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Bartha, Erzsebet; Davidson, Thomas; Hommel, Ami; Thorngren, Karl-Göran; Carlsson, Per; Kalman, Sigridur

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LUND UNIVERSITY

PO Box 117  
221 00 Lund  
+46 46-222 00 00

**Cost-effectiveness analysis of goal-directed hemodynamic treatment of elderly hip-fracture patients—*before* clinical research starts**

Erzsebet Bartha, MD. Ph.D., Research Assistant, Karolinska Institute, CLINTEC, Div. of Anesthesiology, Karolinska University Hospital Huddinge B31, Stockholm, Sweden,

Thomas Davidson, Ph.D., Assistant Professor, Center for Medical Technology Assessment, Linköping University, Linköping, Sweden.

Ami Hommel, Reg. Nurse, Ph.D., Assistant Professor, Dept. of Health Sciences, Lund University, Lund, Sweden.

Karl-Göran Thorngren, MD. Ph.D., Professor, Dept. of Orthopedics, Lund University Hospital, Lund, Sweden.

Per Carlsson, Ph.D., Professor, Center for Medical Technology Assessment, Linköping University, Linköping, Sweden.

Sigrídur Kalman, MD. Ph.D., Professor, Karolinska Institute, CLINTEC, Div. of Anesthesiology, Karolinska University Hospital Huddinge B31, Stockholm, Sweden.

**Corresponding author:**

Erzsebet Bartha, Ph.D.

Karolinska Institute, CLINTEC, Div. of Anesthesiology, Karolinska University Hospital Huddinge B31, Stockholm, Sweden.

Dept. of Anesthesiology, Karolinska University Hospital Huddinge B31, SE-141 86 Stockholm, Sweden

Phone: +46 8 58 58 7187

Fax: +46 8 77 95 424

erzsebet.bartha@karolinska.se

**This work attributed to:**

Karolinska Institute, CLINTEC, Div. of Anesthesiology and Dept. of Anesthesiology and Intensive Care, Karolinska University Hospital, Stockholm; Center for Medical Technology Assessment, Linköping University, Linköping; Dept. of Orthopedics, and Lund University Hospital, Dept. of Health Sciences, Lund University, Sweden.

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**Number of words.** Abstract: 237. Introduction: 500. Discussion: 1031.

**Abbreviated title:** Cost effectiveness as a guidance for a clinical trial

**Summary:** Before starting a clinical trial on goal-directed hemodynamic treatment of elderly patients with hip fracture, the treatment's cost effectiveness was analyzed using an analytical model to guide initiation of the clinical trial.

## Abstract

**Background:** Health economic evaluations are increasingly used for decision to adopt new medical interventions. Before such decisions, various stakeholders have invested in clinical research. But health economic factors are seldom considered in research funding decisions. Cost-effectiveness analyses could be informative *before* launch of clinical research projects, particularly when a targeted intervention is resource-intensive, total cost for the trial is very high and expected gain of health benefits is uncertain. This study analyzed cost effectiveness using a decision analytic model before initiating a large clinical research project on goal-directed hemodynamic treatment of elderly patients with hip fracture.

**Methods:** A probabilistic decision analytic cost-effectiveness model was developed; the model contains a decision tree for the postoperative short-term outcome and a Markov structure for long-term outcome. Clinical-effect estimates, costs, health-related quality-of-life measures, and long-term survival constituted model input that was extracted from clinical trials, national databases, and surveys. Model output consisted of estimated medical care costs related to quality-adjusted life years.

**Results:** In the base case analysis, goal-directed hemodynamic treatment reduced average medical care costs by €1882 and gained 0.344 quality-adjusted life years. In 96.5 % of the simulations, goal-directed hemodynamic treatment is less costly and provides more quality-adjusted life years. The results are sensitive to clinical-effect-size variations, although goal-directed hemodynamic treatment seems to be cost-effective even with moderate clinical effect.

**Conclusion:** This study demonstrates that cost-effectiveness analysis is feasible, meaningful, and recommendable before launch of costly clinical research projects.

## Introduction

Medical care resources are limited. In many countries, decisions to adopt, reimburse or issue specific guidance on use of new medical treatments are increasingly based on cost effectiveness. Stakeholders in Australia,<sup>1</sup> Canada,<sup>2</sup> the United Kingdom<sup>3</sup> and the United States<sup>4</sup> first used this approach. In 1997, a law integrated cost- effectiveness consideration into Sweden's medical care system's prioritization processes.<sup>1</sup>

In contrast, funding on applied clinical research decisions are usually not linked to health economic factors, even if research projects are costly and funded by public resources and if resources are scarce.<sup>5</sup> This is particularly striking when research project consider medical treatments that presumably cannot be adopted in the future due to due to limited resources and poor cost effectiveness. In such situations, cost-effectiveness analyses of unproven medical technologies may be reasonable *before commissioning* clinical research projects. This is an issue for policy makers and clinical researchers.

In cost-effectiveness analyses at least two alternative interventions are compared in terms of costs and changes in patients' health, usually using a long time perspective. When relevant data are unavailable, stochastic (probabilistic) decision analytic models are used to apply best (or next best) evidence combined with reasonable assumptions.<sup>6-8</sup>

This analysis is tightly linked to the design and launch of a clinical research project on hemodynamic optimization of elderly patients with hip fracture; we use an analytic method that is increasingly being applied in medical care policy decisions.

Each year, about 20,000 patients have hip surgery in Sweden. Four-month mortality is 15% for females and 20% for males, and only 50% of these patients are discharged to their original housing.<sup>ii</sup> In other surgical patients, perioperative fluid overload or deficit may influence

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<sup>i</sup> [www.riksdagen.se/webbnav/index.aspx?nid=3911&bet=1982:763](http://www.riksdagen.se/webbnav/index.aspx?nid=3911&bet=1982:763). Last access date: 6 December 2011.

