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An Iterative Bayesian Approach to Health Technology Assessment: Application to a Policy of Preoperative Optimization for Patients Undergoing Major Elective Surgery

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Purpose*. This article presents an iterative framework for managing the dynamic process of health technology assessment. The framework uses Bayesian statistical decision theory and value of information (VOI) analysis to inform decision making regarding appropriate patient management and to direct future research effort over the lifetime of a technology. Within the article, the framework is applied to a policy decision regarding preoperative patient management before major elective surgery, for which trial data are available.* ***Method****. The evidence available prior to the trial is used to determine the appropriate method of patient management and to ascertain whether, at the time of commissioning, the trial was potentially worthwhile. The prior information is then updated with the trial data via a Bayesian analysis using informative priors. This post trial information set is then used to reassess the appropriate method for patient management and to determine whether there is a requirement for any further research.* ***Results****. Prior to the trial, preoperative optimization with dopexamine is identified as the appropriate method of patient management. The results of the VOI analysis suggest that a short-term trial was potentially worthwhile (population expected value of perfect information [EVPI] = £48 million). Following the trial, the uncertainty surrounding the choice of appropriate patient management and the potential worth of further research had increased (population EVPI = £67 million).* ***Conclusions****. The article demonstrates the value and practicality of applying the iterative framework to the dynamic process of health technology assessment. It is only by formally incorporating all of the information available to decision makers, through informed priors, that the appropriate decisions can be made.*

1. INTRODUCTION

Decisions made by health care systems around the globe regarding which health care technologies to fund from collective resources now routinely incorporate formal economic evaluations.[1] As for all decision making in health care, decisions about

reimbursement are inevitably undertaken in a context of uncertainty concerning the effectiveness and resource costs of health care interventions and programs. Therefore, 2 related sets of decisions need to be taken: those concerning appropriate service provision on the basis of existing information and those concerned with whether to fund additional research to reduce the uncertainty relating to the decision. Information acquisition is not costless, and the allocation of funds to the enhancement of the decision makers' information set, in a budget-constrained health service, reduces the "pot" of resources available for health service provision. Hence, a framework is necessary to unify these decisions and to ensure that health technology assessment (HTA) is subject to the same evaluation of efficiency as

service provision. The Bayesian decision-theoretic approach provides an explicit and rigorous framework within which both types of decision problem posed in health technology assessment can be addressed.

Furthermore, the process of health care decision making is not static. New information affecting health care decisions becomes available throughout the life cycle of all technologies. For example, the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom considers whether a new technology can be considered cost-effective for use in the National Health Service (NHS) based on available evidence, identifies research priorities following that initial decision, and reviews its decision approximately 3 years later.[2] Hence, the process of health technology assessment needs to be iterative over the lifetime of the technology and needs to incorporate some formal process for learning.[3,4] This requires the use of a Bayesian approach, which provides a dynamic framework to incorporate learning and assist decision making throughout the life cycle of the technology. In the framework, the decision-analytic model becomes the vehicle of health technology assessment, informing decision making regarding routine service use as well as directing future research effort, on an iterative basis, from the emergence of a new technology as feasible for use with patients and throughout its life cycle.

Although the potential value of applying the Bayesian decision-theoretic approach for health technology assessment has been discussed,[5–9] it has not been placed formally within the iterative framework that is increasingly important in decision making.

The aim of this article is to demonstrate the iterative framework, from the characterization of prior uncertainty through to the incorporation of new information and the reassessment of policy decisions, for a specific health technology. The chosen application relates to the evaluation of alternative arrangements for the preoperative management of

high-risk surgical patients. This application was selected due to the availability of data from a randomized trial conducted in the United Kingdom in 1999.[10] The analysis examined the decision uncertainty and value of information both before and after the trial was conducted, addressing the sequence of decisions common to the assessment of any health technology. The application demonstrated that an explicit and rational approach to the sequence of decisions in health technology assessment is possible, valuable, and practical.

The application has 2 key features that are important to reflect within the analysis. First, there is limited prior evidence available concerning the effects and, in particular, the costs of the various patient management strategies. For one of the patient management strategies (pre-op with adrenaline), there is no direct prior information at all. Second, the additional evidence with which the information set is updated comes from a small clinical trial with no prospective economic evaluation, although information on resource use was collected and an economic evaluation undertaken retrospectively.[11] As such, this example illustrates that the iterative framework can be applied to situations of limited evidence availability.

In addition to demonstrating the iterative framework, this article explores methods for capturing the correlation between cost and effect within the Bayesian analysis. This was undertaken as a sensitivity analysis through consideration of 3 alternative model structures. The article also reports the results of an analysis by surgical subgroup, on which the trial was originally stratified.[10]

The article is organized as follows: section 2 provides the methodological background to the analysis; the application is presented within section 3, with the prior analysis in section 3.1 and the posterior analysis in 3.2. Section 4 presents a discussion of the issues surrounding the iterative framework, both generally and specific to the application presented. Finally, some general conclusions are drawn.

2. METHODOLOGICAL BACKGROUND

The important role fulfilled by decision analysis in public policy decision making has been discussed by practitioners[6] and policy makers.[2] In recent years, a Bayesian decision-theoretic framework has been presented for addressing the 2 key decisions for public policy decision making in health care.[5,7,9] These 2 separate but complementary decisions involve the selection of health care policy on the basis of current information and the decision to collect further information to

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inform the policy-making process in the future. Within the framework, the choice between mutually exclusive strategies is made on the basis of expected utility. This has long been accepted as a rational basis for decision making[12–14] and renders irrelevant traditional rules of inference and issues of statistical significance.[9] Instead, the uncertainty surrounding the decision based on expected utility is formally valued to establish the worth of acquiring additional information, through further research. This formal assessment of uncertainty involves the established techniques of Bayesian value of information analysis[15] that have also been applied to decisions in environmental economics[16,17] and clinical decision-making.[18]

Value of information analysis involves establishing the difference between the expected value of a decision made on the basis of existing evidence and, following the collection of further information, the expected value of a decision made on the basis of new evidence. The expected value of perfect information (EVPI) values the resolution of all uncertainty, through the provision of perfect information, and provides a measure of the maximum return to further research.

Within the framework, the EVPI for the decision can be determined directly from the results of the probabilistic analysis, with each iteration representing a possible future resolution of the existing uncertainty for which the optimal decision (the intervention that maximizes net benefit) can be identified. For a decision involving j interventions where net benefit is dependent on a set of unknown parameters θ, the EVPI is simply the difference between the expected value of the decision made on the basis of existing information ($\max_j E_\theta \, NB(j, \theta)$) and the value of the decision made with perfect information ($\max_j NB(j, \theta)$) averaged over all possible realizations of uncertainty ($E_\theta \max_j NB(j, \theta)$):

$$EVPI = E_\theta \max_j NB(j, \theta) - \max_j E_\theta \, NB(j, \theta).$$

Information is a public good; as such, generation of perfect information for 1 instance of a decision ensures that the information is available for other instances of the decision. Hence, the overall value of perfect information surrounding a health care policy decision depends on the number of times that the decision is faced over the lifetime of the technology.[8,9] The population-level EVPI is determined by scaling up the individual EVPI according to the incidence of the decision.

In addition, the EVPI can be calculated for individual or various combinations of parameters to assess the potential worth of research concerning particular elements of the decision. This process involves determining the reduction in the costs of uncertainty associated with resolving the uncertainty concerning sets of parameters. For a subset of parameters φ, the expected value of partial perfect information (EVPPI) is simply the difference between the expected value of the decision made on the basis of existing information ($\max_j E_\theta \, NB(j, \theta)$) and the value of the decision made with perfect information about φ and current information about the remaining parameters (ψ) ($\max_j E_\psi|_\varphi \, NB(j, \varphi, \psi)$) averaged over all possible realizations of uncertainty about φ ($E_\varphi \max_j (E_\psi|_\varphi \, NB(j, \varphi, \psi))$):

$$EVPPI_\varphi = E_\varphi \max_j E_\psi|_\varphi \, NB(j, \varphi, \psi) - \max_j E_\theta \, NB(j, \theta).$$

There has been an increase in the application of Bayesian methods within health care.[19–21] The potential of Bayesian approaches to health care evaluation was recognized by the NHS Health Technology Assessment program in the United Kingdom, which commissioned a review of methods[22] that was subsequently published as a book.[23] To date, however, there have been no publications detailing the application of a fully informed decision-theoretic Bayesian analysis.

