in Paper I); it illustrates the clinical pathways of completed treatment, change of treatment strategy, unsuccessful attempt to introduce epidural catheter, early dislocation of catheter, reinsertion of epidural catheter, and need for additional pain treatment. The probabilities of the selected pathways were extracted from the database. The measure of effect was the number of pain-free days at rest; the costs of human resources, medical devices, drugs, and postoperative care were quantified. The expected costs and effects were analysed using the decision tree, as described in Chapter 3. One-way sensitivity analyses were performed to handle the following data uncertainties: fixed price of the length of stay on PCU/ICU, the better analgesic effect of EDA over PCIA during activity, the technical failure of EDA that might characterize only the actual clinical settings, and the potential bias of a non-randomized data source. The influence of technical failure of EDA was tested by the ‘optimal scenario’ analysis, where the probabilities for catheter dislocation, unsuccessful attempt, reinsertion of catheter, and change of treatment due to analgesic failure were reduced. The possible bias related to the non-randomized data was tested by a matching procedure: each PCIA patient was matched in a pair with one EDA patient, using first the age and type of surgical intervention and then the gender and ASA group (the five-category physical status classification adopted by the American Society of Anaesthesiologists).

### 4.1.3 Results

In the base case analysis the incremental effect (EDA vs. PCIA) is 0.19 pain-free days at rest, the expected incremental cost is €1 074. The cost per pain-free day at rest is €721/patient for EDA and €289/patient for PCIA; the ICER at rest is €5 653 (Table 3). The probability of achieving 3 pain-free days without any additional pain treatment and without any technical problem is 0.49 at rest and 0.41 during activity for EDA. The corresponding values for PCIA group are 0.56 at rest and 0.28 during activity (these values can be found in the decision tree in Fig.2 in Paper I).

**Table 3.** The expected number of pain-free days (rest and activity) and the costs of postoperative epidural analgesia and patient-controlled intravenous morphine analgesia. The incremental effect, cost, cost-effectiveness ratio (CER), and incremental cost-effectiveness ratio (ICER) are calculated as described in Chapter 3

	Cost/patient €	Effect Number of pain-free days		CER*
		Rest	Activity	Cost/pain-free day/patient €
EDA	1701	2.36	1.86	721
PCIA	627	2.17	1.27	289
Incremental EDA/PCIA*	1074	0.19	0.59	5653 (ICER)

\* For base-case analysis incremental effect at rest is used.

The sensitivity analyses confirm that PCIA is the cost-effective alternative, even if the ICER is sensitive for some changes in the input parameters, and it varied between €1448–€4308 (Table 4).

**Table 4.** Sensitivity analysis is performed to estimate the influence of uncertain items on the incremental cost-effectiveness ratio (ICER). The model was run using the lowest price of stay on the postoperative care unit (PCU), the higher incremental effect of epidural analgesia (EDA) over patient-controlled intravenous analgesia (PCIA) during activity, an optimized scenario, and a matching procedure.

	<b>Base case</b>	<b>Lowest price of PCU</b>	<b>Pain at activity</b>	<b>Scenario analysis</b>	<b>Matching procedure</b>
Cost/patient for EDA	1701	992	1701	1666	1704
Number of pain-free days	2.36	2.36	1.86	2.56	2.42
Effect <sub>EDA</sub> – Effect <sub>PCIA</sub>	0.19	0.19	0.59	0.39	0.25
ICER	5653	1448	1896	2664	4308

## 4.2 PAPER II: COULD BENEFITS OF EPIDURAL ANALGESIA FOLLOWING THORACOABDOMINAL OESOPHAGECTOMY BE MEASURED BY PERCEIVED PERIOPERATIVE PATIENT WORKLOAD?

Even if the postoperative epidural analgesia has poor cost-effectiveness, even if there is no evidence of benefit expressed by clinical or patient-oriented outcome in general surgical patients,<sup>10,20</sup> and even if the statistically significant lower pain scores compared with intravenous analgesia do not reach a clinically appreciable superiority,<sup>6,20</sup> the epidural analgesia is regarded as the gold standard. These facts induced the hypothesis of Paper II, namely, if ordinary measures of outcome cannot capture the benefits that give epidural analgesia its status as the gold standard, probably the caregiver experience, for example, nursing workload during the care of the patient, could affirm the supposed superiority.

### 4.2.1 Aims

The aim is to analyse whether the postoperative epidural analgesia may decrease the nursing workload and hence the costs of postoperative care. The hypothesis is that due to superior efficacy of EDA compared with intravenous analgesia influences the perceived perioperative workload following thoracoabdominal oesophagectomy.

### 4.2.2 Methods

This was a cost minimization analysis (Chapter 3). The costs were based on 2005 health care prices; the equivalent value of one euro was assigned nine SEK.

The population of a published trial (n = 201) on patient-controlled epidural (n = 166) and patient-controlled intravenous analgesia (n = 35) following thoracoabdominal oesophagectomy was selected for this analysis. The trial was conducted at the University Hospital of Lund,<sup>46</sup> and a standard clinical pathway was used: the patients were postoperatively treated on the ICU. The ICU costs incorporate the length of ICU stay and scores using the Nursing Care Recording System,<sup>47</sup> This scoring system measures the nursing workload associated with patient care and medical procedures.

The compared strategies were patient-controlled epidural analgesia (PCEA: bupivacaine 2.5 mg ml<sup>-1</sup> and morphine 0.05 mg ml<sup>-1</sup>, at a rate of 1–5 ml/h<sup>-1</sup>; bolus doses of 1–5 ml, lockout interval of 30 minutes) and patient-controlled intravenous analgesia (PCIA: morphine infusion of 1–2 mg/h<sup>-1</sup> and 0.5–2 mg bolus doses with a lockout interval of 10 minutes). The treatments were not randomly allocated, the choice was based on individual prerequisites with the primary

aim to use PCEA; both treatments were planned to run for 6 days and a standardized clinical pathway was used.

Two strategies were used to analyse the costs: i) a decision tree model was used for the pain treatment procedures; ii) individual postoperative ICU costs were collected and analysed. The ICU costs were recorded and calculated by the Accounting Department in real time, but were extracted retrospectively for this analysis. The null hypothesis was tested by t-test.

### 4.2.3 Results

For the cost analysis, data on 132 patients are complete; the patient characteristics are similar in the two groups with the exception of a previous history of angina (Table 5). No differences in morbidity, time on ventilator, or ICU stay are found between the two groups (Table 6).

**Table 5.** Patient characteristics for patient-controlled epidural analgesia (PCEA) and patient-controlled intravenous analgesia (PCIA), given as percentage (%) and number (n) when not stated otherwise. The data are extracted from the study of Rudin and colleagues. There are no significant differences found between the groups.

Patient characteristics	PCEA	PCIA
	n = 110 % (n)	n = 22 % (n)
Age in years, mean (range)	64 (10)	64 (11)
Female	26 (29)	42 (9)
Male	74 (81)	58 (12)
ASA I	29 (32)	14 (3)
ASA II	57 (63)	72 (16)
ASA III	14 (15)	14 (3)
Previous MI	6 (7)	5 (1)
Previous CHF	6 (7)	0 (0)
Previous angina	5 (5)	18 (4)
Previous COPD	7 (8)	5 (1)
Diabetes mellitus	9 (10)	0 (0)

MI: previous myocardial infarction, CHF: chronic heart failure, COPD: chronic obstructive pulmonary disease

The estimated cost of pain treatment is €1 037 for PCEA and €410 for PCIA (Table 6). Patients given intravenous analgesia have a tendency to use more intensive care resources, representing a difference of €2350/patient (p = 0.33).

**Table 6.** Postoperative data, the cost of pain treatment, and intensive care unit cost/patient (euros).

Postoperative data	PCEA	PCIA	p-value
	n = 110	n = 22	
Postoperative respiratory complication	0.17	0.27	0.27
Postoperative cardiovascular complication	0.09	0.18	0.21
Postoperative intubation time, h	12.5	11.7	0.58
Length of stay on the ICU, h (range)	30 (13–169)	28 (12–377)	0.73
Cost of pain treatment	1 037	410	n.a.*
Cost of ICU	5 571	7 921	0.33

ICU: intensive care unit. \* costs of pain treatment are expected cost per patient, are not sampled but deterministic data, calculated by a model analysis and T-test is not appropriate

### **4.3 DISCUSSION OF PAPERS I-II**

The main results are summarized as follows:

1. The estimated cost of epidural analgesia is approximately 3 times higher than intravenous analgesia, independent of which kind of delivery system is used: fixed rate pressure-volume device (Paper I) or patient-controlled pump (Paper II).
2. One additional pain-free day costs €5 653 if epidural is compared with intravenous analgesia (Paper I).
3. High-risk surgical patients treated by epidural analgesia have a tendency to use slightly less postoperative intensive care resources compared with intravenous analgesia, though no difference is found in the length of ICU stay (Paper II).

#### **4.3.1 The strengths of Papers I-II**

In the field of postoperative pain treatment no cost-effectiveness analysis was found in the literature that satisfies the requirements of a health economic evaluation. The most central tenet of evidence-based medicine is that the highest degree of evidence is extracted from randomized clinical trials. Using a decision tree, information in a clinical database is refined.