<sup>ii</sup> [www.rikshoft.se/se/images/stories/arsrapporter/Arsrapport2008.pdf](http://www.rikshoft.se/se/images/stories/arsrapporter/Arsrapport2008.pdf) . Last access date: 6 December 2011.

postoperative outcome, and in past decades, many fluid treatment protocols were studied.<sup>9-15</sup> One is goal-directed hemodynamic treatment (GDHT) that is targeted to increase global blood flow. As per meta-analyses,<sup>12-14</sup> GDHT is beneficial for high-risk surgical patients. In elderly patients with hip fracture, current evidence suggests that GDHT might reduce hospital stay.<sup>16,17</sup> However length of hospital stay is a surrogate endpoint. For policy decision on GDHT in elderly patients evidence is required on clinical effectiveness, on patient-oriented benefits and on the used resources. The authors planned a clinical trial (n=460) for the actual population to find evidence on clinical benefit (postoperative complications). But commissioning and funding such a trial could be questioned because it has been suggested that that only “25 to 60% of the mortality will be potentially susceptible to the intervention” due to high age and co-morbidities.<sup>18</sup> In addition, if GDHT cannot be used in the future, due to limited resources, then clinical trials on this vulnerable patient group would be inappropriate for economic and ethical reasons.

We aimed to *estimate* cost effectiveness *before* commissioning a clinical trial on GDHT in elderly patients with hip fracture in order to guide researchers and those who set research priorities—if a future GDHT trial for the elderly is potentially meaningful.

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## Materials and Methods

This section describes (i) this investigation's perspective, (ii) the decision analytic model,<sup>6</sup> and (iii) various analysis phases.

### *Perspective*

Cost-effectiveness analyses always compare *alternative* treatment strategies. In this investigation, routine fluid treatment is compared to GDHT for *hypothetical* individuals with hip fracture (age >80). Routine fluid treatment represents current clinical practice in Sweden. Blood pressure and heart rate guide administered fluid volumes. GDHT represents a treatment protocol to be targeting Shoemaker's<sup>19</sup> proposed objectives (oxygen delivery >600 ml · min<sup>-1</sup> · m<sup>-2</sup>, cardiac index >4.5 l · min<sup>-1</sup> · m<sup>-2</sup>) when using the Lithium Dilution Cardiac Output monitor (LiDCO™, LiDCO Ltd., Sawston, Cambridge, United Kingdom). Our analysis takes a medical care perspective<sup>i</sup> on costs and it follows effects of interventions, 5 years postoperatively. Model output is the estimated incremental cost-effectiveness ratio (ICER).

### *Decision analytic model*

The analysis is done using a decision analytic model. It applies mathematical relationships that illustrate consequences of both treatment strategies. The model consists of two parts. A decision tree<sup>7</sup> that was developed for short-term postoperative outcome and a Markov structure<sup>6</sup> that was developed for long-term outcome (Figure 1 A and B). The next section briefly describes various analysis phases. A more comprehensive description of the model structure, data collection, and data incorporation (into the model) are available elsewhere.<sup>ii</sup>

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<sup>i</sup> The societal perspective is preferable, but we could not identify reliable data on use of support from society, so our analysis has a limitation in the Swedish context. As per health technology assessment guidelines, medical care perspective in the analysis can be selected.

<sup>ii</sup> <http://publications.ki.se/jspui/handle/10616/4040>. Last access date: 6 December 2011.

## *Analysis phases*

### *1. Decision tree development*

The decision-tree is used to estimate the short-term costs and postoperative outcome (Figure 1 A and B). It starts with a decision between two fluid treatment strategies (rectangle). A chance node (circle) follows the decision, where various events may occur by chance, and hypothetical individuals may make transition (arrows) toward one of the selected postoperative outcomes (triangles in Figure 1 A and B): uncomplicated recovery, cardiovascular complications, stroke, other complications (i.e., pulmonary and urinary tract infections, postoperative confusion, kidney insufficiency, wound infection, and pulmonary embolism), and death. Each postoperative outcome (triangles) is accounted for with estimated occurrence probability, health-related quality-of-life (QoL) index, and cost. So the model translates selected postoperative complications into health states (exemplified by health-related QoL) that are measured by the EQ-5D instrument.<sup>20</sup> The decision tree's time line is 4 months after the operation.

### *2. Model inputs into the decision-tree*

For routine fluid treatment, probabilities for each postoperative outcome were generated with data drawn from a Swedish trial (n=402; 100% follow-up rate).<sup>21</sup> For GDHT, probabilities for each postoperative outcome were generated using estimates of relative risk (GDHT vs. routine fluid treatment) for mortality and morbidity. These were extracted from the scientific literature. Appendix 1 and 2 display the search strategy and results. No data were found on the clinical benefit of *the actual GDHT protocol on the actual population*, so next-best data were used. The relative risk for postoperative morbidity was directly calculated from findings of Venn and colleagues<sup>17</sup> (actual population but another GDHT strategy). The relative risk for mortality was

extracted from meta-analysis<sup>13</sup> (actual strategy but younger population). Table 1 lists clinical effect estimates.

Pre- and post-fracture QoL indices were derived from (i) the age-matched non-fractured Swedish population<sup>22,23</sup> and (ii) a longitudinal Swedish clinical trial.<sup>24</sup> Decrements of QoL (difference between pre- and post-fracture QoL indices) were calculated and used for the analysis (Table 1).

Short-term medical care costs consisted of fluid treatment costs including (i) medical devices—monitoring with LiDCO™ and (ii) human resources during the perioperative period (Table 1). Hospital costs for each postoperative complication and for uncomplicated recovery included hospital stay length, cost per one bed-day, plus laboratory, microbiology, radiology, and operations expenses. Fluid treatment cost data were calculated at the Karolinska University Hospital, Huddinge, Sweden. Hospital cost data were based on individual patient-specific cost data at University Hospital in Lund, Sweden.

### *3. Markov structure development*

A Markov structure was developed for modeling long-term survival, medical care costs, and QoL. After hospital discharge, hypothetical individuals are categorized into health states in the Markov structure (circles in Figure 1 and B). QoL, which is aligned with each postoperative outcome, exemplifies these health states. *Hypothetic* individuals may make transitions along the arrows (Figure 1 A and B) among health states or stay in the same state during one year, i.e., one cycle. Note that this model simplifies real life, because it *allows* for recovery only from the “other” complications state. So after cardiovascular complications or stroke, hypothetical individuals continue to live with consequences of these complaints. These factors describe the health states (circles): estimated survival probabilities, QoL, and medical care costs. During one cycle, survival decreases and survivors’ QoL declines by decrements. One cycle is repeated five



times—representing five postoperative years. Here, a QoL index was multiplied by the time spent in the current health state (one year), which generated the number of quality-adjusted life years (QALYs). Each life year of a hypothetical individual is associated with medical care costs. Costs and QALYs were aggregated, which yields the expected, *estimated* mean costs and QALYs of both treatment strategies.