3. AN APPLICATION OF BAYESIAN DECISION ANALYSIS

Preoperative optimization for high-risk patients undergoing major elective surgery is a goal-oriented policy that involves admitting surgical patients ahead of surgery, inserting a pulmonary artery catheter to monitor cardiac index, and administering inotropes. The aim is to enhance presurgical cardiovascular flow and oxygen delivery and hence improve chances of survival postsurgery. As such, the policy involves increased resource use before surgery (including a stay in an intensive or high-dependency care unit), with the prospect of reduced resource use (due to reductions in complications) postsurgery. Two inotropes are available for administration during preoperative optimization—namely, dopexamine and adrenaline. The policy issues for the decision maker are first, on the basis of the available evidence, whether preoperative optimization is cost-effective, employing which inotrope for which patient groups, and, second, whether more evidence is required to support this choice of strategy.

The most recent study of preoperative optimization involved a randomized controlled trial comparing 2 methods of delivering preoperative optimization (through adrenaline and through dopexamine) with

standard patient management. The study was conducted in a population of high-risk patients undergoing major elective surgery and found a mortality benefit for patients in the preoperative optimization groups.[10] In addition, the study showed a lower rate of complications and resource use associated with preoperative optimization. A retrospective cost-effectiveness analysis found that preoperative optimization (with either inotrope) dominated usual care, whereas adrenaline was both more effective and more expensive than dopexamine (with each additional life-year costing £23,940).[11] Previous trials comparing preoperative optimization with dopexamine (*pre-opd*) and standard patient management found similar clinical results.[24,25] In addition, there was some evidence that the use of dopexamine reduced hospital costs and constituted a cost-effective method of managing high-risk surgery.[26] Given this prior evidence, a decision regarding preoperative management of patients undergoing major elective surgery could have been taken before the most recent trial was conducted. In these circumstances, it is not clear that the recent study was worthwhile. However, regardless of the cost-effectiveness of the recent trial, once the results are available, they should be incorporated with the prior evidence and estimates of cost-effectiveness to form an updated information set. This posterior information set should then form the basis for readdressing the decisions regarding patient management and the need for further evidence.

The analysis of preoperative optimization is organized as follows: in section 3.1, the information position that existed before the most recent trial is used to estimate prior cost-effectiveness, determine the appropriate method of patient management before the trial was commissioned, and consider whether, at the time of commissioning, the trial was potentially worthwhile. In section 3.2, this prior analysis is updated with the results of the most recent trial. From this posterior information position, the decision concerning the appropriate method of patient management is readdressed and an assessment made of whether further research is potentially worthwhile.

3.1. Prior Analysis

3.1.1. Background

The aim of the prior analysis was to model the information position that existed *before* the most recent trial to estimate the prior cost-effectiveness of the management strategies, determine the appropriate method of patient management *before* the trial

was commissioned, and consider whether, at the time of commissioning, the recent trial was potentially worthwhile.

The first step in the prior analysis involved identifying the evidence available prior to the recent trial. A search of the literature (see the appendix for details of the search strategy) identified 3 articles as relevant to the decision question being addressed prior to 1999 (Shoemaker and others 1988; Boyd and others 1993; Guest and others 1997).[24,25,26] Two of these articles detailed randomized trials of preoperative optimization (employing the inotropic agent dopexamine to enhance oxygen delivery) versus standard patient management in high-risk patients undergoing major elective surgery.[24,25] The first[24] was undertaken in the United States, the second[25] in the United Kingdom. Both trials measured effectiveness in terms of 28-day survival postsurgery. The third article provided a basic cost analysis of the UK trial.[26] Table 1 presents a summary of the results from the trials and the cost analysis.

3.1.2. Methods

3.1.2.1. Model structure. The structure of the decision model is presented in Figure 1. Figure 1a illustrates the decision concerning the choice of management strategy for high-risk patients undergoing major elective surgery. Figure 1b illustrates the sequence of events that a patient might experience for each management strategy. The sequence of events represented in the model includes the emergence of complications within 28 days of surgery and postsurgical mortality. Mortality postsurgery includes surgical mortality (that occurring within 28 days of surgery) and other mortality (occurring after 28 days postsurgery). Nonsurgical/other mortality is further split according to time period: mortality within 6 months, mortality within 1 year, and mortality 2 years postsurgery.

The model was constructed within Excel™ incorporating the Crystal Ball™ add-in program.

3.1.2.2. *Characterizing decision uncertainty.* The uncertainty that existed prior to the recent trial was reflected in the model through prior probability distributions, which were assigned to each of the parameters. These distributions were specified from the prior evidence identified from the literature, using patient-level data where possible.

1) Probabilities

Beta distributions were used to represent the uncertainty surrounding each of the probability parameters in the model.[12,27]

Table 1 Summary of Clinical Trial Results

	UK Trial Published 1993[25] Cost Analysis Published 1996[26]		US Trial Published 1988[24]	
	Active Intervention	Control	Active Intervention	Control
Number of patients	53	54	28	30
Age, yr	69 (61, 77)[a]	72.5 (66, 80)[a]	56.4 ± 3.1[b]	53.4 ± 2.5[b]
Sex, males/females (%)	74/26	61/39	75/25	39/61
Intensive care unit days	1.67 (0.79, 5)[a]	1.8 (0.83, 4.1)[a]	10.2 ± 1.6[b]	15.8 ± 3.1[b]
Hospital days	12 (7, 40)[a]	14 (7, 37)[a]	19.3 ± 2.4[b]	25.2 ± 3.4[b]
Complications	0.68 ± 0.16[b]	1.35 ± 0.20[b]		
Postoperative death, n (%)	3 (5.7)	12 (22.2)	1 (4)	10 (33)
Patient cost	£ 6525 (£4201, £17,469)[a]	£7525 (£4660, £16,156)[a]	£19,127[c,d]	£39,300[c,d]

a. Median (interquartile range).
b. Mean ± standard error of the mean.
c. Average patient cost.
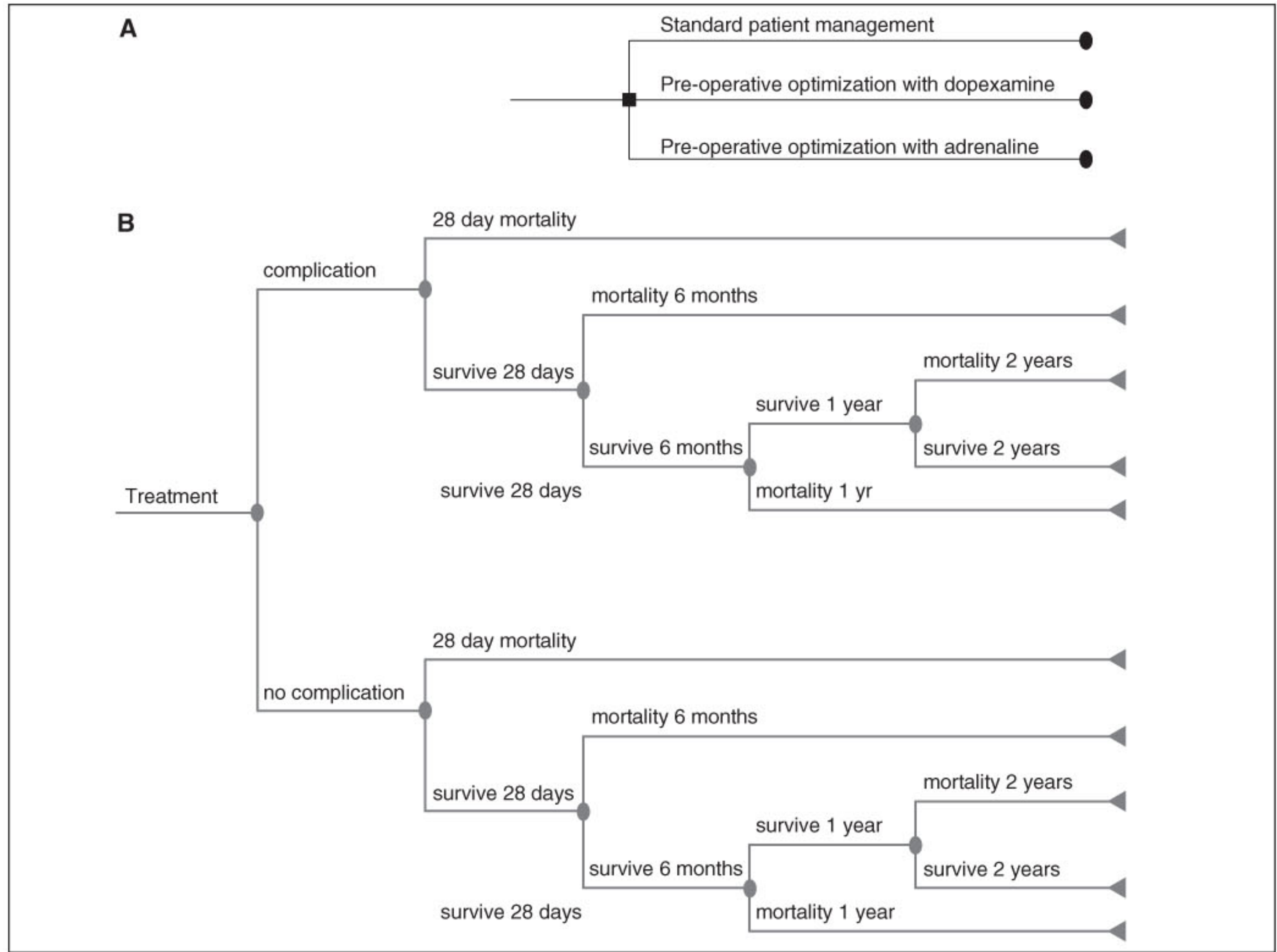d. Converted to £UK using an exchange rate of $1.50 to £1.