1. The limited clinical effectiveness of EDA becomes prominent in the decision tree; this disadvantage of EDA is not reported in the randomized clinical trials.
2. The uncertainty of data due to the non-randomized data source is handled by sensitivity analyses in the model.
3. The consequences of the limited clinical effectiveness of EDA are quantified by the expected costs per pain-free day, placing the epidural behind the intravenous analgesia in a health economic context.

Paper II situates the postoperative use of resources in the Swedish context. The selected population is suitable to assess the postoperative ICU costs, because no fixed prices are used. The lack of lower health care costs (based on t-test) is in line with findings of others.<sup>13-16</sup> However, it is a matter of interpretation whether the tendency to lower ICU costs using epidural analgesia is relevant or not. If the analysis addresses information on budget needs, the incremental cost of €2 350 Euros per patient (PCEA vs. PCIA) may become relevant if it considers a large number of high-risk surgical patients in Sweden.

#### **4.3.2 The limitations of Papers I-II**

The main limitations of both Papers are related to the use of non-randomized data sources, and these are discussed in detail in the Papers. Below, three further limitations are considered.

1. The use of number of pain-free days as a measure of effect does not describe the patient's health, which is required for health economic evaluations. However, the use of any health outcome and the calculation of QALYs would be inappropriate, as the decision tree illustrates short-term consequences of treatment. This shortcoming prevents the comparison of the ICER across other diseases, and it cannot be related to the willingness to pay.
2. It can be questioned whether the nursing workload could be transformed into ICU costs. The ICU costs are based on both nursing scores and length of ICU stay, but the latter may be influenced by attitudes instead of medical fitness, and therefore may shadow the impact of nursing scores on the ICU costs. Regardless of this drawback, the postoperative ICU

cost is a relevant measure, because reduced ICU costs are expected, especially for high-risk patients.

3. A methodological limitation is that deterministic analyses are used instead of a probabilistic approach. Paper I is the first one of four studies on applying decision-analytic models in perioperative care, and the most fundamental analytic strategy was tested first.

The robustness of the cost-effectiveness (Paper I) and of the cost analysis (Paper II) is not influenced by these limitations, and the higher costs of epidural analgesia are in line with others findings.<sup>13-16,22,48,49</sup>

### **4.3.3 Implications for policy decisions**

Usually policy decisions at the clinical level are based on the evidence of efficacy.<sup>50</sup> The presented analyses are aimed to assist clinical policy decisions by providing additional information on clinical effectiveness, cost-effectiveness, and the use of postoperative resources.

In Sweden the patients have the right to choose a more expensive treatment if it is more effective. However, it could be debated whether the additional cost of €5 653 for pain-free days gained is reasonable when the cost of €55 000 per one life-year gained with full health is a concern for other interventions in Sweden. Another question for the clinical decision is who will suffer because of the lack of resources. The clinical budget is usually strained, and the allocation of human resources to ensure epidural analgesia for all kinds of major surgery may be challenged if the same resources could be used for other activities that are supported by evidence for improving the postoperative outcome.

The present studies indicate that under clinical circumstances the patient-controlled intravenous analgesia is a cost-effective alternative following major abdominal surgery, and in high-risk patients (e.g. cases of thoracoabdominal oesophagoectomy), epidural analgesia may save postoperative costs. Bearing in mind that only high-risk patients following high-risk surgery may have benefit in clinical outcome from epidural analgesia, clinical pathways have to be designed to select the appropriate pain treatment strategy, also considering the optimal use of resources.

## 5 STUDIES ON HAEMODYNAMIC OPTIMIZATION

Studies III and IV are presented separately, followed by a merged discussion. In the Appendix of this thesis further details of the decision analytic model used for cost-effectiveness analysis and the value of further research on haemodynamic optimization can be found.

### 5.1 PAPER III. TIME FOR CLINICAL RESEARCH? GOAL-DIRECTED HAEMODYNAMIC TREATMENT OF ELDERLY PATIENTS WITH PROXIMAL FEMORAL FRACTURE IS PROMISING FROM A HEALTH ECONOMIC PERSPECTIVE

The poor postoperative outcome of elderly patients following proximal femoral fracture is well known. In Sweden the postoperative four-month mortality is 15 per cent for females and 20 per cent for males, and only 50 per cent of patients are discharged to their original form of housing.<sup>i</sup> There is growing evidence that perioperative fluid overload or deficit may contribute to increased postoperative morbidity and mortality.<sup>51</sup> According to meta-analyses,<sup>5,32,34</sup> a large number of trials on GDHT have been conducted on high-risk surgical patients, but only two small trials have addressed the benefit of GDHT in elderly patients following proximal femoral fracture. The current evidence for GDHT in elderly patients suggests that the length of hospital stay may be reduced, but this is not sufficient to support a decision to adopt the GDHT. Large longitudinal clinical trials are required, which address both clinical outcome and cost-effectiveness, because all GDHT strategies are resource intensive. Given the cost and complexity of such a trial, a prior cost-effectiveness analysis could be done to estimate whether the GDHT may be worthwhile for elderly patients and to guide the initiation of a large trial.

#### 5.1.1 Aims

The primary objective is to construct a decision analytic model<sup>42</sup> to estimate the cost-effectiveness of GDHT compared to traditional fluid treatment by synthesizing the currently available evidence in elderly patients before initiating a large clinical trial. The secondary objective is to direct the attention of researchers and financiers of clinical research to consider whether large, costly trials are reasonable on the elderly with proximal femoral fracture.

#### 5.1.2 Method

A two-part model was developed: a decision tree for the postoperative short-term and a Markov structure for the long-term outcome (Fig1 A and B in Paper III). The model was fed with data from published trials<sup>5,26,52</sup> and a wide range of Swedish data sources<sup>ii</sup> (national registries and hospital administration) in order to estimate costs and health outcomes over a 10-year horizon. As there was a lack of data on size of effect in elderly patients, the model was run according to prior estimates of effect size: i) first, published 'baseline' values on relative risk of mortality and morbidity were used;<sup>5</sup> ii) these were then increased stepwise between 25 and 90

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<sup>i</sup> <http://www.rikshoft.se/se/images/stories/arsrapporter/Arssrapport2008.pdf>.

<sup>ii</sup> Swedish National Register on Hip Fracture, Swedish National Stroke Registry, Swedish National Registry on Secondary Prevention in Cardiac Intensive Care (SEPHIA), Epidemiological Centre of the Swedish National Board of Health and Welfare, and the Accounting Departments of the Karolinska University Hospital, Huddinge, and of the University Hospital Lund.

per cent by taking into account the expected limited efficacy of GDHT due to age and co-morbidities of elderly patients.<sup>53</sup>

For sensitivity analyses two alternative scenarios were tested:

1. The pre- and post-fracture quality-of-life weights were obtained from the general population,<sup>54,55</sup> not from those with proximal femoral fracture, and the estimated postoperative QALYs could be overstated. For that reason the model was run by applying lower QALY weights.
2. It is unclear which approach to GDHT should be used; one alternative is to extend the treatment in the postoperative period. For this reason the model was also run using a three-fold increase of the perioperative costs of GDHT, assuming 12 hours of treatment in a postoperative care unit.

The model structure (Fig. 1 in Paper III) and the identification and incorporation of relevant data are given in Paper III, and further details in the Appendix. The model was programmed and analyzed by Microsoft Excel (Microsoft Corporation 1985–2001, version 10.0.6856.0).

### 5.1.3 Results

When the estimated relative risk for morbidity is between 0.63 to 0.926 and for mortality is between 0.49 to 0.898, the GDHT is dominant compared with the traditional fluid therapy (less costly and better) on 75 years old hypothetical individuals, applying a 10-year horizon. When the relative risk for mortality and morbidity are 0.949 and 0.963, respectively, the GDHT may still influence the outcome by 0.068 QALYs gained, resulting in a reasonable ICER of €3 162 per QALY gained (Table 7).

**Table 7.** The mean health care costs, effects, incremental costs and effects, and the incremental cost-effectiveness ratio (ICER) of goal-directed haemodynamic therapy (GDHT) and traditional fluid therapy. The model is run according to the baseline relative risk<sup>5,26</sup> and the stepwise increased values of relative risk. The ICER is not expressed when the GDHT is dominant over the traditional fluid therapy.

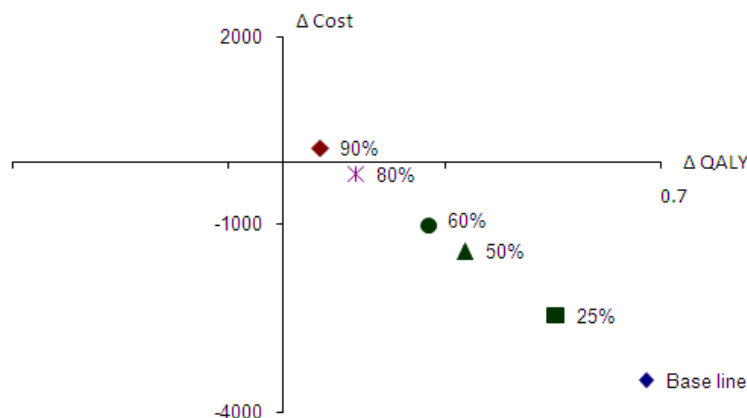
	Traditional fluid therapy	GDHT* by estimates of relative risk for morbidity/ mortality					
		Baseline 0.63/0.49	+ 25 % 0.72/0.62	+ 50 % 0.82/0.75	+ 60% 0.85/0.80	+ 80% 0.93/0.90	+ 90% 0.96/0.95
Costs €**	25 118	21 626	22 661	23 685	24 097	24 921	25 333
Effect***	4.628	5.302	5.133	4.965	4.898	4.763	4.696
ΔCost € †		-3 492	-2 457	-1 433	-1 021	-197	215
ΔEffect ††		0.674	0.505	0.337	0.270	0.135	0.068
ICER †††		dominant	dominant	dominant	dominant	dominant	3 162

\* GDHT = goal-directed haemodynamic treatment, \*\* Cost = total direct health care cost in a 10-year period,

\*\*\* Effect = QALY = quality-adjusted life-years, † ΔCost = Cost<sub>GDHT</sub> – Cost<sub>traditional</sub>,

†† ΔEffect = Effect<sub>GDHT</sub> – Effect<sub>traditional</sub>, ††† ICER = ΔCost / ΔEffect

The incremental costs are plotted against the incremental effects for all simulated values (Fig. 6).