#### *4. Model input into the Markov structure*

Age-adjusted standard mortality<sup>i</sup> was used for hypothetical individuals with no postoperative complication. For those with cardiovascular complications or stroke, yearly mortality was estimated using age- and disease-related mortality from the Swedish National Stroke Registry<sup>ii</sup> and the Swedish National Registry on Secondary Prevention in Cardiac Intensive Care<sup>iii</sup> (Kalle Spångberg, Ph.D., section manager, Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden, written communication: 15 May 2009). Mean in- and outpatient long-term medical-care-cost data came from the Swedish National Board of Health and Welfare for patients who received hip fracture surgery in 2007 and were hospitalized in 2008 (Table 1). (Leif Forsberg, statistician, Department of Statistics, Monitoring and Evaluation, Swedish National Board of Health, Stockholm, Sweden, written communication: 7 December 2009).

#### *5. Assumptions used in the model*

For the base case analysis, following assumptions were made:

- a) GDHT may influence each of the selected postoperative complications.
- b) GDHT may influence postoperative mortality in elderly patients.

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<sup>i</sup> Official Statistic of Sweden, Life Tables, 2008. [www.scb.se/Statistik/BE/BE0101/2009M03/Be0101Livsl%c3%a4ngdstabeller\\_08\\_eng\\_ny.xls](http://www.scb.se/Statistik/BE/BE0101/2009M03/Be0101Livsl%c3%a4ngdstabeller_08_eng_ny.xls). Last access date 6 December 2011.

<sup>ii</sup> *Annual report*. National Stroke Registry, 2008. [www.riks-stroke.org/content/analyser/Rapport08revnov09.pdf](http://www.riks-stroke.org/content/analyser/Rapport08revnov09.pdf). Last access date 11 February 2012.

<sup>iii</sup> [www.ucr.uu.se/sephia/](http://www.ucr.uu.se/sephia/). Last access date 12 February 2012.

- c) Pre-fracture QoL is equivalent to the non-fractured, aged-matched population.
- d) Post-fracture QoL—associated with postoperative stroke and cardiovascular events—is equivalent to non-fractured patients with stroke and cardiovascular diseases.
- e) Post-fracture QoL associated with “other” complications is equivalent to QoL reported for healing complications after hip fracture.

### *6. Cost-effectiveness analysis*

Data uncertainty was accounted for by defining probability distributions for all model inputs that were applied in the base case analysis (Table 1). First the model was run with average values of all model inputs that yield average costs and QALYs. Then a second-order Monte Carlo simulation was performed, and the cohort was simulated through five cycles (years). In each simulation, input data values were randomly drawn from the defined probability distributions; the simulation was performed 1000 times—generating 1000 estimates of aggregated costs and QALYs. The model was programmed and analyzed using Microsoft Excel (Microsoft Corporation 1985–2001, version 12.0.6554.5003, One Microsoft Way, Redmond, WA). Costs and effects (QALYs) were discounted by 3% annually. The ICER was calculated dividing the difference between costs (incremental cost) by the difference between the QALYs (incremental effect) for the two strategies. The ICER is an estimate of additional costs for getting one additional life year with full health when the two alternatives are compared. The ICER is always related to one possible threshold value that society is willing to pay for one additional life year with full health (cost-effectiveness threshold,  $\lambda$ ). In Sweden, there is no fixed official threshold or range accepted, but a cost of between €20,000 and €50,000 is discussed depending of the severity of the condition (in exceptional cases even higher). Standards within Sweden’s medical care system guided this analysis, which applied Swedish hospital costs that are converted to euros using this exchange rate: €1 = SEK 9.41.

### *7. Sensitivity analyses of uncertain data*

Probabilistic sensitivity analyses were done to account for uncertainty of model assumptions and to address variability in data that were used. One-way sensitivity analyses were performed over upper and lower limits, respectively, of 95% CI for the model inputs. The model was also run using stepwise, increased estimates of relative risk for morbidity and mortality that represent lower expected clinical effect, compared to the base case analysis.

## Results

### *1. Analysis of the average incremental cost-effectiveness ratio*

The base case analysis compared QALYs and costs for a hypothetical cohort of hip fracture patients, age 80+, who were treated with preoperative GDHT or routine fluid treatment. The analysis accounted for five postoperative years (Table 2). In average the GDHT leads to reduced costs by €-1882 and to increase of QALYs by 0.344 which yields a negative average ICER (when the ICER is negative it should not be expressed). Consequently the GDHT is dominant.<sup>i</sup>

### *2. One-way sensitivity analyses*

The cost-effectiveness analysis was generally robust to changes of model inputs within ranges of 95% CIs (Figure 2)—with one exception. The ICER was sensitive to relative mortality-and-morbidity risk-value changes. Relative risk influence was separately tested with stepwise increased values by 25 to 90% (Appendix 3). When clinical effect is reduced via a 90% relative risk increase, then GDHT dominance disappears, which yields an ICER of €383 per gained QALY (Figure 3).

### *3. Probabilistic analysis*

Figure 4 shows the Monte Carlo simulation results; here, differences between costs are plotted against differences of effect for all simulated values. Figure 4 demonstrates how the combined uncertainty of model inputs is translated into the uncertainty of model outputs. For 96.4 % of the simulated values (right lower quadrant), GDHT for hypothetic individuals (ages 80+) is dominant; it is less costly and more effective as measured by QALYs on a 5-year time line—

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<sup>i</sup> Dominance: when the incremental cost is negative and the incremental effect is positive for a treatment option vs. control, the ICER should not be expressed, so the treatment option is less costly and better.

compared to traditional fluid treatment. For 3% of the values (right upper quadrant), GDHT is more costly and more effective; here, GDHT may still be cost effective. The governing factor in this quadrant is a threshold value of how much society is willing to pay for one additional life year with full health for the target population. The slope of the dotted line ( $\lambda$ ) represents one possible cost-effectiveness threshold value. Values below the dotted line represent simulations when GDHT is cost effective. So the combined uncertainty of model inputs and the cost-effectiveness threshold value determine the probability of cost-effectiveness.