Figure 1   (a) The patient management decision. (b) Decision tree for each patient management strategy.

Both the probability of complication and the probability of 28-day mortality were calculated directly from information contained within the reports of the trials for standard patient management and preoperative optimization with dopexamine (*pre-opd*).[24,25] The impact of employing preoperative optimization with adrenaline (*pre-opa*), rather than dopexamine, on the probability of complications was modeled via a relative effect. This relative effect was specified as a normal distribution with a unitary mean (*pre-opa* is expected to be associated with the same probability of complications as *pre-opd*) and a 5% chance that the probability was equivalent to that of standard patient management. The profile of complications and the probability of 28-day mortality were linked to the relative effect to reflect expected differences between dopexamine and adrenaline "on circulation to the gut"[28] and consequent differences on postoperative morbidity. When the probability of complications for *pre-opa* was equal to or less than that of *pre-opd*, the profile of complications and the probability of 28-day mortality were equivalent to the values for *pre-opd*, but when the probability of complications was higher than that for dopexamine, the profile of complications and the probability of 28-day mortality were equivalent to those associated with standard patient management.

The probability of mortality for the remaining time periods was based on standard mortality rates.[29] This implies that after 28 days postsurgery, 1) the probability of mortality returns to the standard rate for a population of the same age, and 2) the probability of longer term mortality is independent of the complication status. These assumptions are both implicit in models or trials that restrict follow-up to 28 days.

2) Survival

The distributions of expected survival duration for the pathways involving mortality within 28 days were derived directly from a Bayesian bootstrap of the UK trial data for the standard patient management and *pre-opd* strategies.[30] These distributions were applied to the 28-day mortality pathways for *pre-opa* according to the prior on the relative effect, as with the probability of 28-day mortality.

For each time period beyond 28 days, survival duration was represented by a uniform distribution, reflecting the assumption of an equal probability of dying on any particular day within the interval.

3) Costs

The UK cost analysis detailed the median and interquartile range of the procedure costs broken down by stage (preoperative, intraoperative, and postoperative) and the costs of managing complications.[26] This evidence was used as an input into a series of patient-level simulations that provided patient cost profiles for each possible patient pathway. These simulations were in turn used as inputs within a Bayesian bootstrap to generate a distribution of the mean costs for each of these pathways.[30]

The process of constructing the cost profiles required the compilation of all of the appropriate cost elements occurring at each stage and in the event of complications. For *pre-opd* and standard patient management data for the elements of the cost profiles were provided in the cost analysis.[26] Two sets of cost profiles were constructed for *pre-opa*, incorporating the actual cost of the drug, for use in conjunction with the relative effect (see above). The first set reflected the situation where *pre-opa* was considered equivalent to *pre-opd* and used the data from the cost analysis concerning *pre-opd*. The second set used the data from the cost analysis concerning standard patient management to reflect the situation where *pre-opa* was considered equivalent to this method of management.

3.1.2.3. Adoption decision. Following the characterization of the parameter uncertainty, Monte Carlo simulation was used to propagate the uncertainty through the model. The results were used to identify the adoption decision (based on expected net benefit) and to represent the uncertainty surrounding the decision, in the form of cost-effectiveness acceptability curves and frontiers.[31]

3.1.2.4. Value of additional information. The EVPI for the decision made prior to the recent trial was calculated, using nonparametric methods direct from the results of the simulation. The population-level EVPI was determined by scaling up the individual EVPI according to the incidence of the decision. Here, the EVPI per surgical procedure was translated into a population value through reference to the estimated number of qualifying surgical procedures[a] over the expected lifetime of the decision, discounted at 6%. It was estimated that 0.4% of all surgical procedures undertaken in the United Kingdom (3.3 million per annum) could be considered to be qualifying procedures. The lifetime of the decision was assumed to be 15 years for the prior analysis.[b]

a. A qualifying surgical procedure is defined as an elective procedure, undertaken on a high-risk elderly patient, in cardiovascular surgery, gastrointestinal surgery, or general surgery.

b. Fifteen years was chosen because the date of the original trial was 1993; the policy decision continues to be relevant today, and it is estimated that it will continue to be relevant for a further 2 years at least.
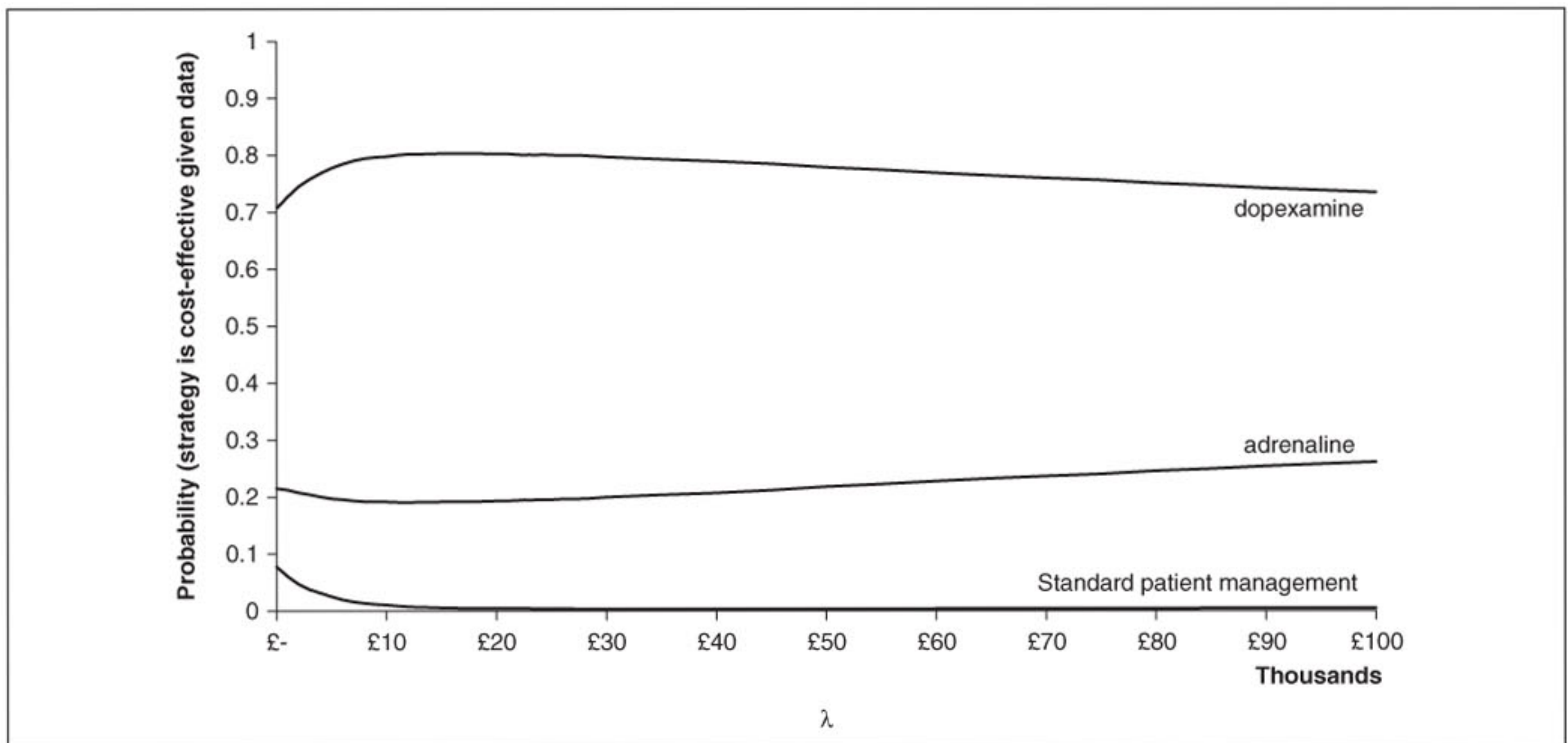
Figure 2 Prior cost-effectiveness acceptability curves for each patient management strategy.

