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BUILDING A REFERENCE CASE FOR BAYESIAN APPLICATIONS TO HEALTH ECONOMICS AND OUTCOMES RESEARCH

Karl Claxton
Elisabeth Fenwick
Stephen Palmer
Mark Sculpher
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Alex Sutton

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Karl Claxton[b],
Elisabeth Fenwick[b],
Stephen Palmer[a],
Mark Sculpher[a],
Keith Abrams[c],
Alex Sutton[c]

a. Centre for Health Economics, University of York
b. Department of Economics, University of York
c. Department of Epidemiology and Public Health, University of Leicester

Summary

The aim of this study is to demonstrate that Bayesian decision theory and value-of-information analysis is a valuable and practical framework within which two conceptually separate decisions problems can be addressed: (i) the selection of the optimal treatment strategy given existing information, and (ii) identification of the worth of further information collection to inform this choice in the future. The specific objectives were: (1) to combine prior decision theoretic modeling with patient level trial data, and (2) to relax the restrictions of using conjugate prior distributions and a parametric approach to value of information analysis by using numerical methods to estimate posterior probabilities.

Within this study these methods were developed in the context of two specific decision problems for which published evaluations exist. Both applications used patient level data on costs and effects from recent trials. This enabled an analysis of the decision uncertainty and the value of information both before (retrospectively) and after these trials were conducted. The analysis provides some assessment of whether these trials were worthwhile and whether additional evidence may still be required.

The first application evaluates the decision uncertainty and value of information surrounding the choice between low and high dose lisinopril before and after "The Assessment of Treatment with Lisinopril and Survival" (ATLAS) trial was conducted and reported (Packer et al 1999). The second application evaluates the decision uncertainty and value of information surrounding the choice between standard care and pre-operative optimisation using the inotropes, adrenaline or dopexamine for high risk patients undergoing major elective surgery before and after the most recent trial (Wilson et al 1999) was conducted and reported.

This introductory section provides a brief overview of the common methodological background to this work, an introduction to each of the clinical applications, and an overview of the stages of analysis followed in each of the applications. A brief summary of the results of each application is followed by a discussion of the common issues, which are raised by these applications. Finally we provide an overview of our dissemination of this work through conferences, seminars, workshops, and plans for the submission of three papers to peer-reviewed journals. Full details of the analysis of each of these clinical applications including the particular methods adopted, the characterisation of pre-trial evidence, the analysis of the trial data, the results and discussion of the results are fully reported in Parts I and II of this report, which are intended to be research reports in their own right.

1. Introduction

The aim of this study was to demonstrate that Bayesian decision theory and value-of-information analysis is a valuable and practical framework within which two conceptually separate decisions problems can be addressed: (i) the selection of the optimal treatment strategy given existing information, and (ii) identification of the worth of further information collection to inform this choice in the future. The value of conducting additional research to inform particular clinical decision problems is of general interest. It has implications for the design, conduct and interpretation of research, as well as the more general policy issue of setting priorities in clinical research and development. These issues are also at the heart of the current international debate about the appropriate regulation of new health care technologies (Claxton 1999a; and Neumann et al., 2000). Bayesian decision theory and value-of-information analysis is a useful analytic framework for analysts, designing and conducting research, for clinical decision makers interpreting the results of research and for policy makers, considering research priorities and the appropriate regulation/reimbursement of new technologies. This study demonstrates the benefits and the practicality of this approach by applying it to two clinical decision problems: i) low or high doses of the angiotensin converting enzyme (ACE) inhibitor lisinopril in chronic heart failure; and ii) standard care or a policy of pre-operative optimisation, employing dopexamine or adrenaline, for patients undergoing major elective surgery.

2. Methodological background

A Bayesian decision theoretic framework for the evaluation of health care programmes has previously been presented (see Claxton and Posnett, 1996; Claxton, 1999b; and Claxton et al., 2000a). The framework suggests that an economic choice between mutually exclusive health care programmes should be distinguished from the conceptually separate question of whether more information should be acquired to inform this decision in the future. Within this framework the choice between programs should be based on expected utility (in our analysis, net benefit) and the only valid reason to consider the uncertainties surrounding the outcome of interest to establish the value of acquiring additional information by conducting further research. In this sense Bayesian (as well as Frequentist) inference, including ranges of equivalence and benchmark error probabilities, are not useful or consistent with rational decision making. The possibility of using Bayesian decision theory to establish expected utilities for alternative treatment strategies has been accepted as a rational basis for decision making for some time (Lindley 1994; and Berry 1994). Establishing the prior and posterior distribution of expected utility (or net benefit) may be irrelevant to the adoption decision but is essential in deciding whether further clinical research should be conducted and how this should be designed. This

decision problem is either ignored or remains implicit in both Bayesian and Frequentist inference. However, Bayesian decision theory and value-of-information analysis provides an explicit and rigorous framework within which both of these decision problems posed in health technology assessment can be addressed.

Information is valuable because it reduces the expected costs of uncertainty surrounding a decision regarding service provision. The expected cost of uncertainty is determined by the probability that a treatment decision based on existing (prior) information will be wrong and the consequences of a wrong decision (loss function). The expected costs of uncertainty can also be interpreted as the expected value of perfect information (EVPI) because perfect information would, by definition, eliminate all uncertainty surrounding the decision It is also the maximum a decision maker should be willing to pay for additional evidence to inform this decision in the future (see Claxton and Posnett, 1996; Thompson and Graham 1996; and Thompson and Evans, 1997). If the EVPI exceeds the expected costs of additional research then it is potentially cost-effective to acquire more information by conducting additional research.

This study builds on the large body of Bayesian biostatistics literature (Spiegelhalter and Freedman, 1988; Breslow 1990; Spiegelhalter et al., 1994; Berry and Stangl, 1996; Abrams and Jones, 1997; Abrams and Sanso, 1998; and Spiegelhalter et al, 1999). Whilst these Bayesian approaches to individual clinical trials have considered specific aspects of design, monitoring and interpretation, they have not necessarily considered the trials in a wider context. The same position is also true for most meta-analyses of clinical trials. Whilst some of these have even considered a variety of outcome measures (for example Bhuta and Henderson-Smart, 2000), both harmful and efficacious, few attempts have been made to formally consider the various health care policy options within a decision modeling framework (Sutton et al, 1999). Therefore, the next logical step is to conduct a fully Bayesian decision theoretic analysis, of which there have been relatively few (Parmigiani et al, 1997), which uses all currently available prior evidence to identify the most cost-effective health care policy, and the rationale for, and value of a future trial if considered necessary.

Bayesian decision theory and value of information analysis has a firm grounding in statistical decision theory (see Raiffa and Schlaifer (1959); Raiffa (1968); Pratt et al., 1995; and others), and has been used in other areas of research including engineering (see Howard, 1966) and environmental risk assessment (see Thompson and Evans, 1997; and Hammitt. and Cave, 1991). Some early attempts to use Bayesian decision theory in the analysis of clinical trials failed due partly to the exclusion of an economic input into the analysis (see Armitage, 1985).

More recently a Bayesian decision theoretic framework for the evaluation of health care programmes has been presented (see Claxton and Posnett, 1996; and Claxton, 1999b) and some applications have emerged (see Fenwick et al., 2000; Claxton et al., 1999; and Claxton et al., 2000b). However this recent work has been restricted to prior analysis of decision problems or has used normal prior distributions for net benefit to establish the efficient design and value of conducting further clinical trials.

3 Summary of the analysis

The two applications of Bayesian decision theory and value of information analysis in this study share common objectives, methodological framework and sequence of analysis as outlined below.

3.1 Objectives

The aim of this study is to demonstrate that Bayesian decision theory and value-of-information analysis is a valuable and practical framework within which two conceptually separate decision problems can be addressed: (i) the selection of the optimal treatment strategy given existing information, and (ii) identification of the worth of further information collection to inform this choice in the future. The specific objectives of the study are:

i) To a conduct fully informed Bayesian analyses by combining pre-trial decision theoretic modelling with patient level data.

ii) To relax the restrictions of using normal prior distributions for net benefit and parametric approaches for value of information analysis by using numerical methods to estimate posterior distributions and a non parametric approach to EVPI.

iii) To conduct this analysis in the context of two specific clinical decision problems for which published trial-based evaluations exist.

To provide a description of the analyses undertaken in such a way as to assist others undertaking Bayesian economic evaluation in other decision contexts.

3.2 Clinical applications

The applications selected for this study, differ in a number of important respects, most notably: the size of each of the trials; the amount and quality of evidence available before the most recent trials were conducted; the size of the eligible patient population; the number of alternative interventions to be compared and the opportunities for subgroup analysis. However, both applications provided access to patient level data on costs and effects from recent trials.

3.2.1 Application I

Low versus high doses of the angiotensin converting enzyme (ACE) inhibitor lisinopril in chronic heart failure.

This application evaluates the decision uncertainty and value of information surrounding the choice between low and high dose lisinopril before and after the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial was conducted and reported.

The ATLAS study was an international trial undertaken in 19 countries to compare low doses and high doses of the ACE inhibitor lisinopril (Zestril^{TM}) in the treatment of chronic heart failure (see Packer et al., 1999). Patients with Class II-IV heart failure and left ventricular ejection fraction equal to or below 30% were recruited. Exclusion criteria included acute myocardial infarction, unstable angina or a revascularisation procedure in the preceding two months; the presence of symptomatic ventricular tachycardia; unstable congestive heart failure; and the use of various negatively or positively isotropic drugs. Following an initial open-label period to establish tolerance of a daily dose of 12.5 to 15 mg of the ACE inhibitor, lisinopril, 3164 patients were randomly allocated, double-blind, to a high-dose strategy (daily target dose 32.5-35.0 mg, n=1568) or low-dose strategy (daily target dose 2.5-5.0 mg, n=1596) of lisinopril. After a median follow-up of 46 months (range 39 to 58 months), there was an 8% lower risk of death in the high-dose group. Patients in the high dose group also had a 12% lower risk of death or hospitalisation for any reason. Although patients in the high-dose group experienced more events related to hypertension and renal impairment, these adverse events were generally successfully managed by adjusting therapy. The proportions of patients stopping medication due to adverse events were similar (17% high-dose; 18% low-dose). Heart failure symptoms improved with both high- and low-dose therapy, with no between-group differences during the study.

In addition to mortality and morbidity data, information on the key health service resources consumed by ATLAS study patients was also collected over four years of patient follow-up. Data were collected on the number and cause of hospital in-patient days and day-case visits. Details of each patients dose of study medication were collected over the full period of follow-up, enabling the calculation of the total amount of study medication taken. Information on the use of concomitant ACE inhibitors was also collected. An economic sub-study used these resource data to estimate the differential cost and cost-effectiveness of high- and low-dose lisinopril on the basis of UK health care costs (see Sculpher et al. 2000).

Before the ATLAS trial the comparative costs and effects of high versus low doses had not been

tested adequately in a randomised controlled trial. Of the 5 studies that had previously compared low and high doses of ACE inhibitors in heart failure, all focused on physiological and symptomatic effects and were considered too small to evaluate differences between low and high doses on the risk of major clinical events. The majority of randomised trials undertaken before ATLAS were designed to determine if (as opposed to how) ACE inhibitors should be used in the treatment of heart failure .

The full details of this clinical application including the particular methods adopted, the characterisation of pre-trial evidence, Bayesian analysis of the ATLAS data, the results and discussion are fully reported in Part I of this report.

3.2.2 Application II

A policy of pre-operative optimisation employing dopexamine or adrenaline for high risk patients undergoing major elective surgery.

This application evaluates the decision uncertainty and value of information surrounding the choice between standard care and pre-operative optimisation, using the inotropes adrenaline or dopexamine, for high risk patients undergoing major elective surgery both before and after the most recent trial (Wilson et al 1999) was conducted and reported.

A randomised controlled trial (Wilson et al 1999) assessed the implications of pre-operative optimisation of oxygen delivery. Such pre-operative management involves admitting high-risk elective patients to intensive care; inserting a pulmonary artery catheter to monitor cardiac index; and administering inotropes to achieve target oxygen delivery before surgery. This trial, in high risk patients undergoing major elective surgery, measured outcomes in terms of mortality and complications compared to standard care but also compared the inotropes, adrenaline and dopexamine, in terms of these outcomes. Hence, 46 patients were randomised to pre-optimisation with adrenaline, 46 to pre-optimisation with dopexamine and 46 to a usual care control group. The study found a mortality benefit to patients in the pre-optimisation groups (3/92 versus 8/46), and a lower rate of complications in the dopexamine group compared to the adrenaline group.

The study also found some important differences in resource use between the three groups. In particular, the use of dopexamine was associated with a lower length of stay in hospital. Although there was no prospective collection of economic data within the trial, the resource use

data for all patients were ascertained via retrospective interrogation of patient's notes up to a fixed period of 6 months following randomisation.

Previous to the Wilson et al (1999) trial, a US randomised trial had compared standard patient management with a deliberate policy of pre-operative management using dopexamine in high-risk patients. The results indicated mortality and morbidity benefits associated with a deliberate policy of pre-operative management. These results were replicated in a U.K. trial in 1993. In addition, the trials provided some evidence that the use of pre-operative management reduced hospital costs and constituted a cost-effective method of managing high-risk surgery. However, the results of these trials have not had a major influence on surgical management in the U.K.

The full details of this clinical application including the particular methods adopted, the characterisation of pre-trial evidence, Bayesian analysis of the trial data, the results and discussion are fully reported in Part II of this report.

3.3 Overview of methods

We have applied the Bayesian decision theoretic approach outlined in Section 2 to both clinical applications detailed above. The methods used and the sequence of analysis is common to both. The differences between these applications, including the quality of prior (pre-trial) information, the size of the trials; and the size of the eligible patient population, help to demonstrate the importance of these factors in determining the decision to adopt a new technology and the decision to acquire more information to inform this choice in the future.
In each case patient level clinical trial data were available for the most recent trials, including data on economic as well as clinical endpoints. This enabled an analysis of the decision uncertainty and the value of information both before (retrospectively) and after these trials were conducted, providing some assessment of whether these trials were worthwhile and whether additional evidence may still be required. This required the uncertainty surrounding these decisions to be fully characterised before and after each of these trials.