The 95% CI of the ICER is calculated by the upper and lower limit of 95% of the simulated values of incremental costs (€-3,043 to €+239) and QALYs (0.082 to 0.492). It yields a negative ICER at the lower limit and a cost per QALY gained at €2,915 at the upper limit.

#### *4. Probabilistic sensitivity analysis*

Figure 5 illustrates probabilistic sensitivity analyses; here, probabilities for GDHT being cost effective are plotted against varying values of the cost-effectiveness threshold. The model was run for the base case analysis (dotted line) and two alternative scenarios—to test two main model assumptions. Scenario 1: GDHT does not influence most of the selected postoperative complications that constitute the group of “other” complications (dashed line). Scenario 2: GDHT does not influence the group of “other” complications and mortality (solid line). For the base case analysis and both scenarios the probability of being cost effective is above 0.975 at a cost effectiveness threshold of €10,000.

## **Discussion**

Our main finding is that compared to routine treatment for patients, ages 80+, GDHT yields gained QALYs at lower medical care costs over a 5-year time line (in 96.5% of the

simulations). In health economic terms the GDHT is the *dominant strategy*. The analysis is most sensitive for changes in morbidity-and-mortality relative-risk values. Although with very modest clinical effect size values (relative risk for mortality/morbidity 0.92/0.84), GDHT may be cost-effective. The influence of postoperative complications on post-fracture QoL is probably understated because these were extracted from a non-fractured population. But in the one-way sensitivity analyses, the ICER remained negative when using the QoL decrements within ranges of 95% CIs (Figure 2). The analytic model is used to *estimate incremental* cost effectiveness ratio— with existing data, in a position of uncertainty considering the benefit of the GDHT on the actual population, and before a planned clinical trial. Our cost-effectiveness analysis provides support for commissioning a clinical trial. This analysis was not intended for guiding GDHT implementation in routine clinical practice. Introduction of GDHT should await evidence-based data from future RCTs, which demonstrate that the technology conveys net benefit.

The presented model is a dynamic framework, and it can be updated either when new evidence comes up on the clinical effect size for GDHT or when initially high costs of new technologies decrease over time.

Clinical effect size (relative risk) constitutes the most important variable in this analysis, because when the model was run by the upper and lower limits of 95% CI of relative risk the ICER has changed substantially.

#### *Why cost effectiveness?*

Particular when a new treatment strategy is very resource consuming, and if the strategy accounts for patients with limited life expectancy with uncertain benefit, then a cost-effectiveness analysis may be meaningful (*before* initiating a costly clinical trial) as input for

prioritization of research projects. Several methods exist for setting priorities in clinical research. These include measures of the burden disease,<sup>25,26</sup> the expected “payback” from the research,<sup>27,28</sup> estimated welfare losses<sup>29</sup> or value of information analysis.<sup>5</sup> Before commissioning a large randomized clinical trial, we ran a pilot trial on 40 patients. During the design period, and literature search we could determine that (i) patient recruitment is cumbersome due to the acute confusion of the patients under the circumstances of unscheduled surgery and (ii) there is a huge gap between the numbers of GDHT trials in the elderly patients compared to younger population.

Lack of GDHT trials on elderly patients may be a result of assumptions that such trials are not meaningful due to age and co-morbidities. In this analysis, we found that even modest clinical effect may improve health outcomes and decrease medical care costs (Figure 3).

#### *Analysis strengths and limitations*

This early analysis was done as per health economical evaluation standards. We used a two-part model that is commonly used for reimbursement decisions of new, unproven medical technologies when clinical trials are not yet available. Simplification of real life constitutes an analytical model limitation, but it is possible to model the complexity of expected GDHT influence on postoperative complications. It is unlikely that all postoperative complications may be influenced by GDHT; this complexity is partially modelled by probabilistic scenario analyses (scenarios 1 and 2).

External validity of the results (model outputs) depends on model input validity. In our analysis, model inputs have high external validity. Short-term survival and hospital costs of the traditional fluid treatment were obtained from a trial population with a follow-up rate of 100% on patients at University Hospital in Lund, Sweden.<sup>21</sup> Data from the Swedish National Registry

on Secondary Prevention in Cardiac Intensive Care and the Epidemiological Centre of the Swedish National Board of Health have high validity, because these national registries have data from all Swedish hospitals (100%). The Swedish National Stroke Registry has data from 83% of all hospitals of Sweden but is still the best available data source for survival after stroke.

### *Implications for further research*

Our results show low values of the *estimated* Number Needed to Treat (NNT) using GDHT through the entire range of *estimated* relative risk (Appendix 4). The displayed estimates of NNT in Appendix 4 are the *estimated* number of patients needed to treat to prevent one patient with negative outcome (postoperative complication). GDHT is also predicted to have high probability of being cost-effective (over ranges of confidence intervals) even if GDHT may require more resources during perioperative care. These results support research funding in the area. A future trial should address clinical effectiveness, patient-oriented benefits (QoL), and cost-effectiveness to support future policy decision on the current large patient population. Given the expected absolute risk for postoperative complications (0.6) and the point estimates of relative risk used in the one-way sensitivity analyses (Figure 3), corresponding sample sizes for future clinical trials are calculated (Appendix 4). When the relative risk is between 0.5 and 0.79, then the required sample size is between 84 and 490. When the expected relative risk exceeds 0.88, then the sample size should exceed 1488, which is probably not realistic to aim for in a clinical trial. In a future trial, during an interim analysis, one stopping rule could be relative risk higher than 0.79, because already this effect size would indicate need for a sample size over 490.



### *Conclusion*

Scientific evidence on clinical benefits of GDHT on elderly with hip fracture is scarce. So we addressed the question of whether or not a costly large trial is meaningful due high age and frailty of the patients. Early cost-effectiveness analysis predicts that GDHT may save costs of medical care and may gain QALYs—compared to traditional fluid treatment. Large trials on GDHT for elderly patients should be supported, because even strategies with modest clinical effect promise to be cost effective.

Moreover, when accounting for expected time and cost for a clinical trial, this type of cost-effectiveness analysis was found feasible, meaningful and recommendable *before* launch of costly applied clinical research projects in general. Such analyses might be beneficial even in countries in which cost-effectiveness analyses are not accepted for policy decisions. An early pre-trial analysis might reduce risk for inefficient use of scarce research resources when anticipated societal or patient benefits from clinical research are low.