In addition, value of information techniques were used to calculate the EVPI for various combinations of parameters. These combinations were constructed to represent the type of information collected from research of different forms (e.g., short- v. long-term clinical research, with and without economic data) to determine the maximum return and potential worth of these different types of research.

3.1.3. Results

3.1.3.1. Adoption decision. The mean expected costs associated with patients receiving preoperative optimization were £10,850 and £7,980 for adrenaline and dopexamine, respectively, whereas the mean expected cost for patients receiving standard management was £11,890.

Mortality at 2 years was 29% for patients receiving standard care, compared with 19% for patients receiving pre-op with adrenaline and 13% for those receiving pre-op with dopexamine. Translating 2-year mortality into survival duration generated a mean of 1.68 years postsurgery for patients in the pre-op with adrenaline group and 1.80 years postsurgery for the pre-op with dopexamine group, compared with 1.48 years for patients receiving standard care.

Based on mean values, pre-op with dopexamine dominates both pre-op with adrenaline and standard care because, on average, it was both more effective and less expensive.

Figure 2 illustrates the cost-effectiveness acceptability curves for the comparison between the 3 patient management strategies. If decision makers were unwilling to pay anything for an additional life-year, the probability that *pre-opd* was optimal (i.e., dopexamine is cost saving) was 0.71. If decision makers were willing to pay £20,000 for an additional life-year (λ), the probability that *pre-opd* was optimal was 0.8, compared with probabilities of 0.19 and 0.01 for *pre-opa* and standard patient management, respectively. If decision makers were willing to pay £30,000 per life-year gained, the probability that *pre-opd* was optimal was 0.797, compared with probabilities of 0.2 and 0.003 for *pre-opa* and standard patient management, respectively. The cost-effectiveness frontier for the decision between the 3 patient management strategies traces the cost-effectiveness curve for *pre-opd* due to it being dominant.

3.1.3.2. Value of information. The EVPI for the decision between the patient management strategies was £350 per surgical procedure, given a λ value of £20,000 per life-year, or £370 per surgical procedure, given a λ value of £30,000 per life-year. This translated into a population EVPI of £48 million or £53 million for a λ value of £20,000 or £30,000 per life-year, respectively. Figure 3 illustrates the population EVPI over a range of values of λ. Initially, the EVPI falls as the value of λ increases, as the reduction in uncertainty outweighs the increased valuation of the
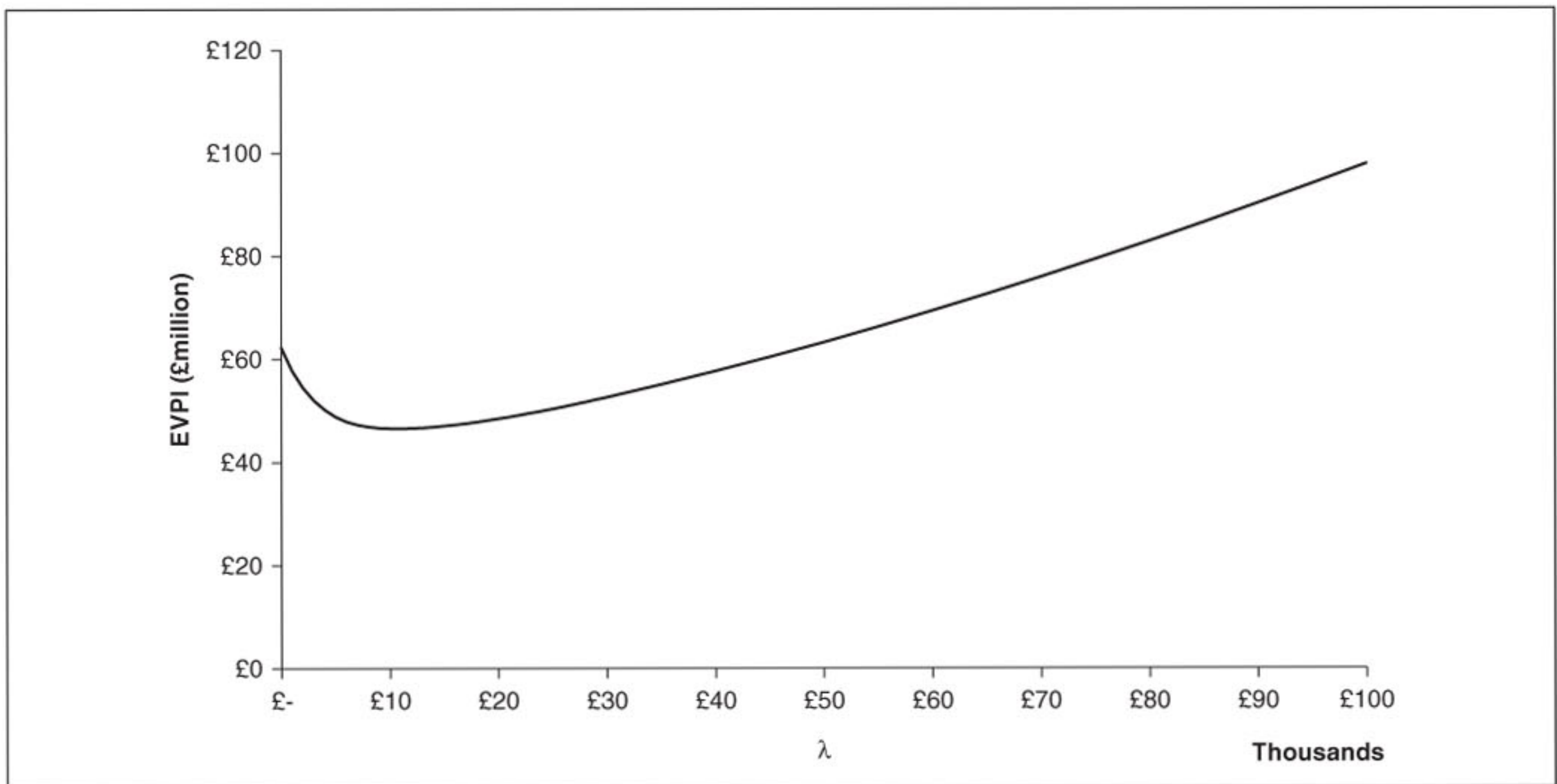
Figure 3   Prior expected value of perfect information (EVPI) for the decision between the 3 patient management strategies (UK population).

consequences associated with an incorrect decision. However, as λ increases beyond £10,000 per life-year, the uncertainty increases along with the valuation of the consequences; consequently, EVPI increases.

Figure 4 illustrates the population EVPPI for combinations of parameters assuming a λ value of £20,000 or £30,000 per life-year. This analysis identified that the cost of uncertainty was greatest surrounding the short-term (clinical and economic) parameters. Given a λ value of £20,000 per life-year, the EVPPI for a short-term trial incorporating costs was £48 million. The majority of this value was related to the uncertainty surrounding the costs and survival associated with the *pre-opa* strategy. Research that eliminated these uncertainties would be worth £37 million, compared with just £1.7 million, to eliminate the uncertainty surrounding the cost and survival associated with *pre-opd* and standard care.

3.1.4. Implications of the Results

The results of the prior analysis suggest that, before the most recent trial was undertaken, a policy of preoperative optimization with dopexamine dominated both standard patient management and preoperative optimization with adrenaline. However, the uncertainty surrounding the adoption of *pre-opd* exceeded the levels considered acceptable by standard conventions of statistical significance or acceptable error probabilities. Adherence to these rules of traditional inference would result in the continuation of standard management for patients. This is a policy that is expected to have a lower net benefit and is associated with a much lower probability of being optimal (0.01). The expected opportunity loss of failing to base the decision on the expected net benefit is the expected net benefit foregone. When λ is £20,000, this equates to a loss of £10,250 per surgical procedure.