The prior (pre-trial) uncertainty in both cases was characterised by developing pre-trial decision analytic models, which were populated with prior distributions based on the evidence available prior to the trial. The decision uncertainty following each of the most recent trials requires the patient-level data from the trials to be combined with the prior evidence from the pre-trial models to form posterior distributions for cost and outcomes. In both cases numerical methods (Markov Chain Monte Carlo simulation) were used to update the priors generated by the decision

analytic model with the clinical trial data. In each case the decision uncertainty before and after the trials is presented in the form of prior and posterior cost-effectiveness acceptability curves. Value-of-information analysis has also been conducted before and after the trial to establish whether the original trials appeared to be worthwhile and to establish, now that these trails have been conducted, whether further evidence may still be required to support the adoption decision. The analysis of each for the clinical applications follows the following four stages:

i) Prior analysis of the decision problem (pre-trial modelling).

The first task undertaken was to model the clinical decision problem, identify the key parameters, and assign prior distributions to characterise the quantity and quality of prior information which was available before the trial was conducted. These prior distributions are propagated through the pre-trial decision analytic model using Monte Carlo simulation. The results of the simulation are used to establish, prior to the trials being conducted, the optimal adoption decision, and to characterise the uncertainty surrounding the adoption decision using cost-effectiveness acceptability curves.

ii) Analysis of the value of information.

The pre-trial models were used to establish the expected value of perfect information surrounding the adoption decisions for a range of cost-effectiveness thresholds. These estimates of EVPI represent the maximum returns which could have been expected from conducting an additional trial. If the EVPI exceeds the costs of conducting further research, then additional investigation was at least potentially worth while. This type of analysis provides a necessary, although not sufficient, condition for conducting further research. It is used to establish whether, on the basis of the existing pre-trial evidence, the trials which were conducted were potentially cost-effective.

iii) Posterior analysis of the decision problem.

The clinical trial data are then used to update the pre-trial model to obtain posterior distributions for costs, effects and net benefit. The prior distributions from the pre-trial model are updated with the patient level data from the trials using Markov Chain Monte Carlo simulation implemented in Win BUGS. This analysis provides fully informed posterior distributions for costs, effects and net benefit. The initial prior adoption decision can be revised in using these posteriors and the uncertainty surrounding this revised adoption decision is presented in the form of posterior cost-effectiveness acceptability curves.

iv) The iterative process of health technology assessment.

Finally we use the updated (posterior) model to establish the value of acquiring further information by commissioning additional research. The posterior distributions from iii) were used as the prior information when considering this next round in the iterative process of health technology assessment. Once again the expected value of perfect information for the decision problem is established to determine whether further evidence may still be required to support the adoption decision.

The analysis and results for each of the clinical applications are detailed in Part I and II of this report. Each application addresses the iterative process, which is common to the assessment of any health technology, where a sequence of decisions must be made: an initial adoption decision based on prior information; a decision to conduct further research; revising the adoption decision in the light of the results of the research and then considering once again whether further investigation is worth while. The analysis of each clinical application demonstrates that an explicit and rational approach to the sequence of decisions in health technology assessment is possible, valuable and practical.

4 Summary of results

Both applications demonstrate that there was substantial value of information surrounding these decision problems before each of the most recent trials were conducted. In each case the additional evidence from the trial could be combined with the prior decision analytic modelling using numerical methods and a number of possible models. The posterior analysis did not necessarily change the adoption decisions but the incorporation of the trial evidence with the prior decision analytic models did change the decision uncertainty and therefore the value of information. The applications also demonstrate that although additional evidence may reduce parameter uncertainty this does not necessarily mean that decision uncertainty and the value of information will also be reduced.

4.1 Low dose or high doses of the ACE inhibitor lisinopril in chronic heart failure

The prior and posterior estimates of expected costs and life-years suggests that high-doses of lisonopril was the optimal decision before and after the ATLAS study was conducted. In fact a comparison of mean cost and life-years indicates that high-dose dominated low-dose treatment (less costly and more effective) in both the prior and posterior analyses. The posterior cost-effectiveness acceptability curves indicated that, while there while there was slightly greater decision uncertainty about whether high dose was cost saving in comparison with the prior,

there was also less uncertainty in the adoption decision provided the decision maker is prepared to pay over £1000 per additional life-year gained. Despite the higher posterior uncertainty for certain threshold values of a life-year gained, the variance around the estimates of cost and effect was significantly reduced in the posterior analysis. As a result the posterior EVPI estimates were lower than the prior EVPI over the entire range of threshold values. The posterior EVPI indicated that the evidence from the pre-trial analysis combined with the additional information from the ATLAS trial had resolved a significant amount of the uncertainty underlying this decision and additional clinical trials are unlikely to be worth while. Furthermore the results demonstrate that a fully Bayesian analysis is needed because failure to consider the prior (pre-trial) information would significantly overestimate uncertainty and the value of additional research in this area.

4.2 Pre-operative optimisation employing dopexamine

Although both the prior (pre-trial) analysis and posterior analysis of the trial suggests that pre-operative optimisation employing either inotrope is expected to dominate standard patient management, the prior and posterior decisions about which inotrope should be used in pre-optimisation did depend upon the value of the cost-effectiveness threshold. Whilst the most recent trial had limited impact upon the decision to adopt pre-optimisation, the informed Bayesian re-analysis of the trial reduced the uncertainty surrounding the estimates of expected cost and expected survival duration. However, reductions in uncertainty surrounding these estimates do not necessarily translate into reductions in decision uncertainty. In this application, the fully informed Bayesian analysis demonstrated great decision uncertainty surrounding the choice of inotropes compared to either the pre-trial analysis or a Bayesain analysis using uninformative priors. Thus the posterior EVPI was greater than either the pre-trial EVPI or the EVPI based on uninformative priors, over a range of cost-effectiveness thresholds. However, the value of information before and after the trial are such that the most recent trial appears to have been worthwhile and additional research still appears to be potentially cost-effective.

5 Implications and future research

This study demonstrated that a fully Bayesian decision theoretic and value of information analysis can be successfully applied to very different clinical applications. In both cases we have been able to demonstrate that using decision analytic modelling to combine evidence already available and characterises prior decision is a useful way to form priors for Bayesian analysis. Each application has also demonstrated that when updating prior distributions generated by pre-trial modelling we do not need to be restricted to cases of conjugacy. In both cases priors were

not conjugate and numerical methods using Markov Cain Monte Carlo were successfully implemented, demonstrating the value and practicality of such methods for future analysis.

The value of information analysis also demonstrated that estimates of the expected value of perfect information do not need to be restricted to situations where net benefit is normally distributed but can easily be implemented using non parametric methods. The results of both applications demonstrate that trials were valuable despite the fact that the prior adoption decision did not change once the prior analysis was updated with the new clinical trial data This value relates to the fact that the information from the trial did reduce decision uncertainty and, therefore, the posterior EVPI. However, the results of one of the applications also demonstrated that although additional evidence will reduce the uncertainty surrounding costs and effects this does not necessarily mean that the uncertainty surrounding the decision will fall. In this case, despite the fact that the trial reduced uncertainty about key parameters, the posterior value of information was greater than the value of information before the trial was conducted.

Overall both applications have demonstrated that a Bayesian decision theory and value of information analysis is a useful and practical framework which addresses directly the iterative process of health technology assessment. This process is common to the assessment of all health technologies, where a sequence of decisions must be made: an initial adoption decision based on existing evidence; a decision to conduct further research; revising the adoption decision in the light of the results of the research; and then considering, once again, whether further investigation is worth while. This study provides retrospective analysis of two clinical applications which demonstrates that an explicit and rational approach to this sequence of decisions in health technology assessment is possible, valuable and practical.

However, there are a number of areas where further methodological work is ongoing, which has limited the scope of this study. In particular: the value of information for model parameters and the value of sample information.

This study has presented prior and posterior expected value of information for the decision problem as a whole. However, it is also possible to consider the value of perfect information associated with each of the uncertain inputs in the decision model. This type of analysis would be useful as it helps future research to focus on those parameters where more precise estimates would be most valuable. However, a number of different and conflicting methods

have been use to establish these “partial” EVPIs and it is only very recently that appropriate methods have been well established (Ades et al 2003). In addition, these methods can be computationally intensive and pose considerable problems when correlations are generated as the prior model is updated. For these reasons, opportunities to conduct this type of analysis have been limited in this study. It was possible to establish the EVPI associated with model parameters for the pre-trial model of pre-operative optimisation. However the structure of the models used to analyse trial data required the use of composite measures, which meant that the posterior analysis was restricted to EVPI for the decision problem as a whole. However, other applications, which demonstrate that this type of EVPI analysis is practical and useful will be forthcoming.

Observing an EVPI greater than the cost of additional research provides only the necessary but not sufficient condition for deciding to acquire more experimental information (conducting a clinical trial). For a full analysis it is necessary to estimate the benefits of sampling, or the expected value of sample information (EVSI) for the patient population, and the cost of sample information, including the additional treatment and reporting cost. The difference between the EVSI and sampling cost is the expected net benefit of sampling (ENBS), or the societal pay-off to proposed research. Estimates of the ENBS can be used to establish technically efficient research design in terms of optimal sample sizes, optimal sample allocation, which endpoint should be included and optimal follow-up periods. This type of analysis has been conducted using analytic methods using assumptions of normality of net benefit (see Claxton, 1999b; and Claxton et al., 1999). It is only very recently that methods for estimating EVSI from conjugate priors on model parameters have been presented (see Ades et al 2003 and Claxton and Ades, 2002), and it has only recently become clear that estimating EVSI for model parameters which are not conjugate and require numerical methods is computationally almost infeasible using existing methods. For these reasons we have not attempted to conduct this type of analysis for this study.

6. Dissemination strategy

There are three broad constituencies, which must be addressed if Bayesian decision theory is to be used more widely and become accepted by policy makers and clinical decision makers. These are the audience with an interest in the methodological issues (these include biostatistics, health economics and decision sciences); the clinical audience interested in the analysis of the clinical applications; and the broader policy audience interested in the way this type of analysis can inform research and development priorities and regulation/reimbursement

issues.

Our dissemination of this work has addressed each of these audiences through conference papers, published abstracts, seminars, and workshops which have used material from these applications. The details of the dissemination of this work in Europe and North America is detailed below. In addition to this dissemination we are planning to submit a further three papers to peer-reviewed journals. These include a paper reporting the results of the Bayesian analysis of the ATLAS trial which will be submitted to the Lancet; a methodological paper reporting the analysis of the pre-operative optimisation will be submitted to Medical Decision Making; and we also hope to develop a policy paper which will draw on both applications to discuss the broader policy issues that can be addressed using this approach.

6.1 Conference papers

Fenwick, E., Palmer, S., Claxton, K., Sculpher, M., Abrams, K.. and Sutton, A. An informative Bayesian re-analysis of a randomized controlled trial: the case of pre-operative optimization for patients undergoing major elective surgery. International Health Economics Association. San Francisco, July 2003.

Fenwick, E., Palmer, S., Claxton, K. And Sculpher, M. An iterative framework for health technology assessment employing Bayesian statistical decision theory. International Society for Technology Assessment in Health Care. Canmore, July 2003.

Fenwick, E., Palmer, S., Claxton, K., Sculpher M., Abrams, K., Sutton, A. An iterative approach to technology assessment using Bayesian methods. Medical Decision Making, Baltimore, October 2002.

Palmer, S., Fenwick, E., Claxton, K., Sculpher M., Abrams, K., Sutton, A. A Bayesian Approach to Cost-Effectiveness Analysis and Value of Information Analysis in Chronic Heart Failure. Medical Decision Making, Baltimore, October 2002.

Palmer, S., Fenwick, E., Claxton, K. and Sculpher M. Applications of value of information using Bayesian numerical methods. Medical Decision Making. San Diego, October 2001.

Fenwick, E., Claxton, K. and Sculpher, M. A Bayesian analysis of pre-operative optimisation of oxygen delivery. International Health Economics Association. York, July 2001.

Fenwick, E., Claxton, K. And Sculpher, M. A Bayesian analysis of pre-operative optimisation of oxygen delivery. Medical Decision Making. Cincinnati, September 2000.

6.2 Published abstracts

Fenwick, E., Palmer, S., Claxton, K., Sculpher M., Abrams, K., Sutton, A. An iterative approach to technology assessment using Bayesian methods. Medical Decision Making, 2002 (22), 4 (Abstract).

Palmer, S., Fenwick, E., Claxton, K., Sculpher M., Abrams, K., Sutton, A. A Bayesian Approach to Cost-Effectiveness Analysis and Value of Information Analysis in Chronic Heart Failure. Medical Decision Making, 2002 (22), 4 (Abstract).

Palmer S, Fenwick E, Claxton K, Sculpher M. Applications of value of information using Bayesian numerical methods. Medical Decision Making, 21(6): 531, 2001 (Abstract).

Fenwick, E., Claxton, K. And Sculpher, M. A Bayesian analysis of pre-operative optimisation of oxygen delivery. Medical Decision Making, 2000(20), 4 (Abstract).

6.3 Workshops

Bayesian approaches to Economic Evaluation in Health Care. XXII Jornadas Asociación de Economía de la Salud, Pamplona, May 2002.

Fenwick, E., Lehmann H., Reed S. The use of Bayesian statistics in medical decision making. SMDM conference, San Diego, October 2001.

Introduction to Bayesian Analysis for the Evaluation of Health Care Technologies International Health Economics Association, York, July 2001.

6.4 Seminars

Fenwick, E. A Bayesian analysis of pre-operative optimisation of oxygen delivery. Presented at Harvard School of Public Health, Boston, September 2000.