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## **Figure legends**

### **Fig. 1** A and B Model structure

A. A decision tree. The short-term model starts with the decision between alternative fluid strategies (rectangle) followed by arrows that represent transitions toward selected postoperative complications.

B. The Markov structure. The long-term model; upon entering the model, hypothetical individuals have quality of life that is associated with postoperative outcome. The individuals make transitions along the arrows among health states or stay in the same state during one year, i.e., one cycle. During this cycle, survival decreases and survivors' quality of life declines by decrements. One cycle is repeated five times—representing five postoperative years.

### **Fig. 2** One-way sensitivity analyses

One-way sensitivity analyses using upper and lower level of a 95% confidence interval (95% CI) of the selected model inputs, respectively. The selected model inputs were the relative risk for mortality and morbidity, prefracture values of quality-of-life index (QoL index), the decrements of quality-of-life (QoL decrements) associated with postoperative complications and hospital costs.

### **Fig. 3** Deterministic analyses with relative-risk point estimates for postoperative mortality and morbidity

Differences in quality-adjusted life years ( $\Delta$  QALY) are plotted against cost differences ( $\Delta$  costs, €). The model was run using the baseline, and the stepwise increased the baseline values (by 25-90%) of relative risk. Appendix 3 displays the stepwise increased estimates for relative risks.

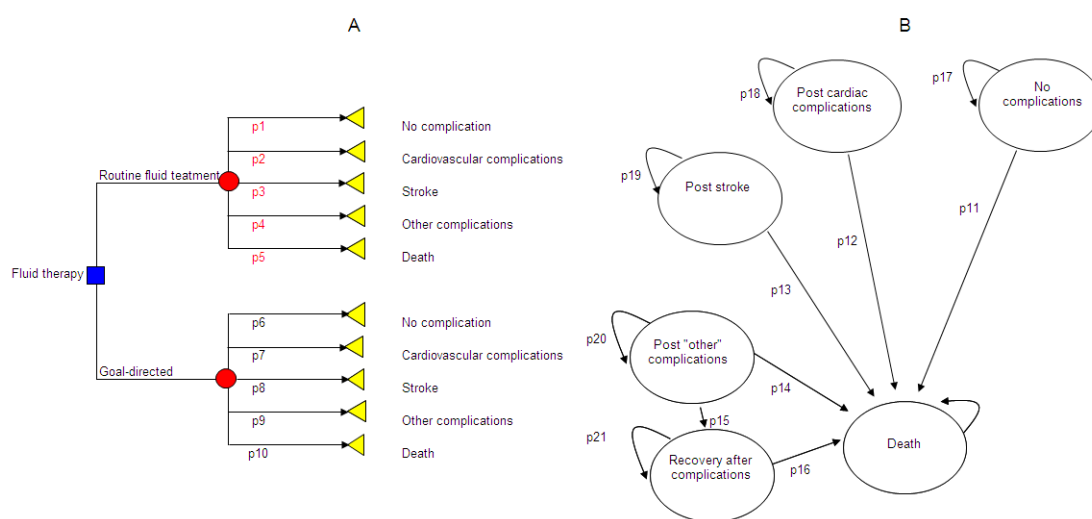


**Fig. 4** Results of the Monte Carlo simulation

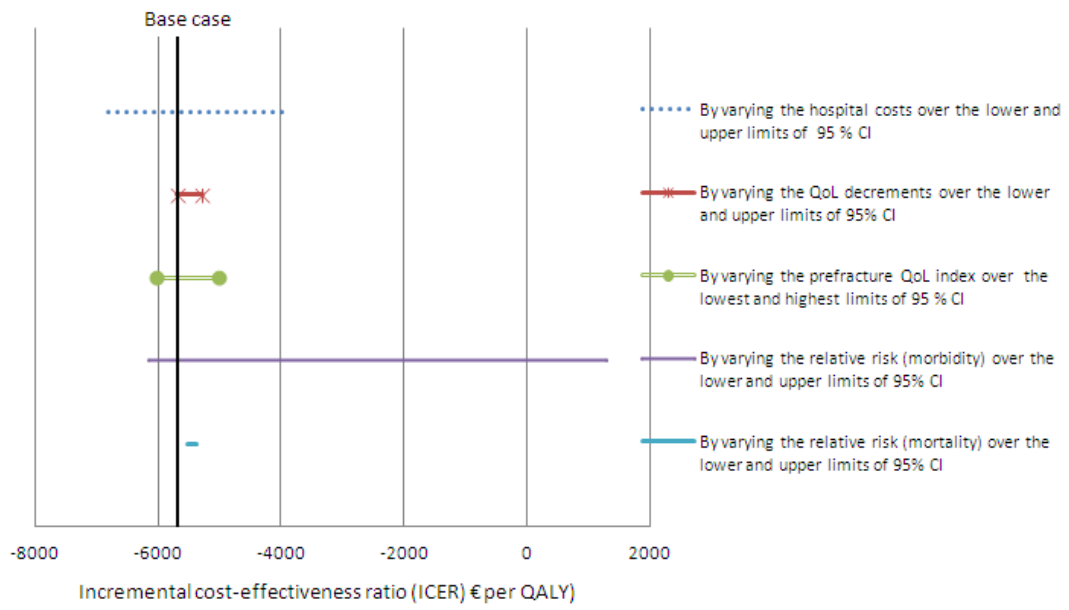
Simulated values of incremental costs and effects ( $\Delta$  costs,  $\Delta$  quality-adjusted life years, QALYs) of goal-directed haemodynamic treatment (GDHT) compared to routine fluid therapy. The slope of the dotted line ( $\lambda$ ) represents one possible threshold value that indicates how much society is willing to pay for one additional life year with full health for the target population (cost-effectiveness threshold).

**Fig. 5** Probabilistic sensitivity analyses

Probabilities for cost effectiveness are plotted against the cost-effectiveness threshold for the base case analysis, when the goal-directed haemodynamic treatment (GDHT) does not influence the major group of complications (other complications) and when the GDHT does not influence mortality and other complications. Other complications are listed in the section on the decision tree.