**Fig. 6.** The result of the simulations. The incremental effects ( $\Delta$ QALY) are plotted against the incremental costs ( $\Delta$ Costs, €). The model is run according to the baseline relative risk<sup>5,26</sup> and the stepwise increased values of relative risk.

When the model is run according to a higher degree of deterioration of postoperative health, the GDHT is still dominant up to an 80 per cent increase of relative risk (Table 8). The simulation with a three-fold increase of the perioperative costs results in the dominance of the GDHT up to a 50 per cent increase of relative risk (Table 8).

**Table 8.** Results of the two scenario analyses. Incremental costs and effects and incremental cost-effectiveness ratio (ICER) when goal-directed haemodynamic therapy (GDHT) is compared to traditional fluid therapy.

	Relative Risk for morbidity/mortality					
	Baseline	+ 25%	+ 50%	+ 60%	+ 80%	+ 90%
Scenario 1*						
$\Delta$ Cost, €	-3 492	-2 457	-1 433	-1 021	-197	215
$\Delta$ QALY	0.710	0.532	0.355	0.284	0.142	0.071
ICER	dominant	dominant	dominant	dominant	dominant	3 028
Scenario 2**						
$\Delta$ Cost, €	-1 929	-885	130	542	1 366	1 777
$\Delta$ QALY	0.674	0.505	0.337	0.270	0.135	0.068
ICER	dominant	dominant	386	2 007	10 119	26 132

\* A 30% reduction of post-operative quality of life compared to what is reported in an age- and disease-matched general population from the Survey of Living Conditions in Sweden.<sup>54,55</sup>

\*\* Using a three-fold increase of cost of GDHT, assuming a 12-hour-long postoperative monitoring. QALY = quality-adjusted life-years.

## 5.2 PAPER IV. A NEW APPROACH TO INTERIM ANALYSIS OF A RANDOMIZED CLINICAL TRIAL. THE VALUE OF FURTHER RESEARCH ON GOAL-DIRECTED HAEMODYNAMIC THERAPY FOR ELDERLY PATIENTS. TRIAL NR (NCT01141894 [CLINICALTRIALS.GOV](https://clinicaltrials.gov))

The prior cost-effectiveness analysis (Paper III) has shown that the GDHT may be cost-effective within a wide range of estimated clinical effects. Both the lack of clinical outcome in



elderly patients and the predicted cost-effectiveness supported the initiation of a large clinical trial that was started in 2008. It is designed to test the hypothesis that goal-directed haemodynamic treatment will reduce postoperative complications in elderly patients (>75 years) operated on for proximal femoral fracture. A sample size of 460 was calculated. A planned interim analysis on safety and efficacy was conducted after inclusion of 100 patients. Given the interim efficacy data, further data collection is required for statistical inference analysis and a further four years of recruitment is planned with a 12-month follow-up period. The predicted cost of the trial is high, and the estimate as to whether it is reasonable to proceed with further data collection is important for economic reasons. Is the additional information to be gained by further data collection worth the extra cost? The monetary value of further research is assessed by the analysis of the expected value of perfect information.

### 5.2.1 Aim

The aim is to estimate the expected value of perfect information (EVPI) based on incremental costs and health outcomes of GDHT vs. traditional fluid therapy, given the interim data on effect.

### 5.2.2 Methods

The EVPI analysis was done by further computation of the previously developed decision analytic model (Paper III).<sup>42,56</sup> The model was updated with probability distributions for all input parameters for a probabilistic analysis. First a brief description of the clinical trial is given, and then data incorporation for the probabilistic analysis is presented.

#### 5.2.2.1 *Outline of the randomized clinical trial on GDHT*

##### Design and objectives

The study was a single-centre, open, randomized (1:1) and controlled, parallel-group superiority clinical trial, blinded for the data analyst; the length of follow-up was 12 months. Eligible patients ( $\geq 70$  years, weight  $\geq 40$  kg) were those scheduled for operation of proximal femoral fracture during regular operating hours.<sup>1</sup> The trial was approved by the Local Research Ethics Committee (ID: 2008–1240–31) and authorized by the Medical Products Agency (MPA ID; 151:2009/81083). The primary objective was to evaluate the postoperative morbidity at hospital discharge; the secondary objective was to evaluate the cost-effectiveness of GDHT vs. traditional fluid treatment.

##### Interventions

Prior to the trial a clinical programme was introduced to standardize the pre-, intra-, and postoperative supplementation of fluids and nutrition, the time between admission and operation, and the preoperative pain treatment. For both groups the lithium dilution cardiac output monitor (LiDCO, LiDCO Ltd., Sawston, Cambridge, UK) was used and spinal blockade was the preferred anaesthesia form.

##### Goal-directed haemodynamic therapy

Fluid challenge ( $3 \text{ ml/ kg}^{-1}$ ) by colloid was given and was repeated if an increase of stroke volume (SV) by 10 per cent was achieved; if there was no increase, and if the oxygen delivery (DO<sub>2</sub>I) was  $< 600 \text{ ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ , an infusion of dobutamine was started at  $0.2\text{--}10 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . The intervention was discontinued at the end of the operation.

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<sup>1</sup> Further details are given at <http://clinicaltrials.gov> (a service of the U.S. National Institutes of Health).

### The control group: traditional fluid therapy

The algorithm of the traditional fluid therapy was identical to the previously introduced clinical programme: colloids (3–500 ml) before spinal anaesthesia, other fluids or vasoactive treatment (phenylephrine or ephedrine) for correction of decreasing blood pressure were given at the discretion of the attending anaesthesiologist. The LiDCO monitor was covered for the attending anaesthesia team.

#### *5.2.2.2 The decision-analytic model and data incorporation*

The model structure was identical to that described in Paper III and in the Appendix (Fig 2. in Paper IV).

For all input parameters probability distributions were defined, with the exception of the long-term health care costs (these were based on fixed prices) and long-term survival, which was extracted from large populations with low standard error. The model was updated by the interim data on relative risk of morbidity (GDHT vs. traditional fluid therapy). The interim mortality was low ( $n = 3$ ) and could not be used in the model. Published valid mortality data in elderly patients using GDHT were not found. Therefore, point estimate of mortality was used: relative risk from high-risk patients was extracted from a recent meta-analysis (0.49),<sup>5</sup> and it was reduced by 50 per cent (0.745).

#### *5.2.2.3 The expected value of perfect information*

The model was run using a Monte Carlo simulation and the EVPI analysis was performed as described in Chapter 3. The effective population, the number of patients who face the decision uncertainty, was 30 378 patients, allowing that there are 6 440 operations per year in Sweden (patients aged >79 years), and assuming that the decision is valid for 5 years and using a 3 per cent discount per year

### **5.2.3 Results**

The patient characteristics and the interim efficacy are given in Table 9. The procedure of inclusion is demonstrated in Fig. 1 (in Paper IV).

**Table 9.** Patient characteristics and clinical outcome of the interim analysis. Values are absolute or mean  $\pm$ SD

<b>Patient characteristics</b>	<b>GDHT</b>	<b>Traditional</b>
Number allocated	49	50
Age, years (mean)	86 ( $\pm$ 7)	85 ( $\pm$ 7)
Sex male/female	13/36	9/41
American Society of Anaesthesiologists grading (1/2/3/4)	0/13/31/5	1/15/29/5
Number of patients with complications	16	20
Relative risk based on intention to treat (95% CI)	0.806 (0.464–1.397)	

CI: confidence interval

The EVPI analysis was done as described in Chapter 3. At a cost-effectiveness threshold of €50 000 the value of perfect information is €407 per patient. At a cost-effectiveness threshold of €20 000 the EVPI per patient is €229. The population EVPI is between €6.9 million and €12.4 million, applying a cost-effectiveness threshold between €20 000 and €50 000. As explained in Chapter 3 the EVPI depends not only on the uncertainty of the input parameters

but also on the willingness to pay. The relationship between the cost-effectiveness threshold ( $\lambda$ ) and net benefit (NB) is shown in Fig. 7.



**Fig. 7.** The expected value of perfect information (EVPI) for a Swedish population aged 75–84 years with proximal femoral fracture. The EVPI is plotted against the willingness to pay (cost-effectiveness threshold).