Fenwick, E. A Bayesian analysis of pre-operative optimisation of oxygen delivery. Presented at Centre for Evaluations of Medicines, St Joseph's Hospital, Hamilton, September 2000.

Palmer, S. A Bayesian Approach to Cost-Effectiveness Analysis and Value of Information Analysis in Chronic Heart Failure. Centre for Health Economics, York, September 2002.

Fenwick, E. An iterative approach to health technology assessment employing Bayesian methods. Presented at School of Health and Related Research, Sheffield, June 2002.
Fenwick, E. An iterative approach to technology assessment using Bayesian methods. Presented at Centre for Evaluations of Medicines, St Joseph's Hospital, Hamilton, September 2002.

Fenwick, E. An iterative approach to technology assessment using Bayesian methods. Presented at Department of Biostatistics, MD Anderson Cancer Centre, Houston, November 2002.

Fenwick, E. An iterative approach to health technology assessment using Bayesian methods. Presented at Harvard School of Public Health, Boston, March 2003.

Fenwick, E. An iterative framework for technology assessment using Bayesian methods. Presented at CCOHTA, Ottawa, May 2003.

Fenwick, E. An application of an iterative framework for health technology assessment using Bayesian statistical decision theory. Presented at Clinical Epidemiology Programme, University of Ottawa, Ottawa, May 2003.

Fenwick, E. An application of an iterative framework for health technology assessment using Bayesian statistical decision theory. To be presented at School of Pharmacy, University of Washington, Seattle, June 2003.

Fenwick, E. An iterative framework for health technology assessment using Bayesian statistical decision theory. To be presented at Centre for Health Evaluation & Outcome Sciences, University of British Columbia, Vancouver, June 2003.

References

Abrams, K.R., Jones, D.R., 1997. Bayesian interim analysis of randomised trials. The Lancet 349, 1911-1912.

Abrams, K.R., Sanso, B., 1998. Approximate Bayesian inference in random effects meta-analysis. Statistics in Medicine 17, 201-218.

Ades, AE., Lu, G. and Claxton, K., 2003. Expected value of information calculations in medical decision modeling. Resubmitted to Medical Decision Making, April 2003.

Armitage, P., 1985. The search for optimality in clinical trials. International Statistical Review 53, 15-24.

Berry, D.A., 1994. Discussion of the paper by Spiegelhalter, et al. Journal of the Royal Statistical Society A 157, 399.

Berry DA. and Stangl DK. eds., 1996. Bayesian Biostatistics (Marcel Dekker Inc).

Bhuta T. and Henderson-Smart DJ., 2000 Elective high frequency jet ventilation versus conventional ventilation for respiratory distress syndrome in preterm infants. In: The Cochrane Library, Issue 1, Oxford: Update Software.

Breslow N., 1990. Biostatistics and Bayes. Statistical Sciences 5, 269-298

Claxton, K and Ades, A., 2002. Efficient research design: an application of value of information analysis to an economic model of Zanamavir. Medical Decision Making, 22, 4 (Abstract).

Claxton, K., Sculpher M., and Drummond, M., 2002. A rational framework for decision making by the National Institute for Clinical Excellence. Lancet, 360, 711-715.

Claxton K., Walker S. and Lacey L., 2000. Selecting treatments: a decision theoretic approach. Journal of the Royal Statistical Society A, 163, 2: 211-225.

Claxton, K. Neuman, PJ. Araki, SS. and Weinstein, MC., 2001. The value of information: an application to a policy model of Alzheimers disease. International Journal of Technology Assessment in Health Care, 17, 38-55.

Claxton K., 1999a. Bayesian approaches to the value of information: implications for the

regulation of new pharmaceuticals. Health Economics 8: 269-274.

Claxton, K., 1999b. The irrelevance of inference: a decision making approach to the stochastic evaluation of health care technologies. Journal of Health Economics 18, 341-364.

Claxton, K., Neumann, P., Araki, S. and Weinstein, MC., 1999. The efficient design of clinical trials: an application to the evaluation of treatment strategies for Alzheimers disease (Abstract). Medical Decision Making 19, 4.

Claxton, K. and Posnett J., 1996. An economic approach to clinical trial design and research priority setting. Health Economics 5, 513-524.

Felli, JC. and Hazen, GB., 1998. Sensitivity analysis and the expected value of perfect information. Medical Decision Making 18, 95-109.

Fenwick, E., Claxton, K. and Sculpher M., 2000. Improving the efficiency and relevance of health technology assessment: the role of decision analytic modelling. Centre for Health Economics Discussion Paper No 179.

Hammitt JK. and Cave JAK., 1991. Research planning for food safety: a value of information approach. RAND Publication Series.

Howard RA., 1966. Information value theory IEEE Transactions on Systems Science and Cybernetics. SSC-2, 122-26.

Lindley, D.V., 1994, Discussion of the paper by Spiegelhalter et al., 1994. Journal of the Royal Statistical Society A 157, 393.

Neumann, PJ., Claxton, K., and Weinstein, MC., 2000. FDA regulation of health economic information: issues and options for section 114 of FDA Modernization Act. Health Affairs, forthcoming.

Packer M, Poole-Wilson PA, Armstrong PW, Cleland JGF, Horowitz JD, Massie BM et al., 1999. Comparative effects of low doses and high doses of the angiotensin converting-enzyme inhibitor, lisinopril, on mortbidity and mortality in chronic heart failure. Circulation 100, 2312-2318.

Pratt J., Raiffa H. and Schlaifer R., 1995. Statistical decision theory (Cambridge MA, MIT

Press).

Raiffa, H., 1968, Decision analysis: introductory lectures on choices under uncertainty (Addison-Wesley, New York).

Raiffa H. and Schlaifer R., 1959. Probability and statistics for business decisions (McGraw-Hill, New York)

Sculpher MJ, Poole L, Cleland J, Drummond M, Armstrong PW, Horowitz JD, et al. Low doses vs. high doses of the angiotensin converting-enzyme inhibitor lisinopril in chronic heart failure: a cost-effectiveness analysis based on the Assessment of Treatment with Lisinopril and Survival (ATLAS) study. *European Journal of Heart Failure* 2000;2:447-454.

Parmigiani G., Samsa, G.P., Ancukiewicz M., Lipscomb J., Hasselblad V. and Matchar D.B., 1997. Assessing uncertainty in cost-effectiveness analyses: application to a complex decision model. Medical Decision Making 17, 390-401.

Spiegelhalter, D.J. and L.S. Freedman, 1988, Bayesian approaches to clinical trials, Bayesian Statistics Volume 3 (Oxford University Press, Oxford).

Spiegelhalter, DJ., Freedman LS., and Parmar MKB., 1994. Bayesian approaches to randomised trials. Journal of the Royal Statistical Society A, 157, 357-416.

Spiegelhalter, D.J., Myles, J.P, Jones, D.R., Abrams, K.R., 1999. An Introduction to Bayesian Methods in Health Technology Assessment. BMJ 319, 508-512.

Sutton, A.J., Jones, D.R., Abrams, K.R., Sheldon, T.A., Song, F., 1999. Systematic Reviews of Trials and Other Studies. Health Services Research and Policy 4, 49-55.

Thompson KM. and Evans JS., 1997. The value of improved national exposure information for perchloroethylene (perc): a case study for dry cleaners. Risk Analysis, 17, 253-271.

Thompson KM. and Graham JD., 1996. Going beyond the single number: using probabilistic risk assessment to improve risk management. Human and Ecological Risk Assessment, 2, 1008-1034.

Wilson J, Woods I, Fawcett J., 1999. Reducing the risk of major elective surgery: randomised

controlled trial of preoperative optimisation of oxygen delivery. BMJ 318,1099-103.
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Part I

A Bayesian Approach to Cost-Effectiveness Analysis and Value-of-Information Analysis in Chronic Heart Failure: An Example Using the ATLAS Trial

The aim of this study was to undertake an informed Bayesian approach to establishing the cost-effectiveness and the expected value of perfect information (EVPI) of high versus low dose angiotensin-converting enzyme (ACE) inhibitors in patients with chronic heart failure. The Assessment of Treatment with Lisinopril and Survival (ATLAS) study was an international trial undertaken to compare high and low doses of the ACE inhibitor lisinopril in the treatment of chronic heart failure. Prior probability distributions were calculated using a stochastic model populated using previously published evidence including the Studies of Left Ventricular Dysfunction (SOLVD) . These prior distributions were combined with patient level data from ATLAS to generate posterior distributions of costs and outcomes using MCMC implemented using WinBUGS. The posterior distributions of survival were derived using a piecewise exponential model and the posterior distributions of costs were derived using the Lin method for handling censoring in cost data.

Mean estimates of the difference in cost and life-years gained were used to establish the optimal adoption decision, before and after the ATLAS trial, based on the prior and posterior distributions. Uncertainty surrounding these decisions were characterised by estimating prior and posterior cost-effectiveness acceptability curves (CEAC). The impact of combining prior evidence with the new trial evidence from ATLAS on the uncertainty surrounding the adoption decision was demonstrated by comparing the prior and posterior EVPI.

Both the prior and posterior mean estimates of costs and life-years identified high-dose as the optimal adoption decision. Based on a comparison of mean cost and life-years, high-dose dominated low-dose treatment (less costly and more effective) in both the prior and posterior analyses. The posterior CEAC indicated that while there while there was slightly greater uncertainty about whether high dose was cost saving in comparison with the prior CEAC (85% vs 88%), there was also less uncertainty in the adoption decision provided the decision maker is prepared to pay over £1000 per additional life-year gained. Despite the higher posterior

uncertainty for certain threshold values of life-years gained (<£1000 per life-year gained), the variance around these estimates was significantly reduced in the posterior analysis. As a result the posterior EVPI estimates were lower than the prior EVPI over the entire range of values for life-years, due to the reduced consequences associated with making an incorrect decision.

The analysis demonstrates the value of a fully Bayesian analysis in the context of chronic heart failure. Although the posterior analysis did not result in a change in the adoption decision from that suggested by prior evidence, the posterior EVPI indicated that the evidence from the pre-trial analysis combined with the additional information from the ATLAS trial had resolved a significant amount of the uncertainty underlying this decision. Furthermore, failure to consider the prior information would have significantly overestimated the value of additional research in this area .

1. Introduction

The Assessment of Treatment with Lisinopril and Survival (ATLAS) study was an international trial undertaken to compare two dosage regimens in the treatment of chronic heart failure with the ACE inhibitor lisinopril (Zestril^{TM})[1]. The study randomised 3,164 heart failure patients to double-blind treatment with either high (32.5-35.0 mg daily, n=1,568) or low (2.5-5.0 mg daily, n=1,596) doses of lisinopril. Patients were followed up for a median of 46 months (range 39-58 months). The primary clinical outcome assessed was all-cause mortality and a separate economic study recorded patient level resource utilisation and cost data from a health service perspective[2].

A stochastic decision model was developed to identify the pre-trial adoption decision (based on mean cost and outcomes), using data available before the trial began. The pre-trial model was also used to generate the prior distributions for an informed Bayesian analysis of the ATLAS trial. The informed Bayesian analysis was used to generate posterior probability distributions for the costs and outcomes of the alternative dosing strategies, based on the combination of pre-trial evidence and the patient-level trial data. Uncertainty surrounding the adoption decisions was characterised by estimating pre-trial and posterior cost-effectiveness acceptability curves for each strategy. Value-of-information analysis was undertaken to estimate the cost associated with the decision uncertainty (pre-trial and posterior) and was used to establish a necessary (but not sufficient) criterion to establish whether the collection of further information was potentially worthwhile. Each stage of the process is described in detail in the following sections.

2. Pre-trial analysis of the decision problem

2.1 Pre-trial Evidence

Before the ATLAS trial the comparative costs and effects of high versus low doses had not been tested adequately in a randomised controlled trial. Of the 5 studies that had previously compared low and high doses of ACE inhibitors in heart failure, all focused on physiological and symptomatic effects and were considered too small to evaluate differences between low and high doses on the risk of major clinical events.[3-7] The majority of randomised trials undertaken before ATLAS were designed to determine if (as opposed to how) ACE inhibitors should be used in the treatment of heart failure .

Randomised studies assessing the clinical outcomes associated with the use of ACE inhibitors were identified from a previously undertaken systematic review [8]. To reflect the evidence

available before the start of the ATLAS trial, only those trials reporting until the end of 1992 were considered in this study. In total there were 27 trials reported in English that met this constraint.[9-35] Of these 27 trials, the results of 18 were published,[9-17 19 24 26-28 32-35] whilst the results of the remaining 9 trials were reported in unpublished reports.[18 20-23 25 29-31]

Of the 27 studies identified from the systematic review, only three used lisinopril . Out of the remaining 24 trials, two trials used benazapil, six trials used captopril, one trial used cilazapril, seven trials used enalapril, two trials used quinapril, and six trials used ramipril.

The majority of trials only reported on short-term outcomes associated with mortality (90 days or less). Only 10 of the 27 trials reported outcomes beyond 90 days, and of these only 2 trials evaluated mortality at 1 year. The 2 studies which evaluated mortality for a follow-up period of at least 1 year were: (1) the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) with 253 patients randomly assigned to placebo (n=126) or enalapril (n=127); and (2) the Studies of Left Ventricular Dysfunction (SOLVD) involving 2,569 patients randomly assigned to placebo (n=1,284) or enalapril (n=1,285). Only the SOLVD treatment trial evaluated outcomes beyond 1 year, with a mean follow-up 41.4 months (range from 22 to 55 months).

Due to the extended period of follow-up reported in the SOLVD treatment trial, it was decided that this trial was the best source of prior information on major clinical events (including data on resource utilisation e.g. hospitalisations) for the planned period of follow-up in the ATLAS trial (which was to be completed when the last randomised patient had been followed for a minimum of three years or until 1600 patients had died). This decision also reflects the evidence used in the original design of the ATLAS trial, where the required sample size was calculated on the basis that the difference in mortality risk between high and low doses would be nearly identical to the observed differences between high doses of ACE inhibitors and placebo in the SOLVD trial[1].