**Fig. 1 A and B**



**Fig. 2**

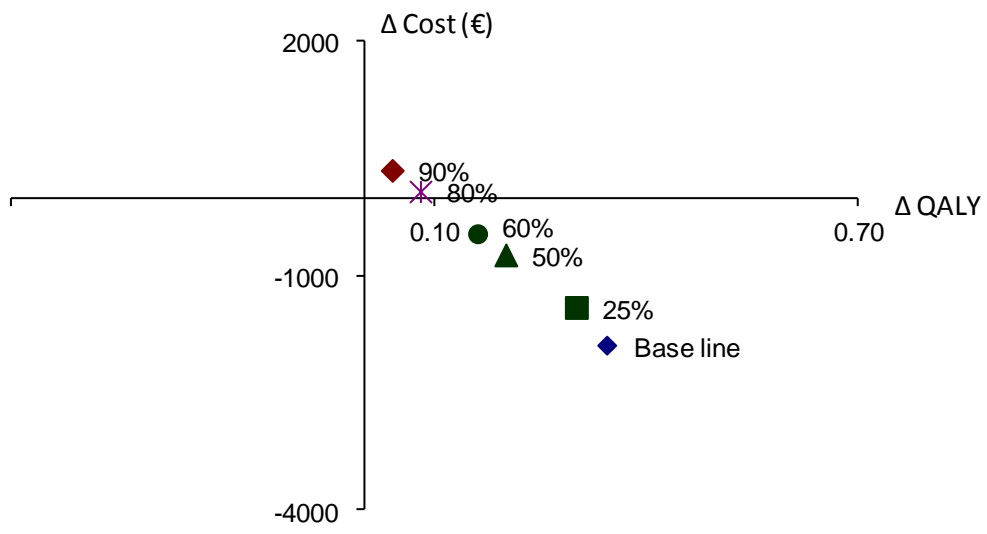
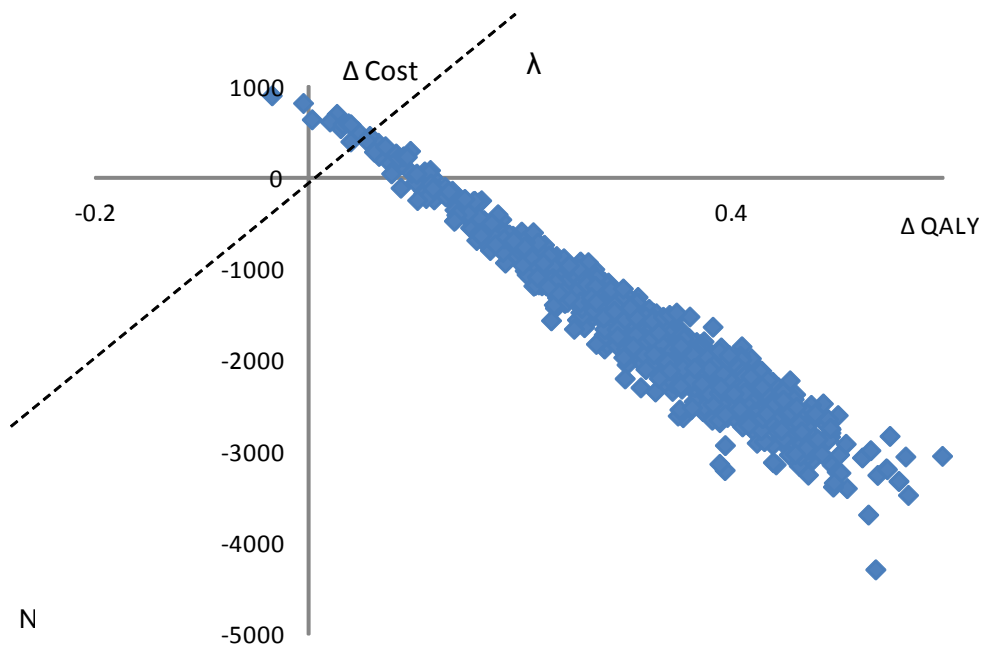
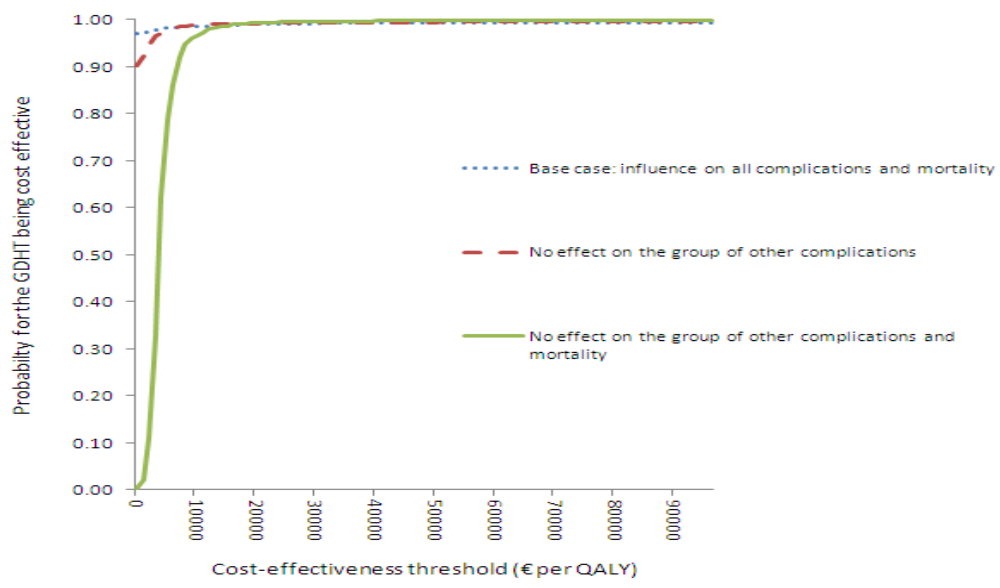


Fig. 3.