### 5.3 DISCUSSION OF PAPERS III–IV

The GDHT is predicted to be cost-effective in elderly patients within a reasonable range of estimated relative risk for mortality and morbidity. If these estimates were accepted as likely estimates, the GDHT should be adopted. However, as there is a lack of valid efficacy and safety data on GDHT in elderly patients, clinical trials are required. The absence of GDHT trials in elderly patients can be explained by the fact that the comorbidity and high age could lead to doubts as to whether anything can be gained in elderly patients: ‘Implementation of any therapy will most probably not have any effect on mortality, as only 25–60 per cent of the mortality will be potentially susceptible to the intervention’, due to the high age and comorbidities.<sup>53</sup> Both the predicted cost-effectiveness of GDHT and the need of valid data on outcome in elderly patients were used in the application for funding of a large clinical trial. The trial is now ongoing and is funded by public resources.

No published paper using the EVPI approach for interim analysis was found; however, in a broader perspective this type of analysis is increasingly used<sup>57,58</sup> and discussed.<sup>42,59,60</sup> Based on the EVPI analysis the statement that further research is required (based on efficacy) is now replaced by the statement that further research is potentially cost-effective, if the costs of the trial do not exceed the EVPI. It is important to see that the EVPI depends on the society’s willingness to pay for a treatment. When the willingness to pay is low, the treatment is not expected to be cost-effective, the society will not adopt the treatment, and therefore additional research is unlikely to change this decision; thus, the EVPI is low. When the willingness to pay increases, the EVPI also increases, because the decision uncertainty increases (probability of ‘wrong decision’) and the consequences of ‘wrong decision’ are valued more highly. Of course, there is no such thing as perfect information, but the EVPI places a first hurdle to identify research that is potentially cost-effective and rule out research that will not be

worthwhile. The EVPI analysis may complement future applications for research funding of the ongoing trial.

#### The risks of an interim analysis

Sharing results of interim analyses could influence an ongoing trial, and it is suggested that results from an interim analysis should not be made public.<sup>i,ii</sup> Further recruitment could be affected, as patients could be influenced by the preliminary efficacy data and reports of adverse events. Also, the risk of introducing bias into the ongoing trial could be substantial,<sup>iii</sup> requiring adjustments of the sample size. The statistical approach to handling this problem will be detailed when results of the trial are reported in the future. The interim efficacy data are shared for several reasons: i) the GDHT algorithm has not previously been systematically used in aged patients and neither the safety nor the efficacy aspects of it are known and ii) the recruitment time has been prolonged unpredictably, as 65 of 187 eligible patients were operated on outside of the normal operating room hours (Fig. 1 in Paper IV). This also increased the cost of the trial and it is reasonable to address the value of further research, given the results of interim analysis. The trial should be considered as a ‘feedback trial’;<sup>61</sup> the awareness of safety, efficacy, and issues of further data collection due to the sample size are more important than the issue of secrecy.

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<sup>i</sup> <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf>.

<sup>ii</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500002928.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002928.pdf).

<sup>iii</sup> <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2279143/>.

## 6 OVERVIEW OF THE STUDIES AND IMPLICATIONS

**Table 10.** Summary of the hypotheses, methods, results, and conclusions in the presented papers

	Epidural (EDA) vs. patient-controlled intravenous analgesia (PCIA)		Goal-directed haemodynamic therapy (GDHT) vs. traditional fluid treatment in elderly patients	
	Paper I	Paper II	Paper III	Paper IV
Hypothesis	EDA is not cost-effective	EDA saves ICU costs	GDHT is cost-effective; clinical trial is indicated	The value of further research is high
Data source	Clinical database	Clinical trial	National registries, published trials	Interim data from the initiated randomized clinical trial* and national registries
Time perspective	Retrospective	Retrospective	Prospective	Prospective
Type of analysis	Cost-effectiveness	Cost-minimization	Cost-effectiveness	Expected value of perfect information
Analytic strategy	Decision tree	Decision tree and clinical trial	Decision tree and Markov structure	Decision tree and Markov structure
Measure of outcome	Number of pain-free days	ICU costs	QALYs	QALYs
Results	EDA is not cost-effective	EDA does not save ICU costs	GDHT is cost-effective	EVPI is high
Conclusion	The gold standard of EDA is questioned in a health economic perspective		The prior cost-effectiveness analysis of GDHT supported the initiation of a large clinical trial.* The EVPI is high, given the interim analysis; further research is cost-effective.	

\* A randomized clinical trial on GDHT in elderly patients following proximal femoral fracture (<http://clinicaltrials.gov>). EVPI: expected value of perfect information, ICU: intensive care unit, QALY: quality-adjusted life-year

The papers in this thesis are unified by using analytic models for health economic evaluations, and in this chapter methodological aspects of using modelling are discussed.

### 6.1 METHODOLOGICAL ISSUES ON MODELLING

Clinical trials where health outcomes and costs are directly measured are considered to be the best tools for economic evaluation. This approach is applied in the ongoing randomized

clinical trial on effectiveness and cost-effectiveness of GDHT in elderly patients. The advantage of an RCT approach is the high internal validity, but the central role of an RCT in a health economic evaluation is questioned.<sup>62</sup> The strongest indication for increasing use of modelling is a method guideline in the United Kingdom<sup>i</sup> and a Swedish guideline for cardiovascular diseases.<sup>ii</sup> It is argued that any framework for economic analysis has to address two key decisions in health care. One is whether or not to adopt a new intervention given the existing evidence, and the other is whether further evidence is needed to support this decision. For such an analysis accumulation of all available evidence is required, including the extrapolation of outcomes over an appropriate horizon of time; also, the decision uncertainty has to be quantified. These requirements make a single RCT as the only data source inadequate, and a single trial should be considered as only one of many sources of evidence. In this context the ongoing clinical trial on GDHT is not sufficient for a future comprehensive cost-effectiveness analysis, because evidence outside the scope of this trial also has to be integrated. Therefore, in a future cost-effectiveness analysis of GDHT, the developed model should be used and the ongoing RCT should represent only one of the relevant data sources. Papers I and II represent another aspect of the value of modelling. The decision analytic model as a framework makes it possible to analyse a large amount of information available in clinical databases and registries. These data offer additional knowledge, especially if there is a lack of relevant information on clinical effectiveness in the literature, or when trials are controversial due to previously made clinical policy decisions, and when these decisions need to be updated.

## 6.2 THE FUTURE IMPLICATION FOR MODELLING

EVPI analysis can be done over particular model parameters separately, by calculating the *expected value of partial perfect information* (EVPPI).<sup>63</sup> The EVPPI analysis can be done, for example, over relative risk for mortality, morbidity, long-term survival, or long or short-term health outcome. With this analysis it is possible to identify which parameters contribute most to the decision uncertainty. For some input parameters the parameter uncertainty does not necessarily contribute to the decision uncertainty. If the EVPPI over parameters of interest is higher than the expected cost of the trial, further data collection is potentially cost-effective. If the EVPPI over a parameter is low, further data collection of this parameter is not cost-effective, because increasing the precision of data will not contribute to the reduction of decision uncertainty. This information can be used for revision of the trial design; for example, in a future interim analysis the model can be updated not only by the interim data on relative risk but also on health outcomes. For parameters with high EVPPI, data collection from randomized clinical trial is cost-effective, while for those with low EVPPI, data collection from cohort trials or registries can be cost-effective.

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<sup>i</sup> [http://www.nice.org.uk/niceMedia/pdf/TAP\\_Methods.pdf](http://www.nice.org.uk/niceMedia/pdf/TAP_Methods.pdf).

<sup>ii</sup> [http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/8592/2008-102-7\\_20081027\\_bilaga\\_2\\_rev1.pdf](http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/8592/2008-102-7_20081027_bilaga_2_rev1.pdf).

## 7 CONCLUSIONS

Epidural analgesia is less cost-effective compared with patient-controlled intravenous analgesia and no saving of the postoperative intensive care costs can be achieved. Therefore, the position of epidural analgesia as a gold standard for postoperative pain treatment is challenged in the context of a broader decision-making perspective.

A prior cost-effectiveness analysis of GDHT in elderly patients with proximal femoral fracture based on reasonable estimates of clinical effect shows that it may be cost-effective. This finding and the lack of valid outcome data on elderly patients supports the initiation of a large costly trial on the elderly patients.

An interim efficacy and safety analysis of the clinical trial was conducted. The efficacy analysis indicates that further data collection is required; the analysis of the expected value of perfect information indicates that further data collection will be cost-effective.

Understanding and performing health economic evaluations is beneficial for a clinician, because these evaluations are required for policy decisions in health care in a broader perspective; these evaluations can assist policy decisions on the clinical level, and furthermore, such analyses may be helpful in decisions on research funding.

## 8 APPENDIX

The Appendix provides a more comprehensive outline of the model structure, alternative fluid treatment strategies, and data collection. It describes the data incorporation for the deterministic analysis in Paper III and for the probabilistic analysis in Paper IV.