In the absence of any direct evidence relating to the effectiveness or cost-effectiveness of low-dose ACE inhibitors, we followed the same assumptions used in the sample size calculations for the ATLAS study (i.e. low-dose is no more effective or cost-effective than placebo) as the best source of prior beliefs relating to the use of low-dose ACE inhibitors. We used the placebo data reported in the SOLVD trial as the basis for the parameter estimates related for the low-dose strategy.

A separate MEDLINE search for cost-effectiveness analysis studies of the use of ACE inhibitors

for heart failure revealed that there were no economic studies published before the start of the ATLAS trial in 1992. To allow for the fact that potentially useful economic data may have been available prior to the start of the ATLAS trial, but was not fully analysed until after this trial had started, the search strategy was broadened to include economic studies reporting on the cost-effectiveness of clinical trials completed before 1992 (but which were published after 1992) . In addition to revising the MEDLINE search, a search of economic studies was also undertaken using the NHS Health Economic Evaluation Database. The searches identified three studies which met this criteria[36-38]; all three studies were retrospective cost-effectiveness analyses of the SOLVD treatment trial. Although none of the results of these studies were used directly to inform the prior estimates of the cost-effectiveness of ACE inhibitors, they were included as relevant data sources for the prior estimates of particular input parameters into the pre-trial decision-analytic model.

2.2 Pre-Trial Decision Model Structure

The pre-trial decision model was developed to estimate costs from the perspective of the UK National Health Service (NHS), and health outcomes in terms of life years associated with high and low dose ACE inhibitors . The pre-trial model was used to synthesise the relevant clinical and economic data sources available before the start of ATLAS. To ensure consistency between the pre-trial model and the economic analysis of the ATLAS trial[2], a four-year time-horizon for the pre-trial model was chosen .

The pre-trial model is probabilistic in that input parameters are entered into the model as probability distributions to reflect second order uncertainty – that is, uncertainty in mean costs and outcomes, and in probabilities. Monte Carlo simulation is used to propagate uncertainty in input parameters through the model in such a way that the results of the analysis can also be presented with their uncertainty. The model has been developed in Excel™ with the Crystal Ball™ 'add-on'. The Monte-Carlo simulation was run for 10,000 iterations. A 1997-98 price base is used, and annual discount rates of 6% for costs and 2% for benefits are adopted based on UK guidance.[39]

The prior model is used to: (i) identify the optimal adoption decision based on a comparison of mean costs and outcomes; (ii) characterise uncertainty and quantify the costs of uncertainty surrounding the adoption decision for the purposes of establishing the value of obtaining additional information, and (iii) to generate prior estimates for the Bayesian re-analysis of the ATLAS trial. Stages (i) and (ii) are reported in sections 4.3-4.7. The process of generating the prior estimates for the informed Bayesian analysis, as part of stage (iii) is reported in detail in

section 6.

2.3 Pre-trial model data sources

Tables 1-3 provide a summary of the major clinical endpoints and hospitalisation data reported in the SOLVD treatment trial.[32] This data formed the basis for estimating the parameters of the prior model. To estimate life-years gained from the data reported in Tables 1 and 2, the model is structured as a decision tree as shown in Figure 1. For both high and low dose treatment, the initial chance node reflects uncertainty in whether a patient survives or dies in the first year following treatment. Conditional upon surviving the first year, the subsequent chance nodes reflects the uncertainty in whether a patient survives or dies in each of the following three years. To incorporate the hospitalisation data into the prior model structure, the basic tree is re-structured to include the uncertainty in whether a patient is hospitalised or not for congestive heart failure (CHF) and/or other non-CHF reasons conditioned upon survival status. This approach allowed for the different levels of uncertainty in both fatal and non-fatal hospitalisation rates reported during each year of follow-up in the SOLVD trial .

The probabilities of death, hospitalisation for CHF and non-CHF and the proportion of patients taking ACE inhibitors for each of the four years of follow-up were defined as beta distributions to represent the uncertainty in the probability of occurrence of an event. Beta distributions were chosen on the basis that the parameters can be defined directly from the number of events reported in the main clinical paper and the resulting distributions are constrained between 0 and 1. Uncertainty in the beta distribution is characterised by two parameters (alpha and beta). The alpha parameter defines the number of patients experiencing an event during each interval and the beta parameter is simply the total number of patients under observation at the start of each interval minus the number of patients experiencing an event. The parameters of the distributions used in the prior analysis are reported in Tables 4 & 5 for high and low-dose treatment respectively and the assumptions used to derive these are reported in the following sections.

2.4 Pre-trial model outcomes (Life-years gained)

The beta distributions for mortality were derived from the number of patients who die in each year as a proportion of patients alive and uncensored at the start of each year (hence the estimates were adjusted for the number of patients censored during each interval) . This data is taken directly from the data reported in the SOLVD trial and is derived from the numbers reported in Table 2 .

Information relating to the timing of deaths during each annual interval in the SOLVD trial is an

important factor in estimating the expected survival duration. Unfortunately the timing of these deaths was not directly observable from the reported trial data and without direct access to the patient-level data an assumption was required concerning the timing of these deaths. To reflect the uncertainty in the timing of death during each interval a uniform distribution was assigned to the time of death (mean 182.5 days, minimum=0 days, maximum=365 days) for each interval. Survival duration for each interval was then estimated by the probability of survival/death weighted by the mean survival time conditional upon survival status (either 365 days for patients who survived each year or the expected survival time for patients who died based on the uniform distribution). The estimated survival time in days was discounted for each interval (2% per annum) and converted to an annual equivalent to provide estimates of life-years gained.

2.5 Pre-trial model resource utilisation and costs

Data on the frequency of hospitalisation for CHF and non-CHF reasons was reported in a highly aggregated format in the SOLVD trial. Data required for the model were: (i) the probability of hospitalisation during each of the four years of the model and (ii) the average number of hospitalisations per patient hospitalised, for CHF and non-CHF reasons, conditional upon survival status. Due to the constraints imposed by the reporting of hospitalisation data, several assumptions were required in order to provide the necessary parameter estimates for the pre-trial model.

Firstly, the data reported in Table 3 were used to determine the total number of hospitalisations for CHF conditional upon survival status (alive/dead). Although the exact number of hospitalisations could be calculated based on the numbers of patients alive or dead and experiencing between 0 and 3 hospitalisations, only the total number of patients experiencing 4 or more hospitalisations were reported by vital status. Of the 683 total CHF hospitalisations in the enalapril group, a total of 433 hospitalisations (63%) could thus be attributed to patients conditional upon being alive or dead (202 and 231 respectively) and experiencing between 1 and 3 hospitalisations . The remaining 250 hospitalisations were then apportioned pro-rata according to the relative number of patients alive or dead and experiencing 4 or more hospitalisations. This assumption was necessary in order to determine the average number of hospitalisations per patient hospitalised. The same procedure was followed for patients randomised to placebo in the SOLVD trial to derive estimates for the low-dose treatment. Applying this method, both the total number of hospitalisations for CHF and the average number of hospitalisations (per patient hospitalised) could be estimated conditional upon vital status.

The probability of non-fatal CHF hospitalisation, across each of the four years of follow-up, was

based on the number of patients in each year experiencing (one or more) non-fatal hospitalisations for CHF reported in the SOLVD trial. Since no information was reported on the timing of fatal CHF hospitalisations, these hospitalisations were allocated pro-rata to each of the four years of the model according to the relative number of patients who died during each yearly interval .

For non-CHF hospitalisations the SOLVD trial only reported the total number of hospitalisations for the enalapril and placebo groups. No information was provided on the allocation of non-CHF hospitalisations conditional upon survival status (alive/dead) or the timing of these hospitalisations over the follow-up period. The following assumptions were made to allocate non-CHF hospitalisations within the decision model. Firstly, the total number of non-CHF hospitalisations were apportioned to survival status using the same rate that was reported for fatal and non-fatal CHF hospitalisations. This assumes that the rates of hospitalisation for CHF and non-CHF hospitalisations follow an identical pattern across each of the years follow-up. Following this initial apportionment, the total number of patients hospitalised, conditional upon survival status, was then estimated by applying the same average number of hospitalisations per patient as incurred for CHF reasons. Finally, the total number of patients hospitalised for non-CHF reasons were then allocated pro-rata across each of the yearly intervals based on the relative number of patients alive (and not censored) at the end of each interval for non-fatal hospitalisations, and the relative number of patients who died during each interval for fatal hospitalisations.

In addition to estimating the probability of hospitalisation during each interval and the mean number of hospitalisations per patient, information was also required for costing purposes on the mean length of stay of CHF and non-CHF hospitalisations. In the absence of any direct evidence from the SOLVD trial on length of hospitalisations for either CHF or non-CHF reasons, the mean length of stay reported in the UK Hospital Episode Statistics (HES) for heart failure (14.5 days) was used for CHF hospitalisations (Ref). Average per diem unit costs were then assigned to CHF hospitalisations in order to determine the mean costs of these hospitalisations.

The HES were also used to estimate the mean length of stay for non-CHF hospitalisations based on following three categories reported in the SOLVD trial: angina/myocardial infarction (6.7 days); other cardiovascular (7.25 days) and non-cardiovascular (7.7 days). Average per diem unit costs were then assigned to the mean length of stay for each category. To reflect the uncertainty in the costs for non-CHF hospitalisation,a uniform distribution was assigned to this parameter, based on the minimum and maximum costs across the three categories. To ensure

consistency between the prior and posterior results we used the per diem unit costs for CHF and non-CHF hospitalisations reported by Sculpher et al[2].

In addition to inpatient hospitalisations, the following resources were also included in the estimates of mean costs: use of ACE inhibitors (including initiation costs); outpatient attendances (including diagnostic tests); and the costs of death incurred outside the hospital. For the use of ACE inhibitors, data from the SOLVD trial on the proportion of patients taking ACE inhibitors after 12, 24, 36 and 48 months were used to determine the number of patients continuing with medication at each annual interval. The same proportions were also applied to the estimates for adherence with low-dose ACE inhibitors. The doses of the study drug, lisinopril, were costed using British National Formulary prices[40]. To ensure consistency between the pre-trial model and the economic analysis of the ATLAS trial, patients in the high-dose group were assumed to need three additional visits to a general practitioner for dose titration; these additional vists were costed at £14 each[2]. The annual medication costs of ACE inhibitors were converted into a daily cost and multiplied by expected survival for each yearly interval (365 days for patients who survived and the expected mean duration of survival in each interval for patients who died) to calculate the mean expected cost of ACE inhibitors.

No data on resource utilisation other than inpatient hospitalisations and use of ACE inhibitors were reported in the SOLVD trial. Data on the mean number of outpatient attendances (and types of diagnostic tests used) and resources associated with death outside hospitalisation were thus derived from the assumptions used in one of the economic studies identifed in the systematic review[38]. The mean costs of outpatient attendance were calculated in a similar manner to the cost of ACE inhibitors, by applying a mean daily cost to expected survival duration for each year, conditional upon survival status .

All unit cost data used in the analysis to value resource use are shown in Table 6, together with the sources of those data. These unit costs are used, together with the resource use, to generate an overall mean cost (and standard deviation) for each of the possible pathways in Figure 1.

2.6 Pre-trial model – Cost-effectiveness analysis

The results of the model are presented in two ways. Firstly, mean costs and life years for high and low dose are presented and their cost-effectiveness compared, using the incremental cost-effectiveness ratio (ICER). The advantage of entering input parameters as uncertain variables is that this uncertainty can be propogated through the model and reflected in model outputs. To

present the uncertainty in the cost-effectiveness of the alternative strategies, cost-effectiveness acceptability curves (CEACs) are used. These show the probability that each strategy is more cost-effective than the other using alternative values for the maximum value the health service is willing to pay for an additional life-year gained in these patients.

2.7 Results of the pre-trial model

Table 4 details the results for mean costs and survival duration for each of the four-years follow-up and in total. Mean total costs were £7519 and £8169 in the high and low-dose alternatives, indicating that a strategy of high-dose ACE inhibitors results in a mean saving of £650 compared to low-dose treatment. Although the mean cost of lisinopril was higher in the high-dose group, this additional cost was more than offset by the reduced hospitalisation costs. The majority of the cost savings were attributable to the lower frequency of hospitalisation for CHF in the initial year following treatments. Despite the high-dose group incurring higher mean costs in the following three years, these additional costs were more than offset by the lower cost incurred during the first year of the model.

Mean survival duration per patient over the four-year period were estimated to be 1129 days (3.09 years) in the high-dose group and 1075 days (2.95 years) in the low-dose group. The use of high-dose ACE inhibitors resulted in an increased expected survival duration of approximately 53 days, equivalent to an additional 0.15 life-years gained (LYG) over four-years. The comparison of mean costs and LYG demonstrate that the use of high-dose ACE inhibitors dominates low-dose (less costly and more effective) and hence that the optimal adoption decision, based on the assumptions used in the pre-trial model, is to select high-dose ACE inhibitors in the treatment of heart failure .

To reflect the uncertainty in the estimates of mean costs and life-years gained, Figure 2 presents a scatter-plot of the mean differences in cost and life-years gained between the high versus low-dose groups, derived from the 10,000 iterations of the Monte Carlo simulation. The x and y-axis divide the graph into four separate quadrants, which represent the following scenarios for high dose in comparison with low dose (clockwise from top right): (i) more effective and more costly; (ii) more effective and less costly; (iii) less effective and less costly, and (iv) less effective and more costly.

The high concentration of points in quadrants (i) and (ii) indicate that high-dose ACE inhibitors appear more effective than low-dose (99.77% of iterations). Furthermore it is evident that the majority of the replicates lie in the quadrant (ii), where high-dose dominates low-dose (and

hence is cost-effective relative to low-dose) (87.93% of iterations). However, the dispersion of points above and below the x-axis indicates that there is some uncertainty about whether this gain in life-years is achieved at a lower or higher cost than low-dose treatment (88.1% of iterations). Clearly if the gain in life-years gained is achieved at a higher cost, then the critical issue that determines whether high-dose ACE inhibitors are deemed cost-effective is how much (if any) the decision maker is prepared to pay for an additional unit gain in health outcome.