**Fig. 4**



**Fig. 5**

**Table 1.**

<b>Model inputs</b>	<b>Estimates</b>	<b>± 95% CI</b>	<b>Distributions</b>
Probabilities of short-term outcome(routine care)*			
Mortality after operation	0.129	0.096 to 0.162	Dirichlet <sup>1</sup> (52; 350)
Cardiovascular complications	0.065	0.036 to 0.08	Dirichlet (26; 376)
Stroke	0.005	0.002 to 0.018	Dirichlet (2; 400)
Other complications	0.403	0.380 to 0.470	Dirichlet (162; 240)
Relative risk of postoperative mortality	0.75	0.6 to 0.95	Lognormal
Relative risk of postoperative complications**	0.5	0.24 to 1.04	Lognormal
Probabilities of long-term outcome (routine care)			
Mortality associated with cardiovascular disease***			
First year	0.107	0.093 to 0.121	Beta (94; 883)
Second year	0.058	0.042 to 0.074	Beta (90; 795)
Mortality associated with stroke at 3 months****	0.15	0.110 to 0.189	Beta (3450; 19,550)
Mortality associated with other complications	0.18	0.123 to 0.237	Beta (31; 140)
Recovery associated with other complications	0.41	0.337 to 0.483	Beta (70; 101)
Mortality after recovery with other complications	0.15	0.083 to 0.217	Beta (17; 95)
Costs/patient for routine fluid treatment (€) <sup>†</sup>			
Medical device for fluid treatment	11		Deterministic
Human resources in preoperative area	27		Deterministic
Human resources during anaesthesia	117		Deterministic
Costs/patient for GDHT (€) <sup>†</sup>			
Medical device for GDHT	221		Deterministic
Human resources in preoperative area	159		Deterministic
Human resources during anaesthesia	401		Deterministic
Postoperative direct medical care costs/patient (€) <sup>††</sup>			
Cardiovascular complications			
Myocardial infarction	7,498	5,947 to 9,049	Gamma (90; 83)
Heart failure	9,903	8,001 to 11,806	Gamma (104; 95)
Stroke	7,550	2,284 to 12,815	Gamma (8; 956)
Other complications			
Pneumonia	8,514	6,889 to 10,138	Gamma (106; 81)
Renal failure	12,197	3,976 to 20,417	Gamma (6; 1442)
Wound infection	8,566	7,428 to 9,703	Gamma (218; 39)
Deep-vein thrombosis	7,617	5,715 to 9,519	Gamma (62; 124)
Pulmonary embolism	10,190	5,345 to 15,034	Gamma (17; 600)
Gastrointestinal bleeding	9,900	7,480 to 12,321	Gamma (64; 154)
Confusion	7,961	7,431 to 8,491	Gamma (866; 9)
Death	9,020	7,951 to 10,089	Gamma (273; 33)
No complications	6,753	6,325 to 7,181	Gamma (956; 7)
Direct medical care costs first postoperative year after...(€) <sup>†††</sup>			
No complications	147		Deterministic
Cardiovascular complications	7,673		Deterministic
Stroke	7,512		Deterministic
Other complications	7,314		Deterministic
Recovery from other complications	396		Deterministic

Death	4,837		Deterministic
Direct long-term (2–5yers) medical care costs after... (€) <sup>†††</sup>			
Cardiovascular complications	386		Deterministic
Stroke	402		Deterministic
Other complications	396		Deterministic
QALY weights, estimates <sup>7</sup>			
>80 years age	0.74	0.699 to 0.780	Beta (322; 113)
Recovered after other complication <sup>9</sup>	0.66	0.611 to 0.709	Beta (227; 117)
Decrements of QALY weights <sup>8</sup> for...			
Cardiovascular complications	0.19	0.168 to 0.210	Gamma (298; 0.0006)
Stroke	0.35	0.280 to 0.420	Gamma (100; 0.0035)
Other complications	0.15	0.130 to 0.170	Gamma (100; 0.0007)

### Model inputs with mean estimates, confidence intervals, and distribution;

Abbreviations: CI: confidence interval; GDHT: goal-directed haemodynamic treatment, QALY: quality adjusted life years

<sup>†</sup>The Dirichlet distribution is a multivariate normalization of beta distribution that considers that the sum of probabilities is 1.0.

\* Swedish hip fracture database

\*\* Goal directed haemodynamic treatment compared to routine treatment

\*\*\* Swedish national database on secondary prevention in cardiac intensive care (SEPHIA)

\*\*\*\*Swedish national stroke database

† Karolinska University Hospital, Huddinge

†† University Hospital in Lund, Sweden

††† Epidemiological Centre of the Swedish National Board of Health

Abbreviations: goal directed haemodynamic treatment (GDHT) and quality-adjusted life year (QALY)



**Table 2.**

	Routine treatment			GDHT		
	Baseline	-95% CI	+95% CI	Baseline	- 95% CI	+95% CI
Costs, €	17,467	16,592	18,379	15,585	14,422	17,707
Effect	2.587	2.423	2.740	2.931	2.622	3.152
GDHT compared to routine fluid treatment						
	Baseline	+ 95% CI		-95% CI		
$\Delta$ Cost, €	-1,882	-3,043		239		
$\Delta$ Effect	0.344	0.492		0.082		
ICER (€/year)	Dominant*	Dominant*		2,915		

Average costs and QALYs, incremental costs and QALYs ( $\Delta$  cost,  $\Delta$  effect), and incremental cost-effectiveness ratio (ICER). Also the 95% CI of ICER is calculated by the upper and lower limits of 95% of the simulated values of incremental costs (€-3,043 to €239) and QALYs (0.082 to 0.492).

\*When new treatment is cheaper ( $\Delta$  cost is negative) and more effective ( $\Delta$  effect is positive), it is dominant and in that case, expression of ICER is unnecessary

Abbreviations: GDHT: goal-directed haemodynamic treatment, CI: confidence interval; ICER: incremental cost -effectiveness ratio; QALY: quality adjusted life year