### 8.1 SHORT-TERM MODEL

#### 8.1.1 The structure of the decision tree

The decision tree represents the short-term postoperative outcome for the traditional and goal-directed haemodynamic therapy (GDHT) following proximal femoral fracture (Fig. 1A in Paper III). The time horizon is 4 months. It starts with the decision (rectangle) between the two alternatives, followed by a circle (chance node) representing a point where alternative events are possible. At this point the patients face a risk of complications of postoperative outcome. These alternative events are illustrated by branches coming out from the chance node representing the clinical pathways. The branches end at end nodes representing the selected postoperative complicated (stroke, cardiovascular or other complications, death) or uncomplicated outcome. These clinical pathways are mutually exclusive and are quantified by the probability of a particular postoperative outcome occurring at the chance node. The sum of probabilities following each node is 1.0. The clinical pathways are quantified by health care costs (C) representing the cost per complication. The selected postoperative outcomes are quantified by health-related quality-of-life weights (QALY weights).

#### 8.1.2 Short-term outcome of traditional perioperative fluid treatment

Randomized clinical trials in elderly patients with proximal femoral fracture using protocol-guided fluid optimization were searched in the literature. Two clinical trials<sup>28,64,65</sup> and one meta-analysis were found. The clinical outcome of the traditional fluid treatment group was not used because of the small sample sizes.<sup>65</sup>

Instead, postoperative outcome was extracted from the Swedish National Register on Hip Fracture on a cohort of patients (n = 402) operated on during the period 1 April 2003–31 March 2004 at the Department of Orthopaedics, Lund University Hospital, Sweden. The cohort had 100 per cent follow-up and the postoperative complications were obtained from individual hospital records, having daily visits during acute hospital stay, and a home visit at 4 months' follow-up. The cohort constituted a population of a consecutive trial on an evidence-based clinical pathway programme.<sup>52</sup> The given perioperative fluid instructions included i.v. saline-acetate 0.5 L before spinal anesthesia; the systolic blood pressure should be kept at  $>2/3$  of baseline or  $>90$  mmHg.

The cohort is considered as the best available data source to estimate the postoperative outcome of traditional fluid treatment because of the lack of a strictly guided perioperative fluid protocol and of stringent postoperative data collection. The postoperative outcome was obtained by personal communication (Hommel A, Thorngren KG).

The probability of a particular postoperative outcome is expressed by the absolute risk (AR) using the following equation:



**Table A1.** The estimates of postoperative short-term outcome (4 months) for traditional fluid treatment **following** operation on proximal femoral fracture at Lund University Hospital, Sweden, according to Hommel<sup>52</sup>

Outcome	Absolute risk	Standard error	Dirichlet distribution
No complications	0.398	0.024	(160, 242)
Cardiovascular complications	0.065	0.012	(26, 376)
Stroke	0.005	0.004	(2, 400)
Other complications	0.403	0.024	(162, 240)
Death	0.129	0.130	(52 350)
Total	1.00		

$$AR_{\text{traditional}} = n_{\text{complication}} / n_{\text{total traditional}}$$

where the  $AR_{\text{traditional}}$  is the risk for a particular complication,

$n_{\text{complication}}$  is the number of observed complications, and

$n_{\text{total traditional}}$  is the number of patients in the cohort

The number of complications was established as follows: patients with multiple complications having also stroke or cardiovascular (myocardial infarction or heart failure) complication were assigned as stroke or cardiovascular complications. No individuals had both stroke and cardiovascular complications. Patients with other complications, including pneumonia, renal failure, wound infections, deep-vein thrombosis, gastrointestinal bleeding, and confusion were assigned as other complications. The fatal outcome was assigned as death and did not contribute to any of the complications. In the deterministic analysis (Paper III) mean values of absolute risk were used. In the probabilistic analysis (Paper IV) Dirichlet distributions were defined, that is, a multivariate normalization of beta distribution that considers that the sum of probabilities of rival events is always 1.00 (Table A1).

### 8.1.3 Short-term outcome of GDHT

The predicted transition probabilities in the decision tree for the individuals treated by

GDHT are calculated by the following equation:

$$AR_{\text{GDHT}} = AR_{\text{traditional}} * RR_{\text{GDHT/traditional}}$$

where  $RR_{\text{GDHT/traditional}}$  is the relative risk of morbidity/mortality (GDHT vs. traditional fluid therapy) and

$AR_{\text{traditional}}$  is the absolute risk for traditional fluid therapy

#### 8.1.3.1 Data collection for the prior cost-effectiveness analysis (Paper III)

There are a large number of trials investigating the influence of the haemodynamic optimization of patients on the postoperative outcome. Generally, single trials are too small to find evidence on mortality; therefore, meta-analysis and systematic review articles were searched.

Only reviews and meta-analyses on the clinical use of GDHT before the onset of organ failure were searched (1997–2010). The following searching strategy was used in the PubMed database:

((("goals" [MeSH Terms] OR "goals" [All Fields] OR "goal" [All Fields]) AND directed [All Fields] AND ("haemodynamic" [All Fields] OR "hemodynamics" [MeSH Terms] OR "hemodynamics" [All Fields] OR "hemodynamic" [All Fields]) AND ("therapy" [Subheading] OR "therapy" [All Fields] OR "therapeutics" [MeSH Terms] OR "therapeutics" [All Fields])) NOT ("sepsis" [MeSH Terms] OR "sepsis" [All Fields]) NOT ("burns" [MeSH Terms] OR "burns" [All Fields] OR "burn" [All Fields]))

("fluid optimization" [All Fields]), ("oxygen delivery" [All Fields]) AND ("fluid" [All Fields]), ("fluid therapy" [All Fields])

Also, searches on author names and related articles were performed.

### Mortality

A summary of findings in meta-analyses and reviews is presented below<sup>4,5,32,34,37,38,65</sup> (Table A2). One meta-analysis on elderly patients with proximal femoral fracture was found, but the included trials were too small and mortality could not be used.<sup>65</sup> Mortality from reviews and meta-analyses based only on oesophageal Doppler technique<sup>35,36,39</sup> or dynamic haemodynamic variables needing controlled ventilation were excluded, because these technologies are not

applicable in elderly patients who are mostly anaesthetized with regional blockade techniques.

Clinical benefit can be achieved when GDHT is applied prior to the onset of organ failure<sup>32-34</sup> and if the baseline mortality is high.<sup>4,32</sup> These findings were confirmed in a more recent meta-analysis<sup>5</sup> where a subset of analyses were performed to assess the effect of

1. treatment before vs. after the onset of organ failure
2. haemodynamic goals proposed by Shoemaker<sup>40</sup> vs. other haemodynamic goals
3. methodological quality using a validated quality scoring system<sup>66</sup>

**Table A2.** The identified meta-analyses and systematic reviews on GDHT. Further details on exclusion of meta-analyses with approaches of GDHT that are not practical in elderly patients are detailed above

Author, (year), number of patients	Type of operation	Before organ failure (yes, no mixed†)	Haemodynamic goals proposed by Shoemaker	Mortality		Mortality rate of control group	Risk reduction (p-value)
				Relative risk (95% CI)	Odds ratio (95% CI)		
Boyd (1999) <sup>4</sup> n = 994	Mixed	Yes	Mixed goals		0.35 (0.23–0.53)	Mixed	
Boyd (1999) <sup>4</sup> (subset*) n = 451	Mixed	Yes	Mixed goals		0.25 (0.15–0.43)	>10%	
Boyd (1999) <sup>4</sup> (subset*) n = 543	Mixed	Yes	Mixed goals		0.88 (0.39–2.00)	<10%	
Kern (2002) <sup>34</sup> (subset*) n = 612	Mixed	Yes	Yes	Not calculated	Not calculated	>20%	-0.23 ± 0.07 (<0.05)
Kern (2002) <sup>34</sup> (subset*) n = 500	Mixed	Mixed†	Yes	Not calculated	Not calculated	<15%	-0.04 ± -0.025 (<0.05)
Boyd (2003) <sup>32</sup> n = 1974	Mixed	Yes	Mixed goals		0.45 (0.33–0.6)	Mixed	
Poeze (2005) <sup>5</sup> n = 5 733	Mixed	Mixed†	Mixed goals	0.75 (0.62–0.9)	0.61 (0.46–0.81)	Mixed	
Poeze (2005) <sup>5</sup> (subset*) n = 4 174	Mixed	Yes	Mixed	0.66 (0.54–0.81)	0.43 (0.28–0.66)	Mixed	
Poeze (2005) <sup>5</sup> (subset*) n = 1 142	Mixed	Yes	Yes	0.49 (0.36–0.65)	0.41 (0.29–0.59)	Mixed	
Poeze (2005) <sup>5</sup> (subset*) n = 3 032	Mixed	Yes	Mixed goals	0.84 (0.64–1.10)	0.83 (0.62–1.11)	Mixed	
Price (2007) <sup>65</sup> n = 130	PFF**	Yes	No		1.44 (0.45–4.62)	<10%	
Giglio (2009) <sup>38</sup> n = 3 410	Mixed	Yes	Mixed goals		Missing***		
Rahbari (2009) <sup>37</sup> (subset*) n = 288	Colorectal	Yes	Mixed		0.33 (0.03–3.17)		

\* subset: a subgroup analysis of the total number of patients included in the meta-analysis, \*\* Proximal femoral fracture, \*\*\* Major and minor gastrointestinal complications are given. † Mixed population with the use of GDHT both before and after the onset of organ failure  
CI: confidence interval.

Trials using goals other than those proposed by Shoemaker and goals applied after the onset of organ failure had no effect on mortality.<sup>5</sup> The mean score on the methodological quality assessment was 9.1, which is 51 per cent of the maximal score of 16. No correlation was found between the quality score and the odds ratio for the individual trials.