Figure 3 presents the cost-effectiveness acceptability curves for high and low dose ACE inhibitors. The curve indicate the probability of treatment being more cost-effective than the comparator for a range of potential maximum amounts a decision maker is willing to pay for an additional life-year gained (ceiling ratio). The x-axis shows a range of values for the ceiling ratio, and the y-axis shows the probability that the data are consistent with a true cost-effectiveness ratio falling below these ceiling amounts.

The curves demonstrate that the probability of high-dose being less costly than low-dose (i.e. the probability of being cost-effective when the decision maker is unwilling to pay anything additional for an extra life-year gained) based on the prior model is 0.881%. If the decision maker is prepared to pay at least £10,000 per life-year gained, then the probability of the treatment programme being cost-effective increases to 0.998.

Although uncertainty surrounding the mean estimates of costs and life-years gained do not affect the choice of optimal strategy (identified by a comparison of the expected values), they directly determine the value of obtaining further information to inform future decisions related to the choice between strategies .

3. Value of Information Analysis for pre-trial model

3.1 Methods

The use of Monte Carlo simulation allows the expected costs of uncertainty associated with the initial adoption decision to be expressed as the proportion of iterations (error probability) in which the uncertainty within the model results in an adoption decision other than that resulting from maximising expected net benefits (the a-priori decision). The benefits forgone are simply the difference in net benefits between the optimal strategy for a given iteration and the net benefit of the a-priori optimal strategy in that iteration. The expectation of benefits forgone over all iterations represents the EVPI for a patient with heart failure.

The overall value of information at a population level for heart failure patients is determined by applying the patient level EVPI to the number of patients that would be affected by the information (i.e. incidence of heart failure) over the anticipated lifetime of the technology:

$$EVPI * \sum_{t=1}^{T} \frac{I_t}{(1+r)^t}$$

Where I = incidence in period

t = period

T = total number of periods for which information from research would be useful

r = discount rate

National statistics suggest the incidence of heart failure is about one new case per 1,000 population per year[41]. Based on current estimates of the UK population, this implies an annual incidence of around 59,987 [42]. Population level EVPI is estimated using this value and assumes that the information would be valuable for 10 years. A 6% rate of discount is applied.

3.2 Results

Figure 4 illustrates the EVPI per patient over a range of estimates for the decision maker's maximum WTP (λ). At a λ value of £10,000 per LYG, the EVPI is approximately £0.67 per patient. This increases to £0.79 per patient when λ is £30,000 and is £1.15 when λ is £50,000. At a population level, the total EVPI is between £313,215 and £538,596 for values of λ between £10,000 and £50,000.Although the error probability associated with making an incorrect decision falls as the value of λ increases, the increased costs associated with making an incorrect decision more than outweigh this reduced error probability (resulting in an overall increase in the EVPI).

4. Posterior analysis of the decision problem

The next stage in the analysis is the posterior analysis of the decision between high and low-dose ACE inhibitors. The objective was to re-address the pre-trial adoption decision regarding the use of high or low-dose ACE inhibitors, following the incorporation of the results of the ATLAS trial. Value of information analysis is then used to formally assess the level and costs of uncertainty surrounding this posterior decision and to determine the potential efficiency of any further research that may be undertaken.

Patient-level data on survival and costs obtained from the ATLAS trial were combined with the prior estimates from the pre-trial model to generate posterior distributions for costs and LYG. The WinBUGS (Windows-based Bayesian Inference Using Gibbs Sampling) computer package was used to undertake the Bayesian analysis[43]. The programme undertakes Markov Chain Monte Carlo simulation via the Gibbs sampling algorithm to construct updated (posterior) distributions[44].

4.1 Posterior Survival and life-years gained

Patient level data on survival reported in the ATLAS study was either time to mortality (666 patient in the high-dose treatment group and 717 patients in the low-dose group) or the time the patient was censored (902 patients in high dose and 879 patients in low-dose). To account for the censoring in the time to event data, parametric survival analysis was used to calculate the expected mean survival duration for each group over the four-years follow-up.

For each treatment group, the patient level survival data from the ATLAS trial was modelled using the exponential distribution. Survival data is modelled using two related functions, the hazard function and the survivor function[45]. The hazard function, h*(t)*, is the probability that an individual dies at time *t*, given that they have survived up to that point in time. The exponential distribution assumes that the hazard function (h*(t)*=λ) is constant with respect to time . Since the hazard is a constant, the probability that an individual survives from the time origin to a point in time beyond t, is given by the survival function:

$S(t) = \exp(-\lambda t)$

Mean survival duration over the four-years follow-up can then be calculated by deriving the area under the survival curve:

Mean survival duration = $\int_0^t S(t)dt$

where t = time in days (4 years = 1460 days)

Closer inspection of the Kaplan-Meier survival curves did not appear to support the assumption of a constant hazard over the entire follow-up period. To overcome this potentially limiting assumption, patient level survival data was modelled using a piecewise exponential distribution. This involves dividing the duration of follow-up into four separate yearly intervals and then

approximating the survival function in each period using a separate exponential function. The use of this distribution requires a less restrictive assumption that the hazard rate is constant over each interval rather than over the entire duration of follow-up. Mean survival duration for each yearly interval is then derived by estimating the area under the survival curve for the relevant interval. The total mean survival duration over the four-year follow-up is then calculated by summing mean survival duration across each of the yearly intervals. Mean survival duration was discounted using an annual rate of 2% .

In the WinBUGS model the survival analysis is undertaken using the log-relative hazard form (i.e. lambda=logλ). Using this form the log-hazard rate (lambda) is modelled as a normal distribution specified by a mean and precision for each separate interval. For the distribution of lambda, the mean parameter represents the expected value of the log-hazard rate, whilst the precision parameter represents the uncertainty surrounding the mean value. For the informed Bayesian analysis, prior values for the mean and precision parameters were derived from the conditional survival probabilities derived from the prior model. The conditional survival probabilities from the pre-trial model, for each interval, were then converted to a log hazard rate using the following formula:

$$\text{Log-hazard rate}_i = \log[-\log(1-P_i)/\text{time}_i]$$

where: P_i = probability of death during interval $_i$,

time_l = length of interval $_i$

The results of the Monte Carlo simulation of the pre-trial model generated distributions for each conditional survival probability. Each iteration was then converted to a log-hazard rate using the formula to give a distribution of lambda values. The resulting distribution of lambda values was then used to derive the values for the mean and precision parameters.

4.2 Posterior Costs

Patient level resource use data, from a health service perspective, were recorded prospectively in the ATLAS trial. Detailed methods related to the measurement and valuation of resource use are reported elsewhere[2]. Resources measured included: days in hospital, day-case visits (defined as visits to the hospital without an overnight stay) and drug use (including additional dose titration visits for the patients in the high-dose group). Unit costs were based on 1997-98 values and were derived from UK specific sources only.

Patients in the ATLAS trial were followed up for differential periods, so costs have been analysed using the method developed by Lin et al to account for the censoring in the cost data[46]. This approach to estimating mean costs combines the survivor function estimate of the probability of survival with the average costs assigned to each interval:

$$\hat{C} = \sum_{k=1}^{4} \hat{C}_k \exp(-\lambda t_k)$$

where $\hat{C}_k$ is the average cost incurred during the interval k among patients under observation at the start of the interval and $\exp(-\lambda t_k)$ is the survivor function of the probability that a patients survives to time k or beyond.

The patient level cost data is assumed to follow a half-normal distribution (i.e. a normal distribution truncated at zero to avoid the possibility of negative values). Priors are then specified for the mean and precision parameters of the half-normal cost distributions. The mean represents second order uncertainty in the costs (the variation in the mean cost). The mean of the log cost is modelled as a normal distribution specified by a mean and a precision.

The parameters of the mean cost distribution were obtained from the results of the Monte Carlo simulation of the pre-trial model. The mean costs of patients surviving to the start of each interval were obtained from the Monte Carlo simulation of the prior model. The expected value for each interval, based on the 10,000 iterations, was used as the prior estimate of the mean parameter. Within the WinBUGS model the precision is also specified using a normal distribution (truncated at zero). The distribution for the precision parameter represents the first order uncertainty in the prior data. As a result the parameters of the precision are left vague because the prior model only provides an estimate of second order uncertainty.

A burn-in of 10,000 updates (which are then discarded) followed by a further 10,000 updates were used to derive the posterior estimates for mean survival duration and costs.

4.3 Posterior optimal strategy

Table 8 details the posterior results for mean costs and life-years gained for each of the four-years follow-up and in total. Mean total costs were £274 lower in the high-dose treatment group (mean total cost = £7,079) compared to the low-dose group (mean total cost = £7,353). The additional costs of lisinopril in the high-dose group were more than offset by the lower costs associated with less frequent hospital treatment.

Mean survival duration per patient was 1,110 days (3.04 years) and 1,069 days (2.93 years) respectively in the high and low dose groups. The use of high-dose ACE inhibitors is predicted to result in an increased expected survival duration of approximately 41 days, equivalent to an additional 0.11 life-years gained (LYG) over four-years. Based on a comparison of mean costs and LYG, the high-dose group dominates the low-dose group by being both more effective and less costly. The optimal adoption decision, based on a posterior analysis of both the prior data and the ATLAS trial data, is to use high-dose ACE inhibitors in the treatment of patients with chronic heart failure .

Figure 5 illustrates the uncertainty in the mean difference in costs and LYG by plotting the results of each of the 10,000 iterations of the WinBugs model. The combined evidence from the prior model and the trial data demonstrate that, while there is some uncertainty about the size of the effect difference between the high-dose and low-dose groups, there is clear evidence that this difference is almost entirely in favour of the high-dose treatment strategy The probability that high-dose is more effective than low-dose treatment is approximately 0.9997.

There is less certainty in whether the high-dose group is less costly than the low-dose group. However, the majority of the posterior replicates from the WinBugs model lie below the x-axis, demonstrating that there is a approximately an 0.8474 probability that the high-dose group is less costly than the low-dose group. Considering the joint uncertainty in costs and LYG together, the majority of the replicates lie in the quadrant (iii) where the high-dose group dominates the low-dose group (84.71% of iterations). However, there also appears to be a sizeable proportion of replicates in quadrant (ii), where the cost-effectiveness of high-dose is dependent upon the decision-maker's maximum willingness-to-pay for an additional LYG (15.22% of iterations).

Figure 6 illustrates the posterior probability that high-dose treatment is more cost-effective than low-dose treatment across a range of threshold values for the decision-makers maximum WTP, presented in the form of a CEAC. The posterior CEAC demonstrates there is a 0.93 probability that high-dose is more cost-effective than low-dose at £1,000 per LYG. This probability rises to over 0.99 if the decision-maker is prepared to pay over £3,000 per LYG.

5. Posterior value of information analysis

The posterior analysis demonstrates that the use of high-dose ACE inhibitors is the optimal adoption decision based on combination of both the pre-trial and the ATLAS trial evidence. The final stage of the posterior analysis reconsiders the value of acquiring further information by

commissioning additional research in light of the results of the updated (posterior) model. Once again the EVPI for the decision problem is established to determine the potential efficiency of additional research.

The results of the value of information analysis of the posterior model suggests there appears little value in obtaining further information on the input parameters to the model (Figure 7). At a λ value of £10,000 per LYG, the EVPI is approximately £0.07 per patient. This increases to £0.11 per patient when λ is £30,000 and £0.19 per patient when λ is £50,000. At a population level, the total EVPI is between £31,012 and £90,502 for these values of λ.

6. Discussion

Both the prior and posterior mean estimates of LYG and costs identified the use of high-dose ACE inhibitors, in comparison with low-dose, as the optimal adoption decision in the treatment of patients with chronic heart failure. The posterior CEAcc indicated that while there while there appears slightly more uncertainty about whether high-dose is cost saving in comparison with the prior CEAcc (85% of iterations in the posterior analysis vs 88% in the prior model), there was now less uncertainty in the adoption decision provided the decision maker is prepared to pay over £1000 per LYG. Despite the higher posterior uncertainty for certain threshold values of LYG (values <£1000 per LYG), the variance around these estimates was greatly reduced in comparison to the pre-trial model results. Consequently the posterior EVPI estimates were lower than the pre-trial EVPI estimates over the entire range of values for LYG. The combined weight of evidence from both the prior model and the results from the ATLAS study appears to have resolved a significant amount of the uncertainty relating to the pre-trial decision.

The analysis demonstrates the value of a fully Bayesian analysis in the context of chronic heart failure. Although the posterior analysis did not result in a change in the adoption decision from that suggested by prior evidence, the posterior EVPI indicated that the evidence from the pre-trial analysis combined with the additional information from the ATLAS trial had resolved a significant amount of the uncertainty underlying this decision. Furthermore, failure to consider the prior information would have significantly overestimated the value of additional research in this area. To illustrate this Figure 10 presents a comparison of the informed and uninformed (ignoring prior evidence) posterior EVPI estimates. The At a λ value of £10,000 per LYG, the EVPI is approximately £0.07 per patient. This increases to £0.11 per patient when λ is £30,000 and £0.19 per patient when λ is £50,000 for the informed and uniformed posterior analyses respectively. At a population level, the total EVPI is between £31,012 and £90,502 for values of

λ between £10,000 and £50,000 in the informed posterior analysis. For comparison the total population EVPI for the uniformed analysis is between £1,759,555 and £8,523,723. Hence ignoring the prior evidence in this analysis would potentially overestimate the uncertainty in the decision by between £1,728,543 and £8,433,221 for values of λ between £10,000 and £50,000. Despite the merits of employing an informed Bayesian approach in this analysis, there are several potential limitations which need to be considered in conjunction with the results presented here. Firstly, the pre-trial model made selective use of the prior evidence by considering only the results from the SOLVD treatment trial in the pre-trial model. Although the SOLVD trial represents the best single source of prior information on major clinical and cost outcomes for the comparison between high and low dose ACE inhibitors (due to extended period of follow-up reported in the SOLVD treatment trial and the reporting of hospitalisation event data), this approach effectively ignored the information from the other studies identified in the systematic review. Despite this limitation it is clear that due to the size of the SOLVD trial in comparison to the other studies considered, the parameter estimates of the pre-trial model would still largely be driven by the SOLVD data. Furthermore due to the limited follow-up of the other studies detailed in Section 4.1, the SOLVD trial was the only trial that provided data beyond 1 year.