## Appendix 1.

Meta-analysis/ systematic review (year), number of patients	Type of operation	Before organ failure	Haemodynamic goals proposed by Shoemaker	Mortality		Mortality rate of control group	Risk reduction (p)
				Relative risk (95% CI)	Odds ratio (95% CI)		
Boyd <sup>30</sup> (1999) n=994	Mixed	Yes	Mixed goals		0.35 (0.23 to 0.53)	Mixed	
Boyd <sup>30</sup> (1999) (subset*) n=451	Mixed	Yes	Mixed goals		0.25 (0.15 to 0.43)	>10%	
Boyd <sup>30</sup> (1999) (subset*) n=543	Mixed	Yes	Mixed goals		0.88 (0.39 to 2.00)	<10%	
Kern <sup>12</sup> (2002) (subset*) n=612	Mixed	Yes	Yes	Not calculated	Not calculated	>20%	- 0.23± 0.07 (<0.05)
Kern <sup>12</sup> (2002) (subset*) n=500	Mixed	Mixed	Yes	Not calculated	Not calculated	<15%	-0.04 ± -0.025 (<0.05)
Boyd <sup>14</sup> (2003) n=1974	Mixed	Yes	Mixed goals		0.45 (0.33 to 0.6)	Mixed	
Poeze <sup>13</sup> (2005) n=5 733	Mixed	Mixed	Mixed goals	0.75 (0.62 to 0.9)	0.61 (0.46 to 0.81)	Mixed	
Poeze <sup>13</sup> (2005) (subset*) n=4 174	Mixed	Yes	Mixed	0.66 (0.54 to 0.81)	0.43 (0.28 to 0.66)	Mixed	
Poeze <sup>13</sup> (2005) (subset*) n=1 142	Mixed	Yes	Yes	0.49 (0.36 to 0.65)	0.41 (0.29 to 0.59)	Mixed	
Poeze <sup>13</sup> (2005) (subset*) n=3 032	Mixed	Yes	Mixed goals	0.84 (0.64 to 1.10)	0.83 (0.62 to 1.11)	Mixed	
Price <sup>15</sup> (2007) n=130	PFF	Yes	No		1.44 (0.45 to 4.62)	< 10%	
Rahbari <sup>31</sup> (2009) (subset*) n=288	Colorectal	Yes	Mixed		0.33 (0.03 to 3.17)		

### Summary of search results on meta-analyses for postoperative mortality

Abbreviations: CI: confidence interval; GDHT: goal-directed haemodynamic treatment; PFF: proximal femoral fracture

The following search strategy was used in the PubMed Clinical Queries:  
systematic[sb]

AND

perioperative haemodynamic therapy OR goal directed haemodynamic therapy OR GDHT OR oxygen delivery OR oxygen consumption OR fluid therapy

AND

haemodynamic

AND

perioperative OR intraoperative OR surgery OR hip surgery

Limits: Publication Date from 1997 to 2010

Also search after authors and related articles was performed.

The searches were undertaken between 2009 and 2010

## Appendix 2.

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>16</sup> (1997) n=40	Blood flow, SV,	Proximal femoral fracture	Yes	LOS	Not reported	Not reported
Wilson <sup>32</sup> (1999) n=138	Oxygen delivery index (PAC / dobutamine or adrenaline)	Major mixed	Yes	LOS	Odds: 0.30 (0.11 to 0.50)	Not reported
Takala <sup>33</sup> (2000) n=412	Oxygen delivery index (PAC / dopexamine)	Major abdominal	Yes	Mortality		No difference
Lobo <sup>34</sup> (2000) n=37	Oxygen delivery index (PAC)	Major abdominal	Yes	Morbidity	RR: 0.47 (0.226 to 0.991)	
Gan <sup>35</sup> (2002) n=100	Blood flow, SV	Major abdominal	Yes	LOS		
Venn <sup>17</sup> (2002) n=90	CVP or blood flow, SV	Hip fracture	Yes	LOS		23% for CVP 26% for OD vs. 49% p=0.078
Conway <sup>36</sup> (2002) n=57	Blood flow, SV	Colorectal	Yes	Cardiac Output	Not reported	Not reported
Sandham <sup>37</sup> (2003) n=1994	Oxygen delivery index	Mixed	Yes	Mortality, morbidity	No difference	No difference
Pearse <sup>38</sup> (2005) n=122	Oxygen delivery index	Major mixed	Yes	Morbidity	RR: 0.63 (0.46 to 0.87)	
Noblett <sup>39</sup> (2005) n=108	Blood flow, SV	Colorectal	Yes	LOS		2% vs. 15% (p=0.043)
Donati <sup>40</sup> (2007) 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>41</sup> (2005) n=128	Blood flow, SV	Colorectal	Yes	LOS		37.5% vs. 59.3% (p=0.013)
Lobo <sup>42</sup> (2006) n=50	Oxygen delivery index (PAC / Dobutamine)	Major abdominal	Yes	Morbidity		16% vs. 52% (p<0.05)
Lopes <sup>43</sup> (2007) n=33	PPV	Major abdominal	Yes	LOS		75 % vs. 45% (p=0.049)
Senagore <sup>44</sup> (2009) n=64	Blood flow, SV	Laparoscopic	Yes	LOS		No difference
Mayer <sup>45</sup> (2010) n=60	SVV	Major abdominal	Yes	LOS		20 % vs. 50% (p=0.001)
Benes <sup>46</sup> (2010) n=120	SVV	Mixed high risk	Yes	Morbidity	RR: 0.518 (0.331 to 0.8)	30% vs. 58.3% (p=0.0033)

Summary of search results on clinical trials which used goal-directed haemodynamic treatment before onset of organ failure

Abbreviations: CVP: central venous pressure; CI: confidence interval; GDHT: goal-directed haemodynamic treatment; ICU: intensive care unit; LOS: length of stay; PAC: pulmonary artery catheter; PPV: pulse pressure variation; RR: relative risk; SV: stroke volume; SVV: stroke volume variation

The following searching strategy was used in the Pubmed Clinical Queries:

Therapy/Narrow[filter]

AND

haemodynamics OR perioperative haemodynamic therapy OR goal directed haemodynamic therapy OR GDHT OR fluid optimization OR oxygen delivery OR oxygen consumption OR fluid therapy OR stroke volume

AND

monitoring OR optimization

AND

surgery OR hip fracture surgery OR surgical procedure

AND

perioperative OR perioperative care OR intraoperative care

Limits: English, Publication Date from 1997 to 2010

Also search after authors found in the meta-analyses and related articles was performed. The searches were undertaken between 2009 and 2010.

### Appendix 3.

	Stepwise increase of relative risk					
	Baseline	+ 25%	+ 50%	+ 60%	+ 80%	+ 90%
Morbidity	0.5	0.63	0.72	0.79	0.84	0.88
Mortality	0.75	0.81	0.86	0.89	0.92	0.94

Estimates of relative risk used in deterministic sensitivity analyses when goal-directed haemodynamic treatment is compared to routine fluid treatment

### Appendix 4.

Given the expected absolute risk for postoperative complications (0.6) and the point estimates of relative risk used in the one-way sensitivity analyses, corresponding sample sizes of a future clinical trials and Number Needed to Treat values are calculated.

\*For the sample size calculation, absolute risk in the control group is 0.6. A two-tailed test for hypothesis testing of categorical data is used.

\*\* Number Needed to Treat (NNT) = 1/absolute risk reduction