The baseline value of 0.49 for relative risk (RR) of mortality (95% CI, 0.36–0.65) was extracted from the subset of trials where GDHT described by Shoemaker was used

before the onset of organ failure. The disadvantage of the data is that the effect size may not necessarily be generalized to elderly patients.

### Morbidity

The result of the literature search is summarized in Table A3.

Two early trials<sup>28,64</sup> on elderly patients were found; both had length of hospital stay as primary endpoint. In the trial of Sinclair no data on mortality and morbidity are reported. In the trial of Venn only a tendency to

**Table A3.** The search result on trials which used GDHT before onset of the organ failure

Author (year) number of patients	Haemodynamic goals (Monitoring techniques/ use of inotropic support)	Type of operation	GDHT before onset of organ failure yes/no	Primary endpoint	Relative risk of morbidity (95% CI)	Absolute risk or incidence (%) of complications GDHT vs. Control (p)
Sinclair <sup>64</sup> (1997) n=40	Blood flow, SV, (OD)	Proximal femoral fracture	Yes	LOS	Not reported	Not reported
Wilson <sup>67</sup> (1999) n=138	Oxygen delivery index (PAC / dobutamine or adrenaline)	Major mixed	Yes	LOS	Odds: 0.30 (0.11-0.50)*	Not reported
Takala <sup>68</sup> (2000) n=412	Oxygen delivery index (PAC / dopexamine)	Major abdominal	Yes	Mortality		No difference
Lobo <sup>69</sup> (2000) n=37	Oxygen delivery index (PAC)	Major abdominal	Yes	Morbidity	RR: 0.47 (0.226-0.991)	
Gan <sup>70</sup> (2002) n=100	Blood flow, SV (OD)	Major abdominal	Yes	LOS		
Venn <sup>28</sup> (2002) n=90	CVP or blood flow, SV (OD)	Hip fracture	Yes	LOS		23% for CVP 26% for OD vs. 49% p=0.078
Conway <sup>71</sup> (2002) n=57	Blood flow, SV (OD)	Colorectal	Yes	Cardiac Output	Not reported	Not reported
Sandham <sup>72</sup> (2003) n=1994	Oxygen delivery index (PAC)	Mixed	Yes	Mortality, morbidity	No difference	No difference
Pearse <sup>26</sup> (2005) n=122	Oxygen delivery index (LiDCO)	Major mixed	Yes	Morbidity	RR: 0.63 (0.46-0.87)	
Noblett <sup>27</sup> (2005) n=108	Blood flow, SV (OD)	Colorectal	Yes	LOS		2% vs. 15% (p=0.043)
Donati <sup>29</sup> (2005) n=135	Oxygen extraction rate Arterial and central venous line	Major abdominal	Yes	Organ failure, ICU care		11.8% vs. 29.8% (p<0.005)
Wakeling <sup>73</sup> (2005) n=128	Blood flow, SV (OD)	Colorectal	Yes	LOS		37.5% vs. 59.3% (p=0.013)
Lobo <sup>74</sup> (2006) n=50	Oxygen delivery index (PAC / Dobutamine)	Major abdominal	Yes	Morbidity		16% vs. 52% (p<0.05)
Lopes <sup>75</sup> (2007) n=33	PPV (IBPplus, Dixtal)	Major abdominal	Yes	LOS		75 % vs. 45% (p=0.049)
Senagore <sup>76</sup> (2009) n=64	Blood flow, SV (OD)	Laparoscopic	Yes	LOS		No difference
Mayer <sup>77</sup> (2010) n=60	SVV (Flotrac, vigileo)	Major abdominal	Yes	LOS		20 % vs. 50% (p=0.001)
Benes <sup>31</sup> (2010) n=120	SVV (Flotrac, vigileo)	Mixed high risk	Yes	Morbidity	RR: 0.518 (0.331-0.8)	30% vs. 58.3% (p=0.0033)

CVP: central venous pressure, CI: confidence interval, ICU : intensive care unit, LOS: length of hospital stay, OD: oesophageal Doppler, PAC: pulmonary artery catheter, PPV: pulse pressure variation, SV: stroke volume, SVV: stroke volume variation  
\*Dopexamin vs. control

decreased short-term postoperative morbidity was found, which possibly could be attributed to the small population (n = 90). Data from these trials could not be extracted.

We aimed to obtain the RR of postoperative morbidity from comparable trial conditions to those that were used in the meta-analyses on mortality. A large number of trials were identified using different monitoring techniques and goals (Table A3).<sup>26-29,31,64,67-</sup>

<sup>77</sup> The criteria for selection of input data in the model were:

1. Use of a haemodynamic monitor and variables that can be applied in the clinical practice to elderly patients during spinal anaesthesia; all trials using oesophageal Doppler, or needing central venous line and/or mechanical ventilation, were excluded.
2. Primary end-point is expressed by relative risk or absolute risk and/or incidence of postoperative complications.
3. GDHT started before the onset of organ failure.

Only one trial was identified.<sup>26</sup> In this study the authors used the GDHT on the intensive care unit postoperatively.

### 8.1.3.2 *Prior estimates of mortality and morbidity (Paper III)*

The relative risk of neither mortality nor morbidity can directly be applied in the model for several reasons.

1. In the early observational trials, Shoemaker described a relationship between outcome and various cardiovascular parameters on patients following high-risk surgery. Survivors consistently had higher cardiac index (>4.5 l/min/m<sup>2</sup>), oxygen delivery (>600 ml · min<sup>-1</sup> · m<sup>-2</sup>), and oxygen

consumption (>170 ml · min<sup>-1</sup> · m<sup>-2</sup>) compared to non-survivors.<sup>40</sup> These values were chosen as cut-off points to test the hypothesis that in critical situations survivors have higher values of oxygen transport compared to non-survivors. The cut-off values have been tested in a large number of randomized trials as goals for haemodynamic optimization.

2. However, the goals are not adjusted to possible different needs as affected by age, comorbidity, level of surgical stress, and past haemodynamic deficit.<sup>34</sup> There is a lack of data on which GDHT approach may achieve any benefit in elderly patients. There are GDHT strategies using other goals than those proposed by Shoemaker. These may have lower clinical benefit.<sup>5</sup>
3. Due to the comorbidity and high age of elderly patients, only a part of the postoperative morbidity may hypothetically be influenced.<sup>53</sup>

In order not to overestimate the benefits of GDHT in elderly patients, the extracted values of RR for mortality (0.49) and morbidity (0.63) were considered as 'baseline' values and were stepwise increased by between 25 and 90 per cent, yielding hypothetical point estimates of RR in elderly patients (Table A4).

The following equation was used:

$$RR_{\text{estimate}} = RR + (1 - RR) * 0.25 \dots (* 0.50 \dots * 0.90)$$

RR<sub>estimate</sub> is the point estimate of relative risk mortality/morbidity.

RR is the relative risk of mortality/morbidity obtained from meta-analysis<sup>5</sup> and clinical trial.<sup>26</sup>

**Table A4.** The hypothetical estimates of relative risk for postoperative mortality and morbidity of goal-directed haemodynamic therapy compared to traditional fluid treatment in routine care

	Estimates of relative risk					
	Baseline	+ 25%	+ 50%	+ 60%	+ 80%	+ 90%
Morbidity	0.63	0.723	0.815	0.852	0.926	0.963
Mortality	0.49	0.618	0.745	0.796	0.898	0.949

### 8.1.3.3 Estimates of mortality and morbidity, given the interim analysis (Paper IV)

The relative risk of morbidity was obtained from the interim analysis of the ongoing randomized clinical trial (NCT01141894 [ClinicalTrials.gov](https://clinicaltrials.gov)). The number of patients was 49 in the GDHT and 50 in the traditional group. One patient in the GDHT group was assigned two randomization numbers: first the patient was excluded because of logistical reasons related to unplanned changes in the operation list and then was re-included next day. The relative risk of morbidity was based on intention to treat and calculated by the number of patients with one or more complication or fatality during the acute hospital stay. Lognormal distribution was defined (Table A5). The relative risk for mortality could not be estimated from the interim data because of the low number of observations (in-hospital fatality was three). The relative risk of mortality was estimated by 50 per cent reduction of relative risk extracted from the same meta-analysis<sup>5</sup> that was used in the prior cost-effectiveness analysis (Table A5).

### 8.1.4 Quality of life

A number of instruments have been developed to measure health-related quality of life (HRQoL), classified by either generic or disease-specific instruments. One of the generic HRQoL instruments is the EQ-5D.<sup>78</sup> This is a general quality-of-life instrument that divides health status into five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is divided into three degrees of severity: no problem, some problems, and major problems. The five health dimensions give 243 (i.e. 3<sup>5</sup>) separated health states. There are different methods of assigning value to the health states. One of them is the time trade-off, based on the valuation of a general population that assigns a single value index for each health state. Since there is no Swedish tariff the UK EQ-5D index tariff constructed in the United Kingdom was used. In the papers and the Appendix the term QALY weight is interchangeable with the EQ-5D index tariff.

In a recent Swedish survey on osteoporosis the pre-fracture quality of life was assessed after the fracture by EQ-5D on patients with

**Table A5.** Estimates of postoperative outcome expressed as relative risk of postoperative mortality and morbidity in Paper IV. The morbidity was obtained from the current clinical trial

	Relative risk mean	95% Confidence interval	Lognormal distribution
Postoperative morbidity	0.806	0.464–1.397	-0.216, 0.281
Postoperative mortality*	0.745	Point estimate	

\* The mortality was obtained from meta-analysis<sup>5</sup> on other high-risk patients and reduced by 50 percent.