Secondly, by only considering prior data from trials reporting before the ATLAS trial started, the iterative approach outlined here did not consider the evidence published during the period of time during which the ATLAS trial was conducted. This suggests an additional step in the iterative approach which would require the results of the pre-trial model to be updated with the additional evidence from studies published during the course of the new trial. These revised estimates would then form the basis of the prior evidence for the informed Bayesian analysis.

Table 1. Number of deaths (and causes) and number of patients who died or were hospitalised for CHF in SOLVD trial[32]

Variable	**Enalapril N (%)**	**Placebo N (%)**	**Risk reduction (95% CI)**
Randomised patients	1285 (100)	1284 (100)	
Deaths	452 (35.2)	510 (39.7)	16 (5 to 26)
Deaths or hosp for CHF	613 (47.7)	736 (57.3)	26 (18 to 34)
Cardiovascular deaths	399 (31.1)	461 (35.9)	18 (6 to 28)
Noncardiovasc deaths	49 (3.8)	53 (4.1)	

Table 2. Survival by time period

Time Period	**Enalapril N**	**Placebo N**
Baseline	1285	1284
6 months	1195	1159
12 months	1127	1085
18 months	1069	1005
24 months	1010	939
30 months	891	819
36 months	697	669
42 months	526	487
48 months	333	299

Table 3. Frequency of hospitalisation for CHF, according to status at the end of study

Status/no. of hospitalisations	**Enalapril N (%)**	**Placebo N (%)**
Alive		
0	672 (52.3)	548 (42.7)
1	95 (7.4)	123 (9.6)
2	31 (2.4)	48 (3.7)
3	15 (1.2)	27 (2.1)
>=4	20 (1.6)	28 (2.2)
Dead		
0	281 (21.9)	266 (20.7)
1	80 (6.2)	113 (8.8)
2	38 (3)	70 (5.4)
3	25 (1.9)	32 (2.5)
>=4	28 (2.2)	29 (2.2)
Patients hospitalised		
At least once	332 (25.8)	470 (36.6)
Twice or more	157 (12.2)	234 (18.2)
All hospitalisations	683	971
Patients dead or hospitalised	613 (47.7)	736 (57.3)

Table 4: Pathway probabilities and distributions – prior model (High Dose)

Parameter	Probability	Alpha	Beta
Die Year 1	0.124	159	1126
Die Year 2	0.105	118	1009
Die Year 3	0.118	119	891
Die Year 4	0.067	47	650
Hospitalised CHF|Survive Yr 1	0.091	103	1024
Hospitalised CHF|Survive Yr 2	0.053	54	956
Hospitalised CHF|Survive Yr 3	0.003	2	695
Hospitalised CHF|Survive Yr 4	0.009	3	330
Hospitalised CHF|Die Yr 1	0.386	61.38	97.62
Hospitalised CHF|Die Yr 2	0.386	45.55	72.45
Hospitalised CHF|Die Yr 3	0.386	45.94	73.07
Hospitalised CHF|Die Yr 4	0.386	18.14	28.86
Hospitalised Non-CHF|Survive Yr 1	0.229	258	869
Hospitalised Non-CHF|Survive Yr 2	0.134	135	875
Hospitalised Non-CHF|Survive Yr 3	0.007	5	692
Hospitalised Non-CHF|Survive Yr 4	0.038	13	320
Hospitalised Non-CHF|Die Yr 1	0.968	154	5
Hospitalised Non-CHF|Die Yr 2	0.968	114	4
Hospitalised Non-CHF|Die Yr 3	0.968	115	4
Hospitalised Non-CHF|Die Yr 4	0.968	46	1
Proportion taking ACE inhibitors Year 1	0.88	1130.8	154.2
Proportion taking ACE inhibitors Year 2	0.845	952.32	174.69
Proportion taking ACE inhibitors Year 3	0.8225	833.25	176.75
Proportion taking ACE inhibitors Year 4	0.8225	575.03	121.97

Table 5: Pathway probabilities and distributions – prior model (Low Dose)

Parameter	Probability	Alpha	Beta
Die Year 1	0.157	201	1083
Die Year 2	0.132	143	942
Die Year 3	0.113	106	833
Die Year 4	0.081	54	615
Hospitalised CHF|Survive Yr 1	0.184	200	885
Hospitalised CHF|Survive Yr 2	0.016	15	924
Hospitalised CHF|Survive Yr 3	0.022	15	654
Hospitalised CHF|Survive Yr 4	0	0.01	298.99
Hospitalised CHF|Die Yr 1	0.484	97.31	103.69
Hospitalised CHF|Die Yr 2	0.484	69.23	73.77
Hospitalised CHF|Die Yr 3	0.484	51.32	54.68
Hospitalised CHF|Die Yr 4	0.484	26.14	27.86
Hospitalised Non-CHF|Survive Yr 1	0.353	384	701
Hospitalised Non-CHF|Survive Yr 2	0.031	29	910
Hospitalised Non-CHF|Survive Yr 3	0.043	29	640
Hospitalised Non-CHF|Survive Yr 4	0	0.01	298.99
Hospitalised Non-CHF|Die Yr 1	0.928	187	14
Hospitalised Non-CHF|Die Yr 2	0.928	133	10
Hospitalised Non-CHF|Die Yr 3	0.928	98	8
Hospitalised Non-CHF|Die Yr 4	0.928	50	4
Proportion taking ACE inhibitors Year 1	0.880	1129.9	154.1
Proportion taking ACE inhibitors Year 2	0.845	916.83	168.17
Proportion taking ACE inhibitors Year 3	0.825	774.68	164.32
Proportion taking ACE inhibitors Year 4	0.825	551.93	117.07

Table 6: Unit cost and resource use estimates for prior model

High Dose Estimates

Item	Frequency of use	Unit cost or range	Expected cost	Period	Source
Ace Inhibitors	1	£329	£329	Per annum	
Initiation costs	1	£42	£42	Per annum	
CHF hospitalisations|survive	1.87	£5,148	£9,611	Per event	
CHF hospitalisations|die	2.20	£5,148	£11,345	Per event	
Non-CHF hospitalisations|survive	1.87	£1,702-£2,849	£4,248	Per event	
Non-CHF hospitalisations|die	2.20	£1,702-£2,849	£5,014	Per event	
Outpatient care - visits	4.00	£44.6	£178	Per annum	
Death outside hospital	1	£580.00	580	Per event	

Low Dose Estimates

Item	Frequency of use	Unit cost or range	Expected cost	Period	Source
Ace Inhibitors	1.	£329	£329	Per annum	
Initiation costs	1	£42	£42	Per annum	
CHF hospitalisations|survive	1.99	£5,148	£9,611	Per event	
CHF hospitalisations|die	2.10	£5,148	£11,345	Per event	
Non-CHF hospitalisations|survive	1.99	£1,702-£2,849	£4,248	Per event	
Non-CHF hospitalisations|die	2.10	£1,702-£2,849	£5,014	Per event	
Outpatient care - visits	4	£44.6	£178	Per annum	
Death outside hospital	1	£580.00	580	Per event	

Table 7: Prior analysis - Mean costs and survival duration (days)

Period	Mean cost per patient (£)		Difference (HD-LD)	Mean survival duration (Days)		Difference (HD-LD)
	High Dose	Low Dose		High Dose	Low Dose	
Year 1	2998	4048	-1050	342	336	6
Year 2	2007	1882	125	297	282	15
Year 3	1495	1282	213	259	242	17
Year 4	1020	957	63	230	214	16
Total	**7519**	**8169**	**-650**	**1129**	**1075**	**53**

Table 8: Posterior analysis - Mean costs and survival duration (days)

Period	Mean cost per patient (£)		Difference (HD-LD)	Mean survival duration (Days)		Difference (HD-LD)
	High Dose	Low Dose		High Dose	Low Dose	
Year 1	2717	3018	-301	342	338	4
Year 2	1851	1898	-47	296	284	12
Year 3	1439	1392	47	254	241	13
Year 4	1072	1046	26	218	206	12
Total	**7079**	**7353**	**-274**	**1110**	**1069**	**41**