The formal valuation of the costs of the uncertainty suggests that resolution of the uncertainty (perfect information) would be worth £48 million for the United Kingdom (assuming a λ value of at least £20,000 per life-year). This provides an absolute limit on the worth of further research concerning all elements of the decision for this value of λ. The analysis of the costs of uncertainty surrounding groups of parameters identified short-term (clinical and economic) parameters as having the greatest value of information. The maximum worth associated with a short-term trial, incorporating costs, was estimated to be £48 million, with the majority of this value related to the uncertainty surrounding the costs and survival associated with the *pre-opa* strategy (£37 million).
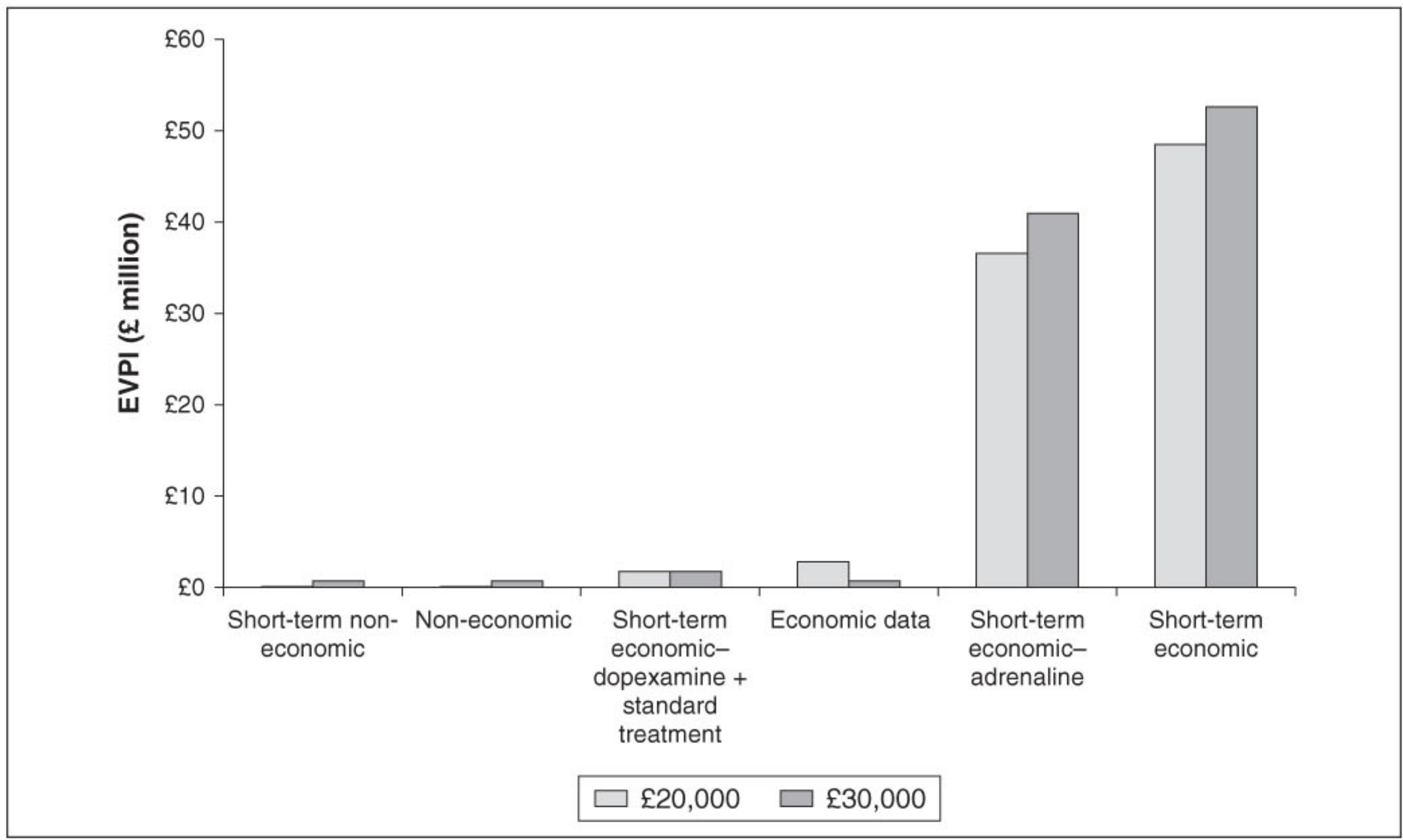
Figure 4   Expected value of partial perfect information (EVPPI) for trial types (UK population).

3.2. Posterior Analysis

3.2.1. Background

The aim of the posterior analysis was to update the prior information set with data from the recent trial (Wilson and others 1999) to estimate the posterior cost-effectiveness of the management strategies, determine the appropriate method of patient management following the trial, and consider whether there remained a need for further research.

The recent trial randomized 138 high-risk patients undergoing major elective surgery to receive pre-op with adrenaline (46 patients), pre-op with dopexamine (46 patients), or standard patient management (46 patients) (Wilson and others 1999)[10]. The randomization was stratified by surgery type (vascular, other abdominal, and surgery for upper gastrointestinal malignancy), although the trial was not powered for an analysis on the basis of surgical subgroup. The methods of patient management were compared on the basis of mortality, complications, and resource use. The results showed a mortality benefit for patients in the preoptimization groups (3/92 v. 8/46) and a

lower rate of complications in the dopexamine group compared to the adrenaline group. A retrospective cost-effectiveness analysis of the trial, with survival duration measured to 2 years and resource use followed up to 6 months, identified some important differences in resource use between the 3 groups.[11] Patients who received preoperative optimization tended to have lower usage of key resources (with those randomized to dopexamine having the lowest usage overall). In particular, the use of dopexamine was associated with a lower length of stay in the hospital. These differences translated into a difference in the mean cost of treatments, and the cost-effectiveness results showed that preoperative optimization (with either inotrope) dominated standard patient management, whereas adrenaline was both more effective and more expensive than dopexamine (with each additional life-year costing £23,936).[11]

3.2.2. Methods

3.2.2.1. Updating the prior model. The updating process combined the patient-level trial data concerning costs and survival duration with the prior estimates

Table 2 Prior Values Used within the Informed Analysis

	Standard	Adrenaline	Dopexamine
Initial model			
nu.trt	N (9, 0.19)	N (9, 0.27)	N (9, 0.14)
sigma.trt	N (0.6, 0.14) I(0,)	N (0.6, 0.15) I(0,)	N (0.4, 0.10) I(0,)
logh 1	N (−4.7, 0.34)	N (−5.5, 0.85)	N (−6.1, 0.61)
logh 2	N (−11.9, 3.78)	N (−11.9, 3.78)	N (−11.9, 3.78)
logh 3	N (−11.5, 3.33)	N (−11.5, 3.33)	N (−11.5, 3.33)
logh 4	N (−10.3, 1.86)	N (−10.3, 1.86)	N (−10.3, 1.86)
Regression model			
beta1	N (−0.5, 0.36)	N (0.18, 0.71)	N (0.12, 0.38)
beta2	N (3.85, 1.31)	N (0.49, 2.29)	N (0.23, 1.32)

N (mean, *SD*) = normal distribution. Within WinBUGS™, the normal distribution is expressed by the mean and the precision (the inverse of the variance).

of mean cost and mean survival duration generated from the prior model. This process resulted in posterior distributions of mean cost and mean survival duration, which incorporated all of the available information for each method of patient management.

The Bayesian updating was undertaken using WinBUGS™ (Windows-based Bayesian inference using Gibbs sampling), which provides a numerical approximation of the posterior through Markov chain Monte Carlo simulation via the Gibbs sampling algorithm.[32]

The primary analyses were undertaken using the initial model (see section 3.2.2.2). However, a sensitivity analysis was undertaken that examined different methods for the inclusion of correlation within the model structure (see section 3.2.2.6).

3.2.2.2. Model structure—initial model

1) Survival Duration

Survival duration, determined up to 2 years postsurgery, was available for each patient from the recent trial. Within the WinBUGS™ model, survival duration was modeled using a piecewise exponential distribution. For this formulation, the follow-up period was split into 4 distinct time periods (each representing an important interval in the postsurgical recovery of the patient[c]), and a separate exponential function was fitted to approximate the survival function for each period. Thus, a constant hazard is assumed within each time period but not across the entire follow-up period. The mean survival for each patient management strategy was calculated by estimating the area

under the survival curve for each interval and summing across the intervals.