**Table A6.** QALY weights and decrements used in the model with the defined distributions

QALY weights and decrements	Mean	Standard Error	Distribution
QALY weights			
Pre-fracture 70–79 years age	0.79	0.012	Beta (901, 234)
Pre-fracture >80 years age	0.74	0.021	Beta (322, 113)
Recovered after other complication	0.66	0.025	Beta (227, 117)
Decrements of QALY weights			
After cardiovascular complications	-0.19	0.011	Gamma (298, 0, 0006)
After stroke	-0.35	0.035	Gamma (100, 0, 0035)
State after other complications	-0.15	0.010	Gamma (225, 0, 0007)

QALY = quality-adjusted life-year

proximal femoral fracture (n = 283).<sup>79</sup> This could lead to some bias, since the pre-fracture health status may have been perceived as better than it actually was. The mean QALY weight was 0.81 (0.78–0.83).

In the Survey of Living Conditions in Sweden for individuals at age 70–79 years the mean QALY weight was 0.79.<sup>54</sup> The latter was chosen as the pre-fracture value in Paper III. In Paper IV, pre-fracture values for patients >80 years were used, because the mean age of the patients in the interim analysis was >80 years. As there is lack of direct QALY weights related to the selected postoperative complications, the following approach was used. Disease-related QALY weights were extracted; for individuals with cardiovascular complication or stroke, QALY weights of the general population with ischemic heart disease or stroke were used.<sup>55</sup> To estimate the influence of ‘other complications’ on health, the QALY weight of the general population with ‘moderate to severe’ health problems was used.<sup>55</sup> For individuals with fatal outcome, the QALY weight was 0.

The QALY weight is the measure of outcome in the decision tree at the actual node. This is how the decision tree provides a bridge between the postoperative complications and the health-related quality of life. For the deterministic analysis, mean values were used (Paper III); for the probabilistic analysis (Paper IV) probability distributions were used (Table A6).

### 8.1.5 The short-term costs

The costs are expressed in euros (1 euro is equivalent to 9.41 SEK).

#### 8.1.5.1 Perioperative costs

The costs of personnel, medical devices, and pharmaceuticals used for each fluid therapy were quantified.

The lithium dilution cardiac output monitor (LiDCO, LiDCO Ltd., Sawston, Cambridge, UK) was the monitor considered for GDHT. The monitor needs arterial and a peripheral venous line. The cardiac output (CO) is measured by a beat-to-beat estimate of stroke volume and CO derived from the arterial pressure waveform. It requires an initial calibration with lithium chloride (0.3 mmol/2 ml) as an indicator.

To quantify the cost of personnel, time devoted to activities that could not be used simultaneously for other activities was measured and estimated (Table A7). It includes the preoperative optimization, the intraoperative interventions, and the postoperative visit on the postoperative unit. If the GDHT continued in the post-operative period, it would consume more resources. In a scenario analysis an alternative was tested, assuming an intervention of 8 hours’ duration.

**Table A7.** Estimated time for activities for each fluid therapy that cannot be used simultaneously for other activities

Activity	Estimated time (minutes)		
	Traditional fluid	GDHT	Scenario of longer treatment for GDHT
Calibration and start of monitoring	0	54	54
Activities for intervention	30	240	720

GDHT: goal-directed haemodynamic therapy.

**Table A8.** The most relevant perioperative cost items (Karolinska University Hospital, Huddinge)

Cost items	GDHT (€)	Traditional fluid (€)
Personal cost per patient in the preoperative area	159	27
Personal costs (nurse, physician) for optimization	401	117
Medical device (arterial line, device for calibration)	181	11
Monitor (LiDCO) (5-year depreciation period)	40	0

The personal cost per hour for the staff, and costs of devices, was obtained from the Accounting Department in the Karolinska University Hospital, Huddinge, Sweden. The itemized costs are presented in Table A8.

#### 8.1.5.2 Costs of hospital stay

Individual costs were obtained from the University Hospital, Lund, on the cohort of patients that was previously presented in the section on ‘Short-term outcome of traditional perioperative fluid treatment’. The Accounting Department collected individual cost data on each of the hospitalized patients. The hospital costs included the following items.

1. Cost per patient: a template of cost per bed-day is multiplied by the length of hospital stay. The template unit cost per bed-day is calculated by the hospital Accounting Department, based on the total costs per previous year and bed-days on the actual ward.

2. Cost of operation, reoperation
3. Cost of intensive care
4. Cost of laboratory tests
5. Cost of microbiology culture
6. Cost of radiology
7. Cost of clinical physiology

To estimate the cost per complication, the same grouping approach was used as was presented in the section on ‘Short-term outcome of traditional perioperative fluid treatment’. Costs for patients having multiple complications in combination with cardiovascular complication or stroke were grouped as cost per patient of cardiovascular complication or stroke. Cost for patients having multiple complications or fatal or uncomplicated outcome contributed to cost per patient of other complications, of death, or of uncomplicated outcome, respectively. The mean costs used in Paper III and the probabilistic distributions in Paper IV for each complication are presented in Table A9.

**Table A9.** Mean and the probability distributions of costs per complication during the acute hospital stay

Cost items	Mean costs (€)	Standard error	Distributions
No complications	6 753	218	Gamma (967, 7)
Cardiovascular complications			
Myocardial infarction	7 498	791	Gamma (90, 83)
Heart failure	9 903	971	Gamma (104, 95)
Cerebrovascular complication, stroke	7 550		
Other complications			
Pneumonia	8 514	829	Gamma (106, 81)
Renal failure	12 197	4194	Gamma (8, 1442)
Wound infection	8 566	580	Gamma (218, 39)
Deep-vein thrombosis	7 617	970	Gamma (62, 124)
Pulmonary embolism	10 190	2472	Gamma (17, 600)
Gastrointestinal bleeding	9 900	1235	Gamma (64, 154)
Confusion	7 961	270	Gamma (866, 9)
Death	9 020	545	Gamma (273, 33)

### 8.1.6 Key assumptions in the decision tree

The selected complicated clinical outcomes were death, cardiovascular (myocardial infarction, heart failure), stroke, and other complications. Other complications include pneumonia, kidney failure, wound infections, postoperative delirium, gastrointestinal bleeding, deep-vein thrombosis or pulmonary embolism. It would be possible to present all of these complications by separated branches, but in the real life patients have multiple complications. The decision tree, as mentioned above, only allows mutually exclusive transitions through the pathways, that is, the hypothetical individuals cannot move along two or more pathways simultaneously. The purpose of the model was not to trace the chain of the pathophysiological consequences of particular postoperative events, but to estimate the influence of the complications on the postoperative quality of life. For these reasons a choice had to be made as how to

simulate the influence of the postoperative complications on the patient's health.

1. An assumption was made that the non-fatal cardiovascular complications and stroke may have the highest impact on health and health care costs for elderly patients.
2. The hypothetical individuals with non-fatal cardiovascular complications or stroke could not have multiple complications. This assumption may lead to an overstated postoperative quality of life in the model, and for this reason the model was run according to scenario analysis using lower quality-of-life weights postoperatively.
3. The same value of relative risk of morbidity was employed for each of the non-fatal postoperative complications, that is, the assumption was made that the GDHT influences each of these equivalently. Currently there are no data on relative risk of morbidity for each of the selected postoperative complications.



## 8.2 LONG-TERM MODEL

### 8.2.1 The Markov structure

The model constructs a simplified course of diseased or recovered individuals after the hospital discharge (Fig.1B in Paper III). The circles represent health states associated with the complicated or uncomplicated postoperative outcome. The arrows show possible transitions through the model during a Markov cycle. One cycle is one year long and 10 cycles were applied.

For individuals with cardiovascular complications or stroke the model allows the patient to stay in the diseased health state or to make the transition to death. Individuals with multiple complications may stay in the same health condition, or they may recover or make the transition to death. The recovered individuals may stay in the same health state or make the transition to death.

At the start of the analysis the proportion of patients in the various health states is provided by the decision tree.

### 8.2.2 Long-term postoperative outcome

#### 8.2.2.1 *Survival after cardiovascular complication*

Mortality associated with cardiovascular complication was obtained by personal

communication from the Swedish National Register on Secondary Prevention in Cardiac Intensive Care (SEPHIA). In recent years nearly 100 per cent of all cardiovascular events were reported to the register. One to three years' risk of mortality following myocardial infarction in individuals >70 years was employed in the model (Table A10). After the first three Markov cycles standard mortality was used.

#### 8.2.2.2 *Survival after stroke*

One-year risk of mortality following stroke was obtained from the Swedish National Stroke Register. In recent years, data from 83 per cent of Swedish hospitals are reported. After the first Markov cycle standard mortality was used (Table A10).

#### 8.2.2.3 *Survival after other complications*

One-year risk of postoperative mortality of individuals having other complications and those who recovered having other complications was obtained from the same cohort of patients that was presented in the section on 'Short-term outcome of traditional fluid treatment' (Table A10).