Figure 1: Basic structure of prior model

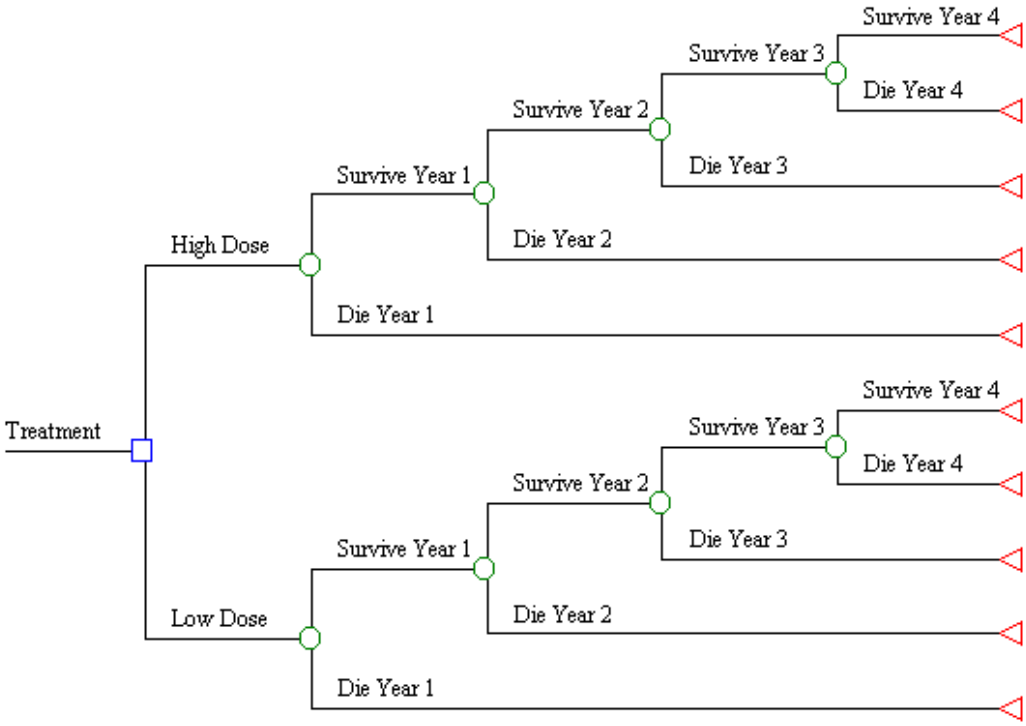


Figure 2: Scatterplot of mean cost and effect differences – prior model

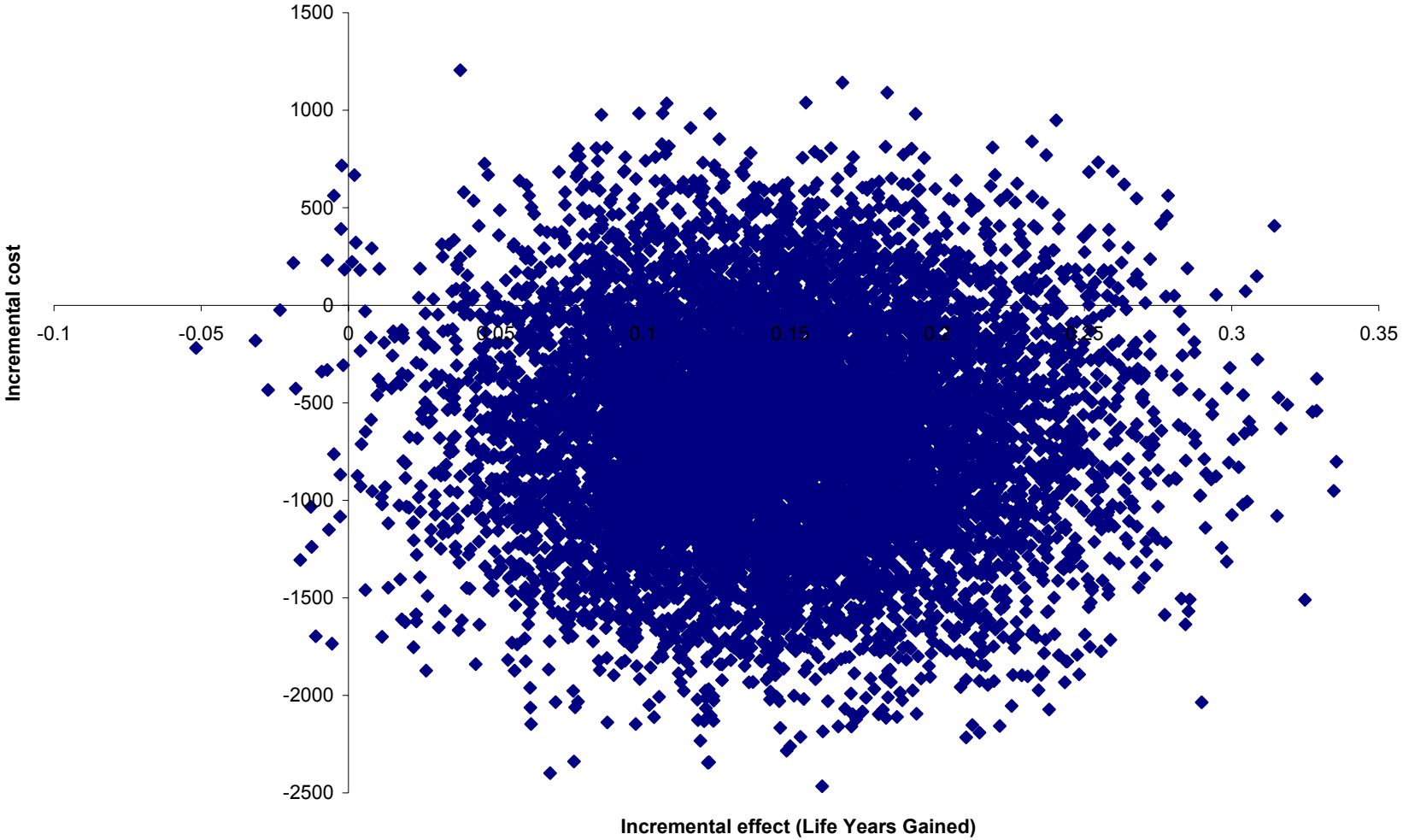


Figure 3: Cost-effectiveness acceptability curve for pre-trial model

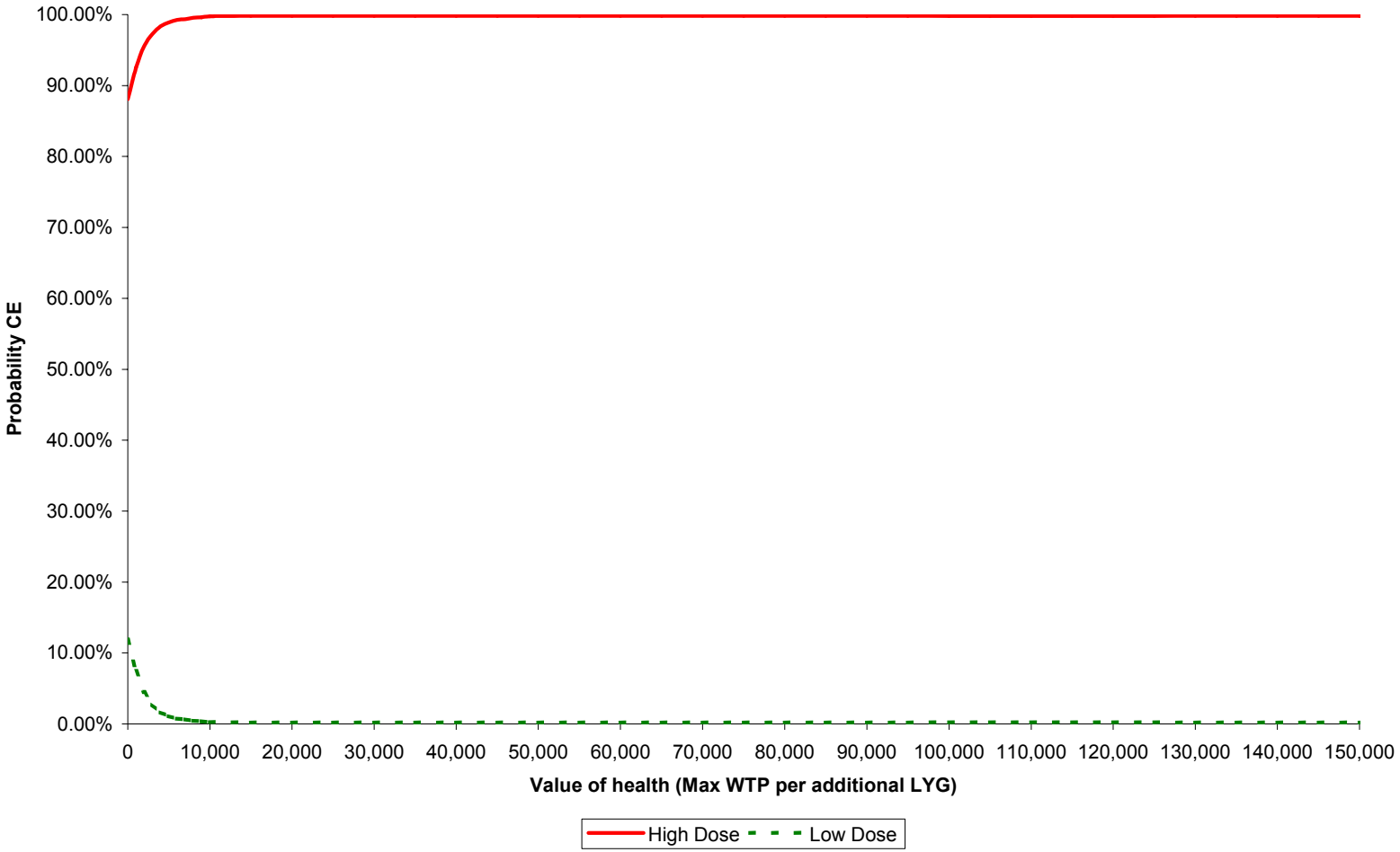


Figure 4: Value of information analysis (EVPI per patient) for pre-trial model

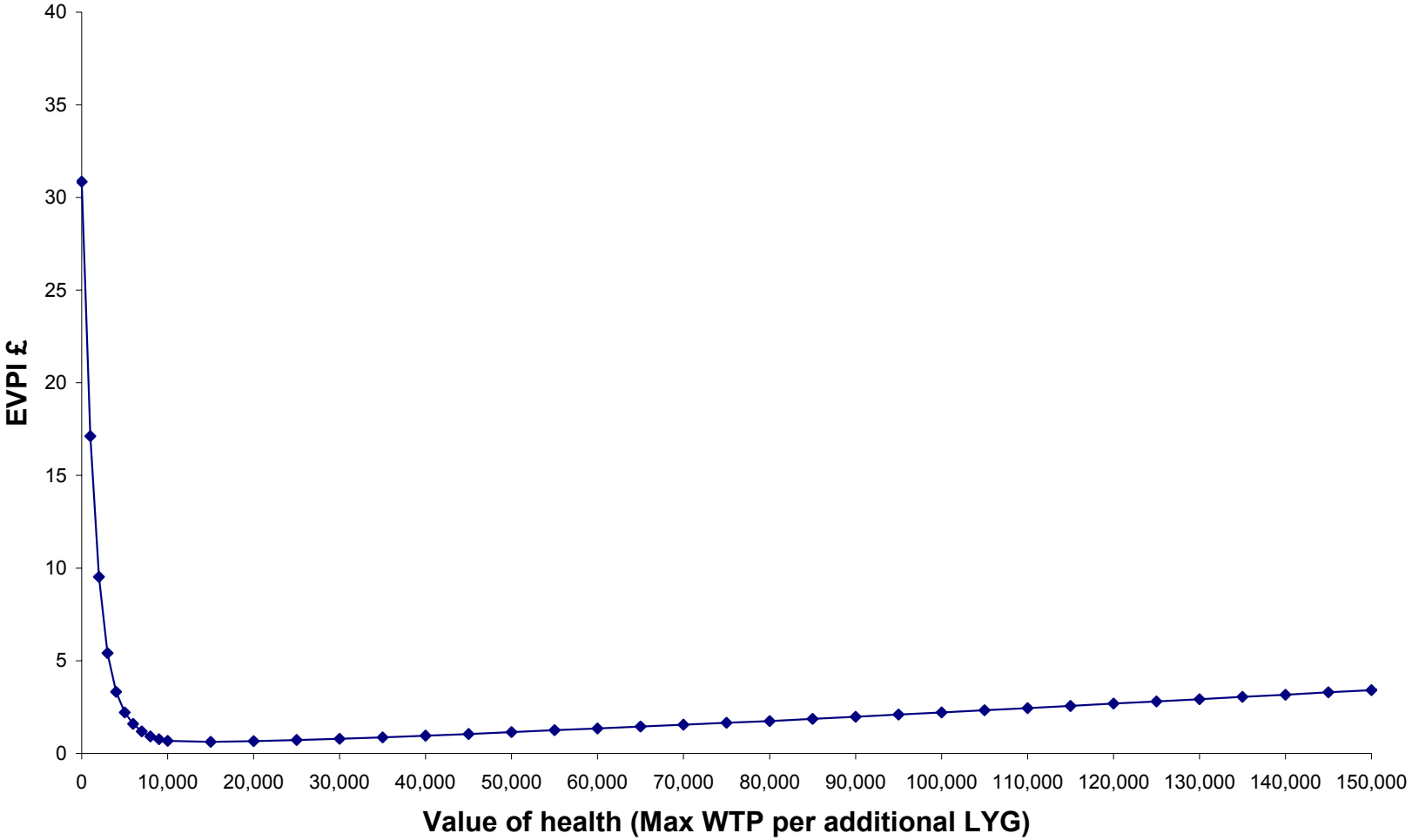


Figure 5: Scatterplot of mean cost and effect differences (LYG) for posterior analysis