The log-relative hazard form was used for the survival analysis in the WinBUGS™ model. For each management strategy, the log hazard rates (*logh*) for each period were modeled as normal distributions specified by a mean (representing the expected value) and precision (representing the uncertainty surrounding the mean). The prior values for the mean and precision were determined from the probabilistic analysis of the prior model by converting the distribution of the survival probability to a distribution of the log hazard rates. Table 2 contains details of the prior values.[d]

2) Costs

Patient-level data on resource use within the trial, with a follow-up of 6 months, were available from the trial. For the cost-effectiveness analysis, this resource use (including days in hospital, drug use, and interventions) was converted to a patient-specific cost (for more details, see Fenwick and others 2002).

In the WinBUGS™ model, the patient-level cost data were modeled as a lognormal distribution, implemented by modeling the log cost as a normal distribution with mean (*nu.trt*) and precision (*tau.trt*). The mean of the log cost (*nu.trt*) was itself modeled as a normal distribution, specified by a mean and precision. This distribution represented the variation in the mean log cost (the second-order uncertainty). The prior distributions for the parameters of this distribution were generated from the probabilistic analysis of the prior model.

c. The first period covered the initial 28 days postsurgery (the standard length of time used to report outcomes in intensive care). The second period extended to 6 months postsurgery (the interval for which complication data and costs were available). The third period extended to 1 year postsurgery, and the final period covered the entire second year postsurgery.

d. The values post 6 months were identical irrespective of the patient management strategy because the longer term survival probabilities (post 28 days) in the prior model were based on published sources and were not treatment specific.

The distribution of the precision of the log cost (*tau.trt*) represented the (first-order) uncertainty in the simulated patient cost data (see section 3.1.2.2) and provided an estimate of the extent of variation within the observed data. To speed up convergence, this distribution was modeled indirectly through the standard deviation of the log cost (*sigma.trt*) and converted to give the precision of the log cost. The distribution of the standard deviation of the log cost (*sigma.trt*) was modeled using a half-normal distribution (a normal distribution truncated at zero to prevent negative values) specified by a mean and precision. The simulated patient cost data, created to populate the prior model (see section 3.1.2.2), were used to specify the mean and precision parameters of this distribution. The prior values are detailed in Table 2.

The mean cost for each method of patient management was determined through a back-transformation of the log costs.[e]

3.2.2.3. Adoption decision. The WinBUGS™ analysis involved a burn-in of 10,000 iterations, followed by a further 10,000 iterations to approximate the posterior distributions for cost and survival duration. These posterior distributions were used to identify the posterior adoption decision (based on mean values) and to assess the posterior uncertainty surrounding the decision, in the form of cost-effectiveness acceptability curves (CEACs) and cost-effectiveness acceptability frontiers (CEAFs).

3.2.2.4. Value of additional information. The EVPI for the decision made following the recent trial was calculated, using nonparametric methods direct from the posterior distributions, to assess the potential worth of further research beyond the trial. The population-level EVPI was determined by scaling up the individual EVPI according to the incidence of the decision. The EVPI per surgical procedure was translated into a population value using the same incidence data as the prior analysis, with the lifetime of the decision reduced to 9 years to accommodate the advancement of time while the trial was undertaken.

3.2.2.5. Subgroups. The use of Bayesian methods enabled analyses to be undertaken on the basis of the surgical subgroup on which the trial was originally stratified[10]. These reanalyses involved partitioning and analyzing the data according to surgical subgroup and were undertaken as sensitivity analyses.

The prior for these analyses was that the subgroups were similar and exchangeable in terms of cost and survival. As such, the priors for each subgroup were those specified for the original model.

3.2.2.6. Alternative model structures. During the updating process, WinBUGS™ handles each node in the model separately and independently. Therefore, relationships between nodes are not taken into account within the analysis unless specified in the model. The initial model makes no allowance for a relationship between costs and survival duration, and hence the results will be uncorrelated. A sensitivity analysis around model structure was undertaken to examine different methods for the inclusion of correlation within the model structure. Within this analysis, 3 additional models, comprising alternative methods for incorporating the relationship between cost and survival, were considered.

The first alternative modeled a causal, structural relationship between cost and survival. The rationale for this model was that the relationship between cost and survival duration was driven by the existence of postsurgical complications; as such, the data set was partitioned and analyzed according to patients' complication status. The model was structured similarly to a regression equation, with dummy variables (*beta1* and *beta2*) representing the existence of complications, to provide overall results for each method of patient management. The prior values for the dummy variables are given in Table 2.

The second alternative modeled the statistical relationship between cost and survival. Here, a "frailty" effect was included in the cost and survival duration equations of the original model, thus ensuring that each node was included within the updating process of the other.[33]

The third alternative combined the regression structure and the frailty terms within one model.

Further details concerning the various model structures are available from the authors.

3.2.3. Results

3.2.3.1. Adoption decision. The mean expected cost for patients was £8590 for those receiving *pre-opa* and £5960 for those receiving *pre-opd*. For those patients receiving standard management, the mean expected cost was £10,180.

The mean survival duration associated with patients receiving *pre-opa* and *pre-opd* was 1.71 years and 1.62 years, respectively. The mean survival duration for patients receiving standard management was 1.39 years.
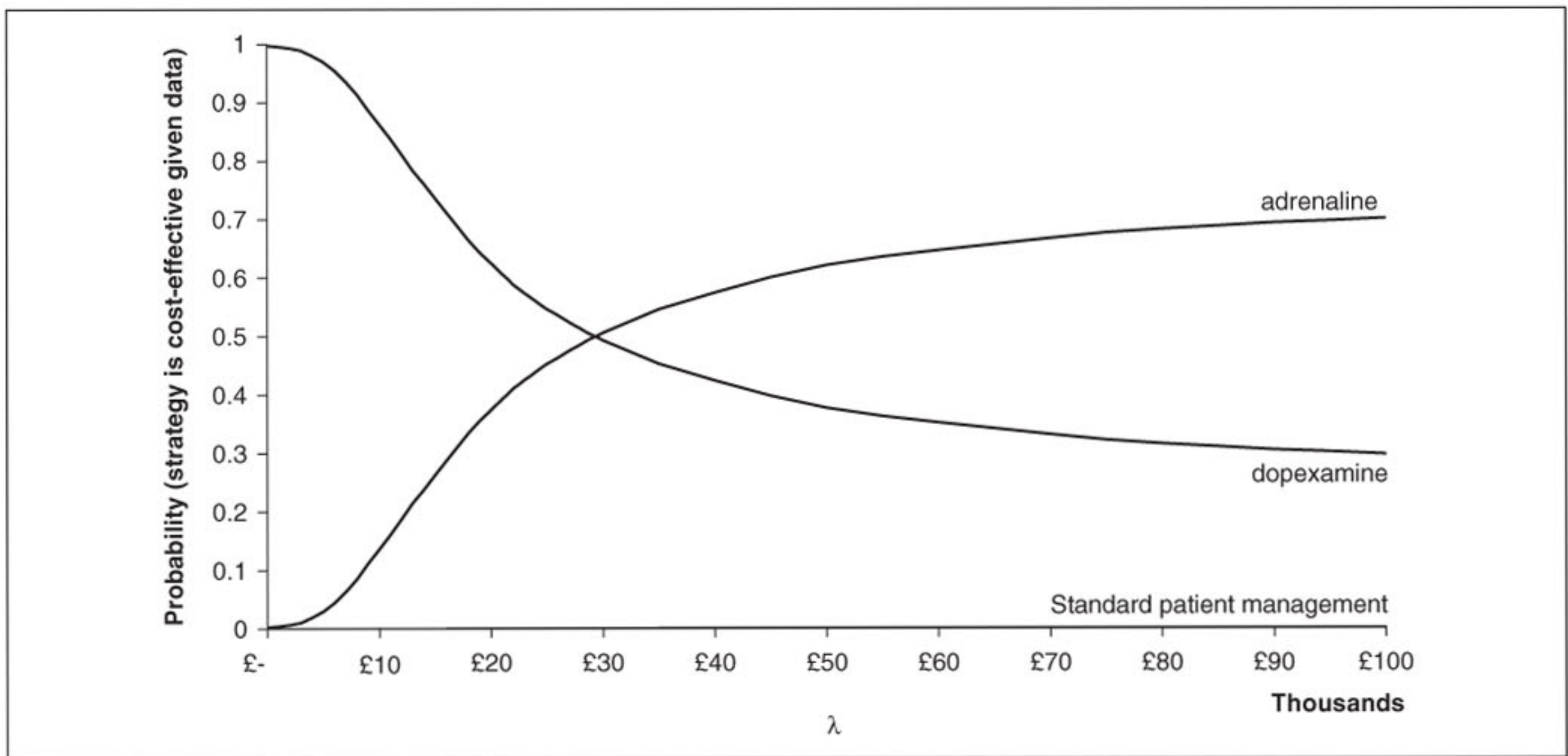
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e. Note that the back-transformation only provides a reasonable estimate of the mean cost if the data are lognormally distributed. If this assumption is inappropriate, the back-transformation will generate inaccurate results.