Also here, after the first Markov cycle standard mortality was used. The uncertainties of long-term survival extracted from SEPHIA and the Swedish National

**Table A10.** Estimated mortality associated with the postoperative outcome. These parameters are used as point estimates

Complication	Mortality absolute risk	Standard error	Distribution
Cardiovascular disease			
In-hospital	0.057		
1 year	0.107		
2 years	0.058		
3 years	0.056		
Stroke (1 year)	0.15		
Other complications within first year	0.18	0.029	Beta (31, 140)
After recovery from other complications, first year	0.15	0.037	Beta (17, 95)

Stroke Register were not defined; these were considered as point estimates, because they were drawn from large populations and the values of standard error were low. For estimates of outcome after other complications probability distributions were used because the values were obtained from the Swedish National Register on Hip Fracture for a cohort of patients (n = 402).

### 8.2.3 Long-term quality of life

Effects (QALYs) were discounted by 3 per cent annually.

Pre-fracture and postoperative QALY weights related to cardiovascular complications, other complications, and stroke are presented in the short-term model (Table A6). For quality of life data on individuals who recovered during the first year after postoperative complication, a literature search on Swedish trials was conducted. Longitudinal trials on healed fractures and healing complications were found.<sup>80</sup> We considered that the group of healed fractures might represent an estimate of QALY weights for individuals who recovered after having other postoperative complications.

Using the pre-fracture and the complication-related QALY weights, decrements of quality of life were calculated (Table A11). The postoperative QALY weights were allocated at the beginning of the first postoperative year at the start of the Markov

structure and the yearly decrements were used for the diseased individuals, applying 10 cycles. The disease-related QALY weights may be overstated for two reasons:

1. They are not age-related but are based on the whole population (16–84 years).
2. An assumption was made in the decision tree that the hypothetical individuals with stroke or cardiovascular complications could not have multiple complications.

In the scenario analysis, therefore, QALY decrements increased by 30 per cent were used to allow more influence of the postoperative complications on the quality of life (Table A11).

### 8.2.4 Long-term health care costs

The costs are expressed in euros (1 euro is equivalent to 9.42 SEK).

The direct health care costs included both in- and outpatient costs.

A large Swedish prospective costing study (KOFOR) on osteoporotic fractures was launched 2002.<sup>79,81</sup> Cost data from this study could not be used in the model because the mean of total community and health care costs per patient were reported and costs per complication were not separated. The approach to estimating the direct health care costs for each of the selected complications was as follows.

The Epidemiological Centre of the Swedish National Board of Health and Welfare

**Table A11.** QALY weights<sup>54,55,80</sup> and decrements used in the Markov structure to estimate the quality of life associated with the postoperative outcome.

Health states	QALY weight	QALY decrements	Hypothetic QALY decrements for the scenario analysis
Pre-fracture values (age 70–79 years)	0.79		
Recovery from other complications	0.66		
Cardiovascular complications	0.60	-0.19	-0.247
Stroke	0.44	-0.35	-0.455
Other complications	0.64	-0.15	-0.195

**Table A12.** Estimated health care cost items per patient per year for complicated and uncomplicated postoperative outcome (Epidemiological Centre of the Swedish National Board of Health and Welfare)

Cost item	Costs per patient per year	Costs per patient per year
	in the first year (mean, €)	after the first year (mean, €)
Cardiovascular complication	7 673	386
Stroke	7 512	402
Other complications	7 314	396
Uncomplicated outcome	147	147
Death	4 837	4 837

database was searched using the following criteria:

1. All patients operated on for proximal femoral fracture during 2007 were selected (n = 16 800).
2. Patients with the World Health Organization International Classification of Diseases codes related to myocardial infarction, cardiac failure, stroke, renal failure, pneumonia, wound infections, gastrointestinal bleeding, thrombo-embolic events, and confusion were selected. Both hospital and outpatient costs during 2008 for the selected patients were extracted.
3. Costs per patients were grouped using the previously described grouping approach for the postoperative complications.
4. Mean cost per complication for hospital stay was calculated.
5. Mean outpatient cost per complication was calculated.

The health care cost for uncomplicated outcome was estimated by using the mean value of outpatient costs of the whole group of patients who received surgical treatment (Table A12). In the first Markov cycle both hospital and outpatient costs were allocated. In order not to overestimate the long-term health care costs, it was assumed that after the first year the patients had only outpatient costs. The cost of death after the acute hospital stay was obtained from the

Accounting Department of the geriatric ward (Karolinska University Hospital, Huddinge).

### 8.2.5 Assumptions in the Markov structure

1. The hypothetical individual lives with the consequences of postoperative cardiovascular complications or stroke without recovery. As the hypothetical individuals are aged (>75 years), this assumption and simplification is reasonable.
2. Individuals with other complications if they are non-fatal may recover.
3. Individuals with cardiovascular complications have an increased risk of dying only during the first three years postoperatively. In the following years standard age-related mortality is assumed.
4. Individuals with stroke have an increased risk of dying during the first year. In the following years the risk is comparable to standard mortality.
5. During each cycle the individuals make transitions in the middle of the cycle at the same time, that is, mean values of transition probabilities are used.

An assumption was made that the individuals having any of the postoperative complications had hospital care only during the first postoperative year. The following nine years only use of outpatients care was assumed.

## 9 SWEDISH SUMMARY

*Bakgrund.* För policybeslut avseende valet mellan alternativa behandlingsmetoder inom hälso- och sjukvården är det viktigt att identifiera vilken som ger mest nytta för givna resurser. För sådana beslut krävs hälsoekonomiska utvärderingar. Den här avhandlingen analyserar kostnadseffektiviteten av avancerad postoperativ smärtbehandling och perioperativ optimering av cirkulation hos äldre med höftfraktur genom tillämpning av hälsoekonomiska modeller.

1. De två vanligaste formerna av avancerad postoperativ smärtlindring efter större operationer är epidural och intravenös patientkontrollerad smärtlindring. Epidural smärtlindring har bättre effekt och används som standard. En nackdel med epidurala behandlingarna är den höga andelen avbrutna behandlingar (10-15%). Eftersom cirka 40 000 patienter behandlas varje år i Sverige blir frågan om kostnadseffektivitet betydelsefull.
2. För postoperativ återhämtning är det viktigt med optimalt blodflöde under operation. Detta kan uppnås med hjälp av olika strategier för perioperativ vätskebehandling och optimering av cirkulation. En av dessa är s.k. målstyrd hemodynamisk optimering som ökar blodflödet till definierade mål. Hos högriskpatienter främjar metoden den postoperativa återhämtningen, men nyttan hos äldre är inte klarlagd. I Sverige opereras årligen 20 000 patienter för höftfraktur. Risken för postoperativa komplikationer är hög. Kliniska studier behövs för att analysera den kliniska effekten och kostnadseffektiviteten av målstyrd hemodynamisk optimering. Sådana studier är komplexa och resurskrävande. En förhandsskattning av förväntade kostnader och nytta kan motivera initieringen och genomförandet av studier.

### *Metoder*

1. Epidural smärtlindring jämförd med intravenös patientkontrollerad smärtlindring:  
Studie I: En kostnadseffektivitetsmodell konstruerades för att analysera data från en klinisk kvalitetsdatabas.

Studie II: Postoperativa intensivvårdskostnader analyserades från patienter som ingick i en publicerad studie av postoperativ smärtbehandling efter matstrupsoperation för cancer.

2. Målstyrd hemodynamisk optimering jämfördes med traditionell vätskebehandling:  
Studie III: En kostnadseffektivitetsmodell konstruerades och relevanta uppgifter från studier och nationella register användes. Eftersom det kliniska utfallet hos äldre inte är helt klarlagt försågs modellen med rimliga skattningar.

Studie IV: Baserat på föregående kostnadseffektivitetsanalys startades en klinisk randomiserad studie med planerad inklusion av 460 äldre patienter med höftfraktur. Vid interimanalysen på 100 patienter sågs en effekt men med statistisk osäkerhet. *Det förväntade värdet av perfekt information* analyserades baserat på den konstaterade osäkerheten. Med begreppet avses det samhälleliga värdet, uttryckt i pengar, av att minska den statistiska osäkerheten genom fortsatt datainsamling.

### *Resultat*

1. Epidural smärtlindring är inte kostnadseffektiv och ingen besparing av postoperativa kostnader kan uppnås baserat på uppgifter i klinisk svensk rutin (artikel I-II).
2. Hälsoekonomisk modellanalys gör troligt att målstyrd hemodynamisk optimering av äldre är kostnadseffektiv. Det förväntade värdet av perfekt information är högt (artikel III-IV).

### *Slutsatser.*

1. Analyserna av epiduralbedövning utmanar den epidurala smärtlindringens ställning som gyllene standard i ett hälsoekonomisk perspektiv.
2. Förhandsanalys av målstyrd hemodynamisk behandling hos äldre motiverar en klinisk studie. Analysen av det förväntade värdet av perfekt information i samband med en interimanalys indikerar ett högt samhälleligt värde av fortsatt datainsamling.

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“A pessimist sees the difficulty in every opportunity; an optimist sees the opportunity in every difficulty” (W. Churchill)

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“We can live without religion and meditation, but we cannot survive without human affection”  
(Dalai Lama)

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“It’s not that I’m so smart, it’s just that I stay with problems longer” (Einstein)

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“Science is organized knowledge. Wisdom is organized life” (Immanuel Kant)

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