Figure 5   Posterior cost-effectiveness acceptability curves for each patient management strategy.

Based on mean values, standard care was dominated by preoperative optimization employing dopexamine, whereas preoperative optimization employing adrenaline was associated with an incremental cost-effectiveness ratio (ICER) of £29,580 per life-year gained when compared to *pre-opd*.

Figure 5 illustrates the cost-effectiveness acceptability curves for the comparison between the 3 patient management strategies. If decision makers were unwilling to pay anything for an additional life-year, the probability that *pre-opd* was optimal (i.e., dopexamine is cost saving) was 0.9973. If decision makers were willing to pay £20,000 per life-year gained, the probability that *pre-opd* was optimal was 0.6255, compared with probabilities of 0.3742 and 0.0003 for pre-op with adrenaline and standard patient management, respectively. If decision makers were willing to pay £30,000 per life-year gained, the optimal choice switches to *pre-opa*, with a probability that it was optimal of 0.5059, compared with probabilities of 0.4934 and 0.0007 for pre-op with dopexamine and standard patient management, respectively. The cost-effectiveness frontier (not shown) follows the CEAC for *pre-opd* up to the point where the adoption decision switches to *pre-opa* (λ value of £29,580) and then follows the CEAC for *pre-opa*.

3.2.3.2. Value of information. The EVPI for the decision between the patient management strategies was £650

per surgical procedure (£67 million for the population) at a λ value of £20,000 per life-year and £1440 per surgical procedure (£148 million for the population) for a λ value of £30,000 per life-year (see Figure 6).

3.2.3.3. Subgroups. Table 3 summarizes the expected cost and expected survival duration results, the ICER, and the EVPI for the subgroup analyses. Standard care was dominated for each of the subgroups, although the choice between the inotropes for achieving oxygen delivery varied between the subgroups. In addition, the extent of the uncertainty and the value of information surrounding the decision varied between the subgroups, with the upper gastrointestinal malignancy group facing the largest uncertainty (both parameter and decision) and the highest EVPI. This was reflected in the high population EVPI for this group, despite the small population of patients facing this type of surgery.

3.2.3.4. Alternative model structures. Table 4 summarizes the expected cost and expected survival duration results, the ICER, and the EVPI for the sensitivity analyses on model structure. The results show that when some allowance is made for a relationship between costs and survival duration, the expected mean cost (and standard error) falls, whereas the expected mean survival duration (and standard error) increases. These results hold across all of the model structures employed and concord with the empirical
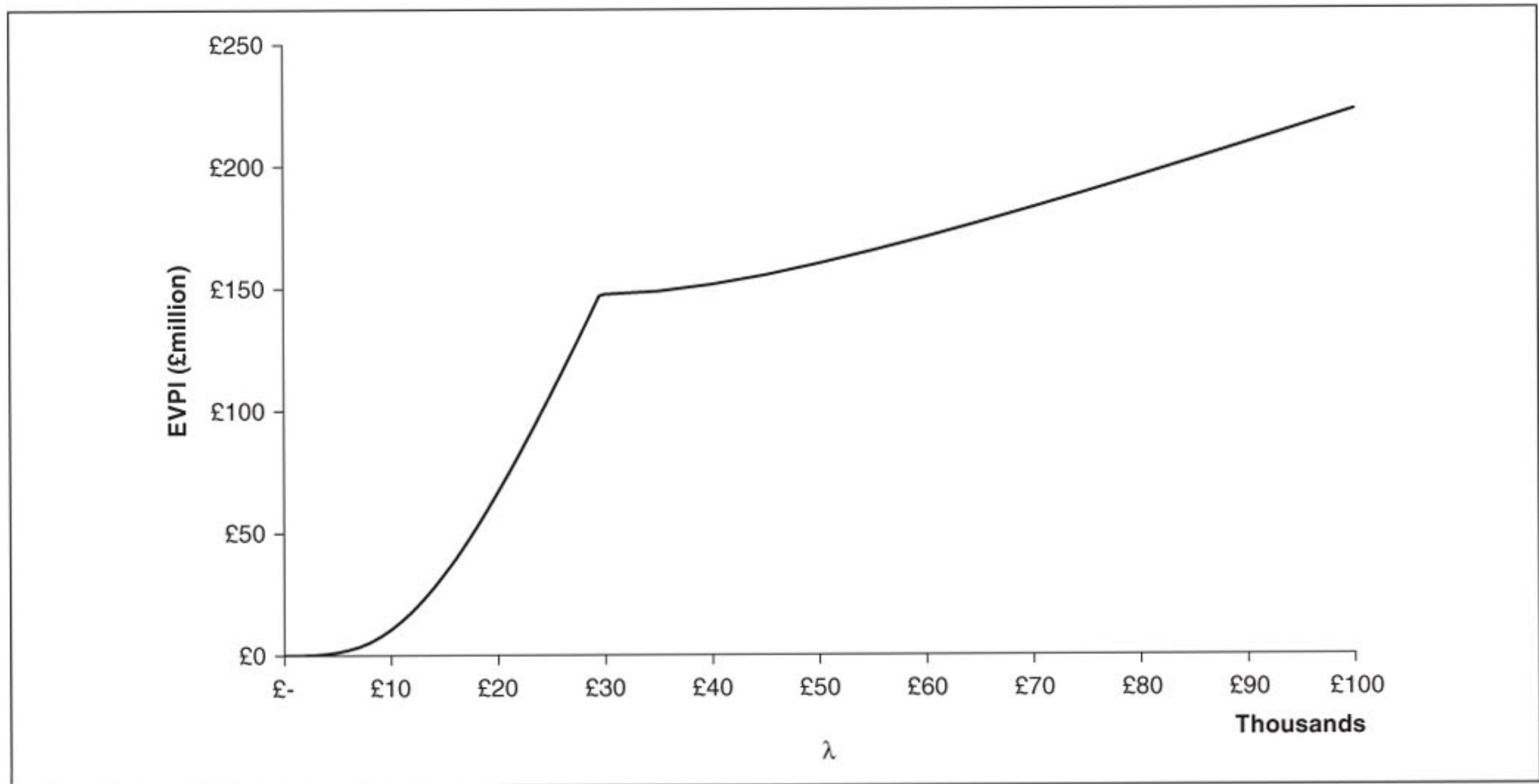
Figure 6   Posterior expected value of perfect information (EVPI) for the decision between the 3 patient management strategies (UK population).

Table 3   Results for the Surgical Subgroups: Expected Costs, Expected Survival Duration, ICER, and EVPI

Mean (SEM)	Pre-op with Adrenaline	Pre-op with Dopexamine	Standard Management	Population EVPI	
				λ = £20k	λ = £30k
Other abdominal				£17 million	£24 million
Cost (£)	5810 (740)	5980 (572)	6820 (1130)		
Survival (days)	660 (30)	630 (40)	560 (40)		
ICER	—	Dominated	Dominated		
Upper gastrointestinal malignancy				£39 million	£75 million
Cost (£)	11,080 (2010)	7420 (870)	12,640 (2030)		
Survival (days)	460 (80)	430 (70)	420 (80)		
ICER	£40,790	—	Dominated		
Vascular				£2 million	£8 million
Cost (£)	11,190 (2030)	5720 (660)	12,920 (2040)		
Survival (days)	650 (40)	660 (40)	460 (70)		
ICER	Dominated	—	Dominated		

EVPI = expected value of perfect information; ICER = incremental cost-effectiveness ratio.

evidence that there is a small, negative correlation between cost and survival (−0.1). The results, for each of the alternative models, were similar to those of the initial model (with standard care dominated and pre-operative optimization with dopexamine both cheaper and less effective than preoperative optimization with adrenaline), although the ICER varied according to the model structure. The level of uncertainty and the value of information surrounding the decision did not differ markedly between the model structures.

3.2.4. Implications of Results

The results of the posterior analysis suggested that a policy of preoperative optimization was the optimal

Mean (SEM)	Pre-op with Adrenaline	Pre-op with Dopexamine	Standard Management	Population EVPI	
				λ = £20k	λ = £30k
Initial model					
Cost (£)	8590 (980)	5960 (470)	10,180 (1340)	£67 million	£148 million
Survival (days)	620 (30)	590 (30)	510 (40)		
ICER	£29,580	—	Dominated		
Regression model					
Cost (£)	7950 (780)	5670 (390)	9570 (1200)	£87 million	£111 million
Survival (days)	630 (30)	590 (30)	500 (40)		
ICER	£34,140	—	Dominated		
Frailty model					
Cost (£)	8530 (960)	5900 (470)	10,090 (1350)	£60 million	£137 million
Survival (days)	640 (30)	610 (30)	520 (40)		
ICER	£22,740	—	Dominated		
Bivariate regression					
Cost (£)	7910 (770)	5660 (390)	9490 (1220)	£78 million	£126 million
Survival (days)	640 (30)	610 (30)	510 (40)		
ICER	£25,440	—	Dominated		

EVPI = expected value of perfect information; ICER = incremental cost-effectiveness ratio.

choice for managing high-risk patients undergoing major elective surgery following the recent trial. The choice concerning inotrope depended crucially on the value that the decision maker was willing to pay for additional life-years in this patient group (λ). For λ values above £29,580, *pre-opa* should be adopted; below this, *pre-opd* was the optimal choice. The uncertainty surrounding the decision also depended crucially on λ. However, the decision uncertainty was much higher than would be acceptable by standard conventions of significance irrespective of the value of λ. Adherence to these conventions would result in the continuation of standard patient management with a much lower probability of being optimal (0.0003) and expected losses per surgical procedure (£114 million annually). The formal valuation of the costs of uncertainty suggested that resolution of the uncertainty would be worth £67 million for the whole population (given a λ value of £20,000 per life-year). This provides an absolute limit on the worth of further research concerning all elements of the decision, for this value of λ, and suggests that further research is still potentially worthwhile following the trial.

4. DISCUSSION

Before the 1999 trial, the optimal adoption decision was a policy of preoperative optimization with dopexamine irrespective of the decision makers' willingness to pay for life-years gained. Following the trial, the optimal adoption decision involved preoperative optimization, although the choice between the inotropes dopexamine and adrenaline was dependent on the willingness to pay. Comparison of the results from the prior and posterior analyses illustrates that the incorporation of the trial data reduced the uncertainty surrounding the estimates of expected cost and expected survival duration.

However, this reduction in parameter uncertainty did not translate into a reduction in decision uncertainty. In fact, the posterior analysis exhibited greater decision uncertainty than the prior model. For the prior analysis, the probability that the adoption decision (*pre-opd*) was cost-effective exceeded 0.71 regardless of the willingness to pay for life-years gained. For the posterior analysis, the probability that the adoption decision was cost-effective dropped to 0.52 at the point where the decision switched between *pre-opd* and *pre-opa* (£29,580).

This increase in decision uncertainty was due to a shift in the positions of the distributions of expected costs and survival duration for *pre-opa* and *pre-opd* following the posterior analysis. These shifts were a result of differential weightings attached to the prior evidence. In particular, the posterior estimate of survival duration for *pre-opa* was heavily influenced by the prior, whereas the estimate for *pre-opd* was heavily influenced by the trial data. As a result, the estimates for survival duration were closer and the incremental survival duration was lower in the posterior analysis

than in the prior analysis, leading to a positive ICER for *pre-opa* (£29,580). This increase in decision uncertainty, between the prior and posterior analyses, was carried through and translated into an increase in the value of information. For the prior model, the resolution of uncertainty would be worth £48 million for the population (£350 per surgery). Following the incorporation of the trial data, the expected value of perfect information was £67 million for the population (£650 per surgery). Thus, the situation occurs where incorporating additional trial data has increased the uncertainty surrounding the adoption decision and increased the worth of further research.

This analysis illustrates that a fully Bayesian decision analysis can be undertaken, even within the context of small trials and with the existence of relatively little prior information. In addition, through sensitivity analysis, this example has illustrated that it is possible to examine the impact of additional data on specific patient subgroups. If the decision maker were able to differentiate policy on the basis of surgical subgroup, the results of the subgroup sensitivity analysis suggest that preoperative optimization should be adopted for all patients, with dopexamine employed to achieve optimization for those undergoing vascular surgery and adrenaline used for those undergoing other abdominal surgery. For those patients undergoing surgery for upper gastrointestinal malignancy, the inotrope employed to achieve optimization depends crucially on the decision makers' willingness to pay for additional life-years.

The sensitivity analyses regarding model structure illustrated that it was possible to incorporate correlation between parameters into the model, although the results suggest that for this particular example, modeling the correlation between cost and effect does not have a great impact on either expected cost-effectiveness or the value of information.

This study has demonstrated that an explicit and rational approach to the whole sequence of decisions in health technology assessment is both valuable and practical. However, some areas of the process remain to be addressed. The retrospective nature of the prior analysis meant that it was not possible to elicit informative prior distributions for the parameters for which there was no information.[34] This particularly affected the estimates of cost and effect for preoperative optimization with adrenaline. These estimates were instead handled through a number of assumptions regarding the relationship between the available data and the required data. The retrospective nature of the prior analysis also affected the structure employed for the prior model. For example, the piecewise

exponential distribution employed 4 time periods, which were largely dictated by the availability of data from the trial. The results of the prior analysis would be affected by this structure. A prospective prior analysis may well have involved a different structuring for survival duration and could have drawn different conclusions.

Within this study, updating was only undertaken for the cost and effect parameters and only as a result of additional data from 1 clinical trial. However, the process could easily be adapted to allow updating of each and every parameter within the model, from any number of disparate sources of information. Cooper and others[35] demonstrated the construction of a comprehensive decision model within WinBUGS™ that would enable this process. The approach would allow all sources of evidence to be incorporated within the model and thus form part of the decision-making process. Where the same evidence source is used to populate different components within the model, this approach would ensure that all sources of uncertainty and correlation were captured within, and propagated through, the model and thus reflected within the decision. Where there are multiple sources of prior evidence available, formal evidence synthesis methods should be used to ensure that uncertainty is incorporated appropriately within the model.[36] These methods can also be incorporated within a single unified Bayesian decision model evaluated within WinBUGS™.[23,35]

The framework, as demonstrated within this study, can only determine the potential worth of further research, with EVPI providing a necessary (but not sufficient) condition for establishing the value of further research. It is only in a situation where the EVPI is low that it can be used to determine whether research is worthwhile per se, by eliminating the requirement for further information. The sufficient condition for the worth of specific further research requires that the expected value of sample information (EVSI) exceed the costs of the specific research. The difference between the EVSI and the costs of research is the expected net benefits of sampling (ENBS), an estimate of the societal payoff from the research. Specific research is worthwhile if the ENBS is positive. Technically efficient research can be identified through manipulation of research design parameters (e.g., sample size, sample allocation, etc.) to maximise ENBS.[6,7,37] Methods are available for establishing EVSI when net benefits are normally distributed[6,7,37] and, more recently, for a range of conjugate data structures.[38] However, the complexity and computational challenges of nonconjugate prior distributions are yet to be resolved.

5. CONCLUSIONS

In conclusion, this study has illustrated that it is possible to implement an iterative framework for health technology assessment. Within this framework, the model is implemented early in the life cycle of the technology, and new information is incorporated into the model, through the use of Bayesian methods, as it emerges. Hence, the model becomes the vehicle for managing the process of health technology assessment throughout the life cycle of the technology, directing each stage on the basis of the current level of information, thus ensuring consistency in decision making over time between health care provision, research and development priorities, and research methods.

APPENDIX
SEARCH STRATEGY FOR LITERATURE SEARCH

Search Strategy
Search terms used:

1. preoperative optimisation/optimization
2. preoperative care
3. preoperative management
4. perioperative optimisation/optimization
5. perioperative management
6. perioperative care
7. goal orientated/oriented management
8. #1 or #2 or #3 or #4 or #5 or #6 or #7
9. oxygen delivery
10. oxygen administration
11. oxygen supply
12. preoxygenation/pre-oxygenation
13. #9 or #10 or #11 or #12
14. #8 and #13
15. cardiac monitoring
16. physiological monitoring
17. cardiac output
18. #15 or #16 or #17
19. #8 and #18
20. #14 or #19
21. #20 and (TG = "HUMAN")
22. #21 and (PY<="1996")

Databases searched:

Medline (204 records)
Embase (35 records)
BIDS Science Citation Index (37 records)

Accepted at title stage: 10 records were accepted at the title stage.

Accepted at abstract stage: 5 records were accepted at the abstract stage.

Accepted at the paper stage: 3 papers were accepted at the paper stage.

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