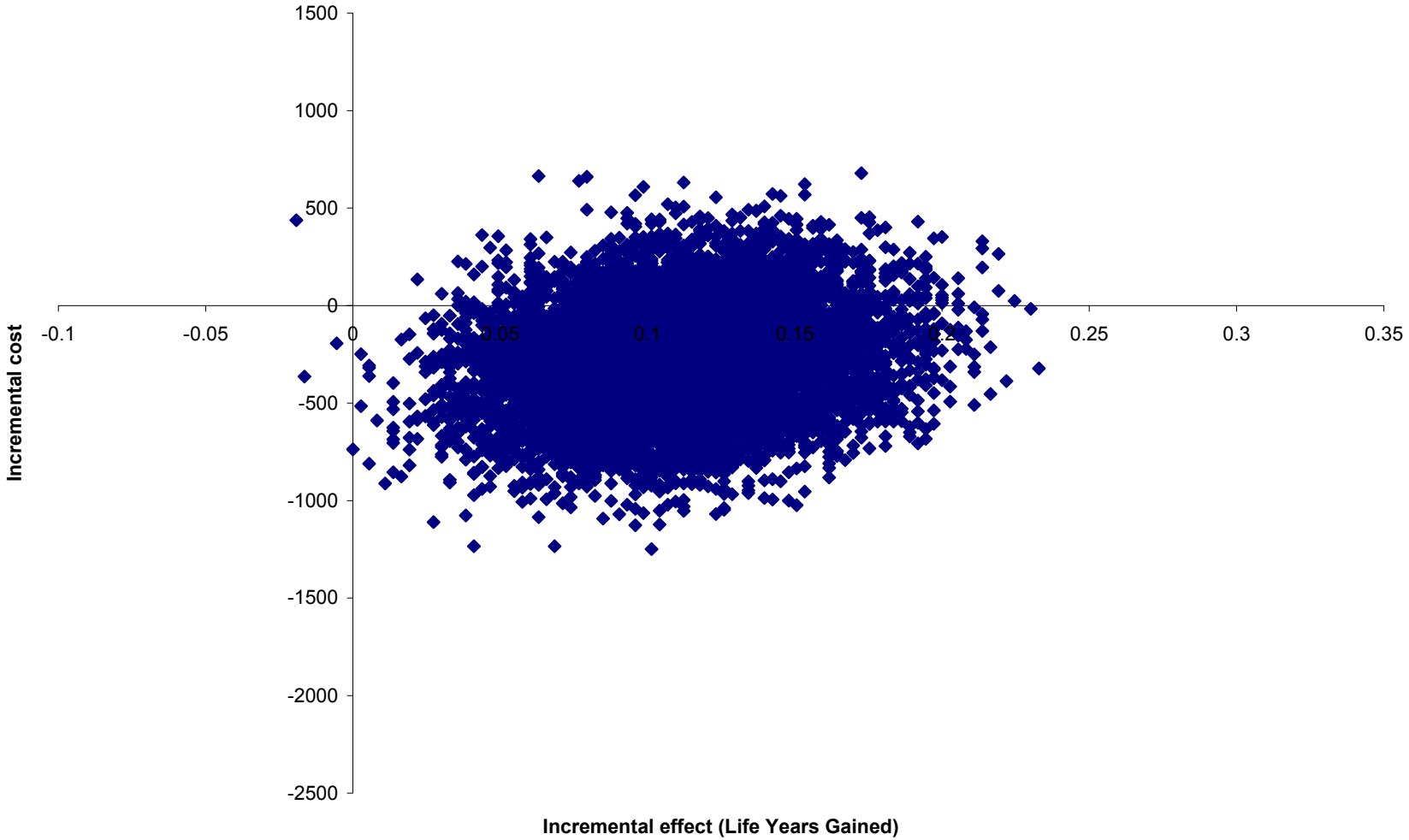


Figure 6: Cost-effectiveness acceptability curve for posterior analysis

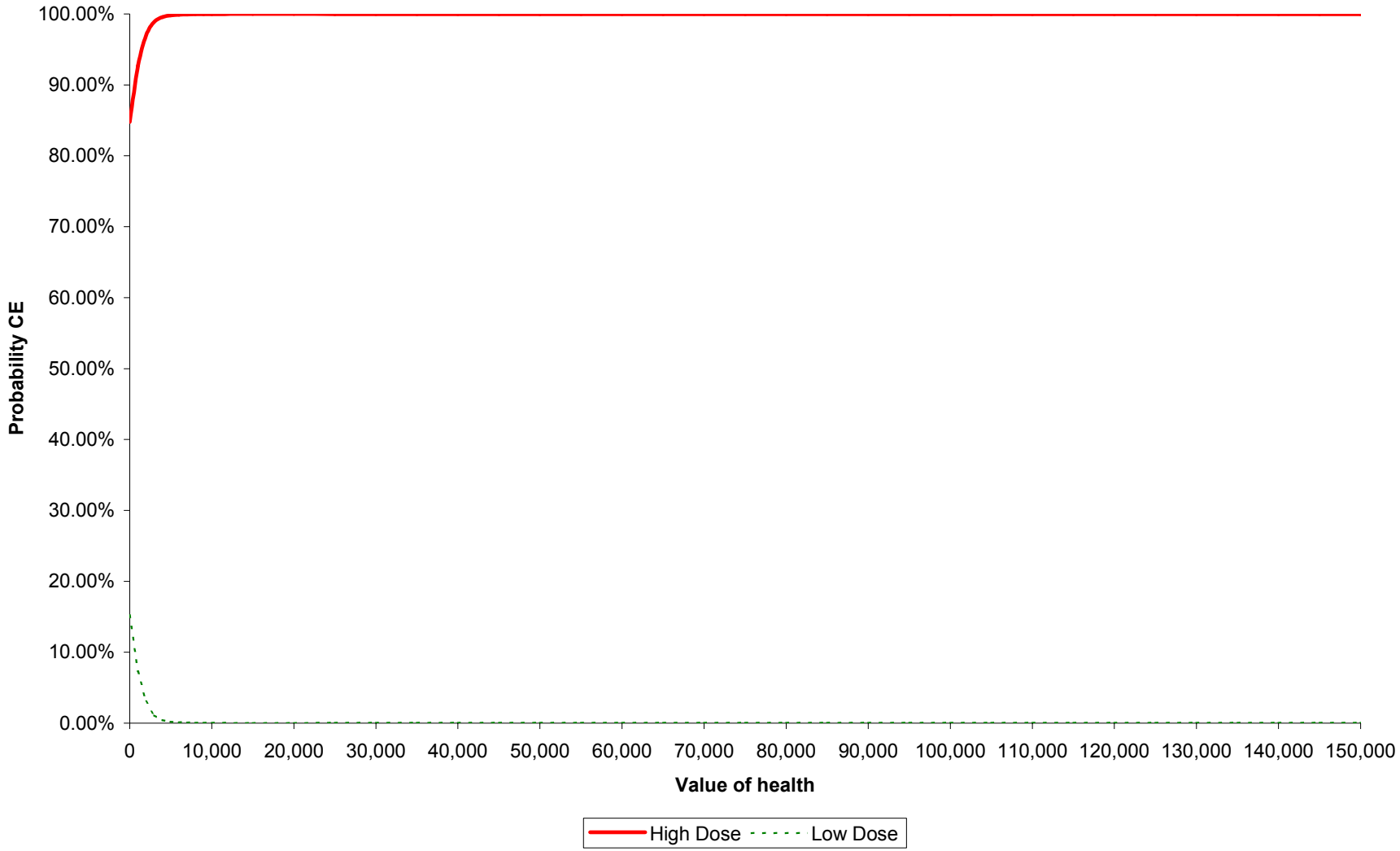


Figure 7: Value of information analysis (EVPI per patient) for posterior analysis

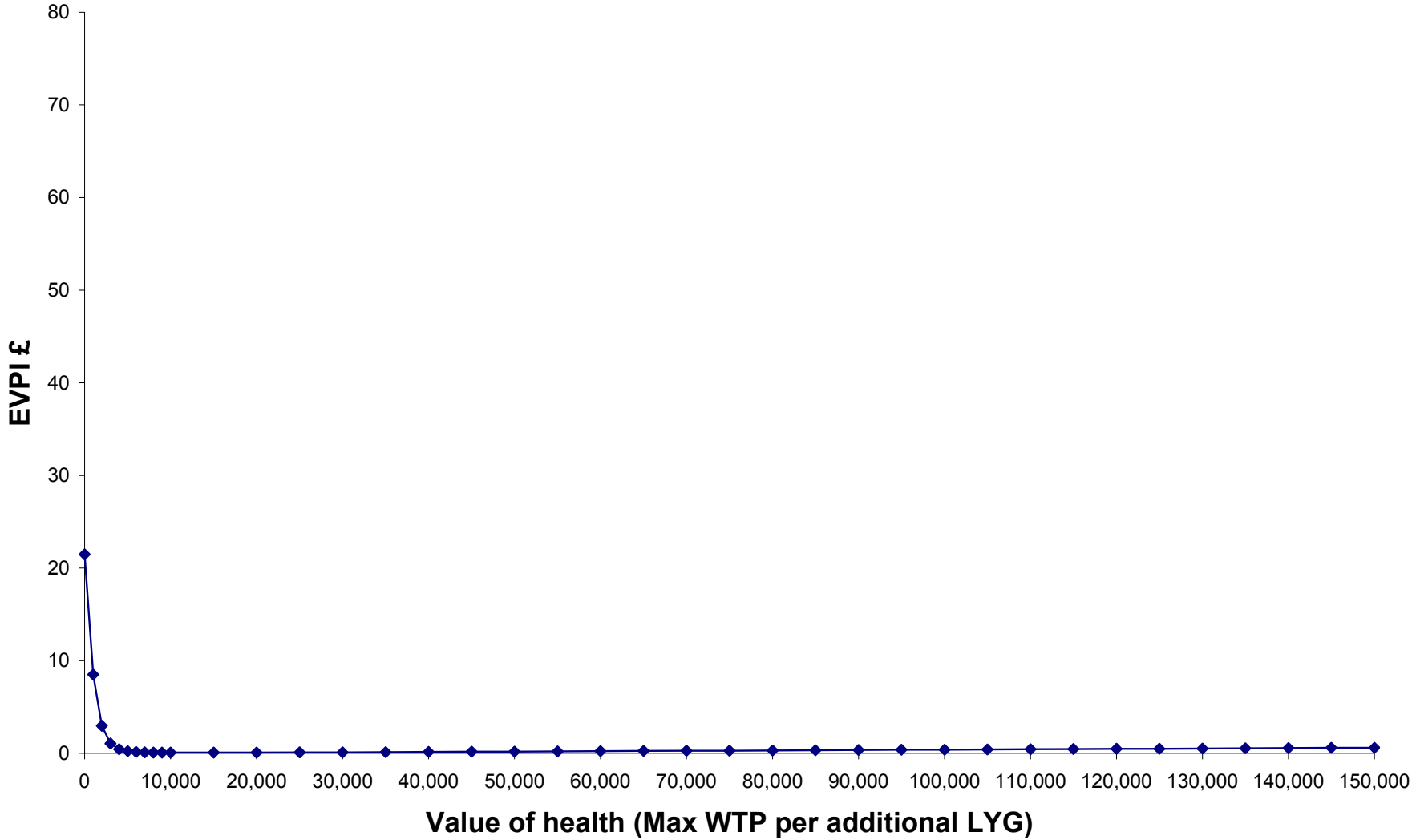


Figure 8: Cost-effectiveness acceptability curve comparison (pre-trial and posterior)

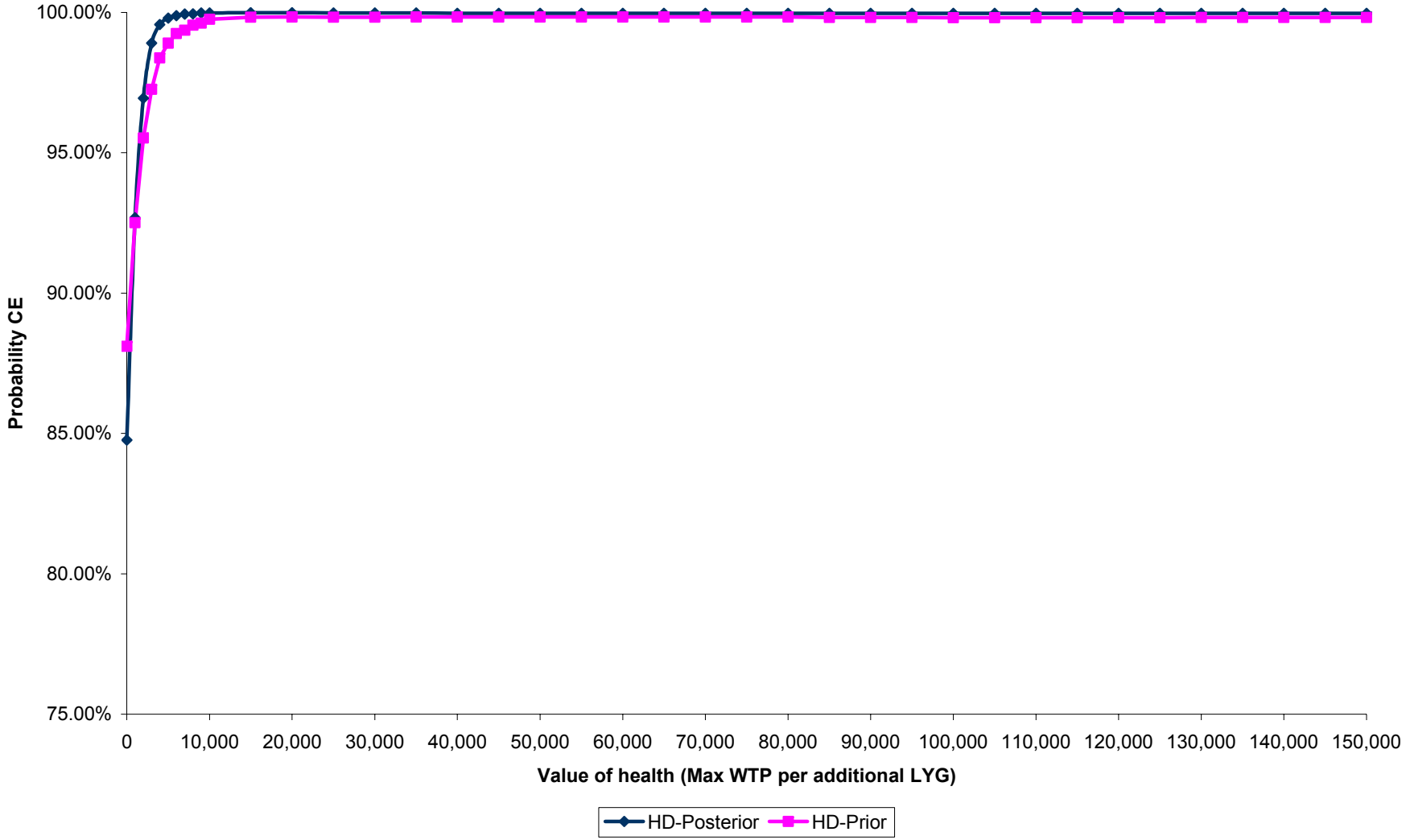


Figure 9: Value of information analysis comparison (pre-trial and posterior analysis)

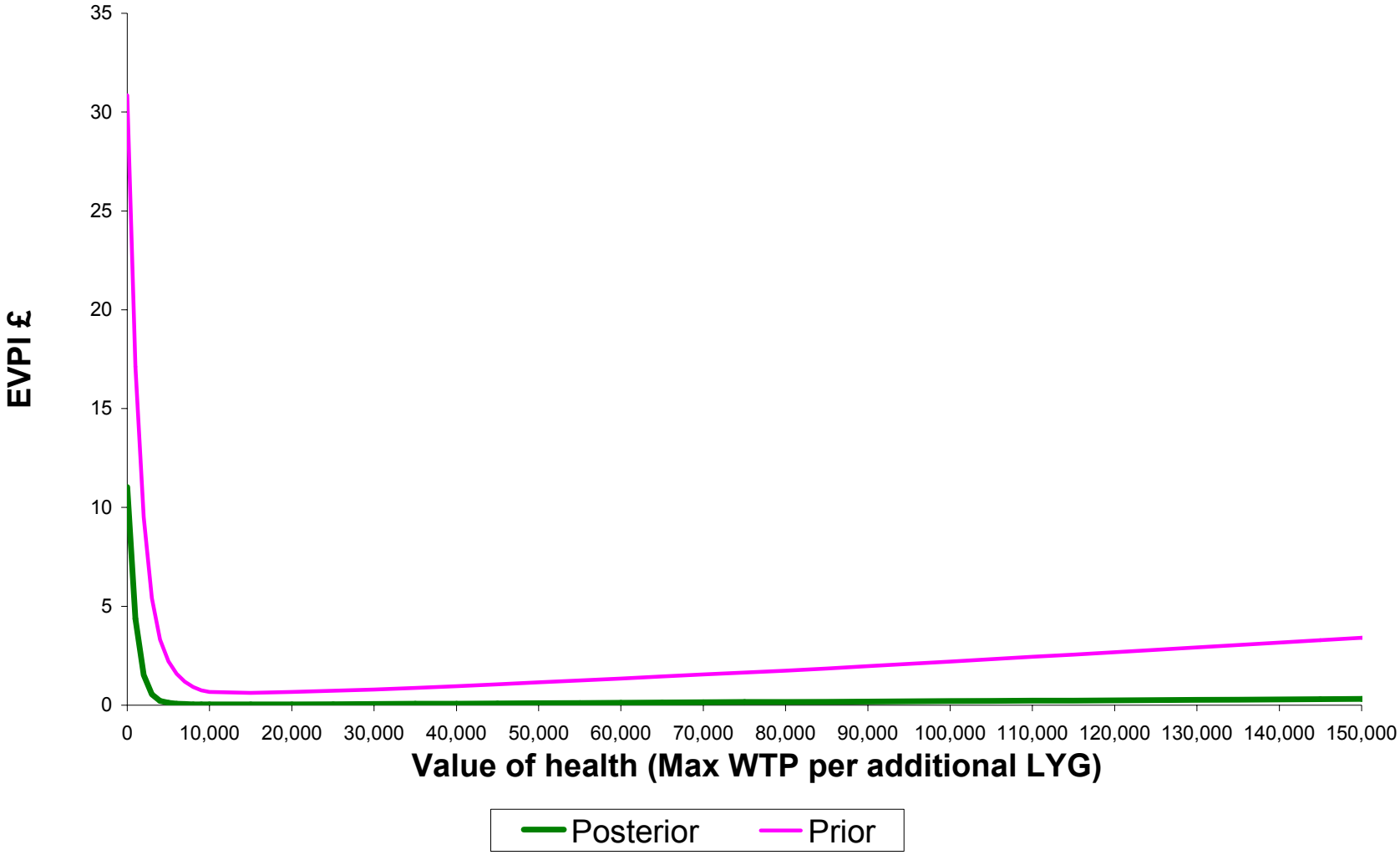
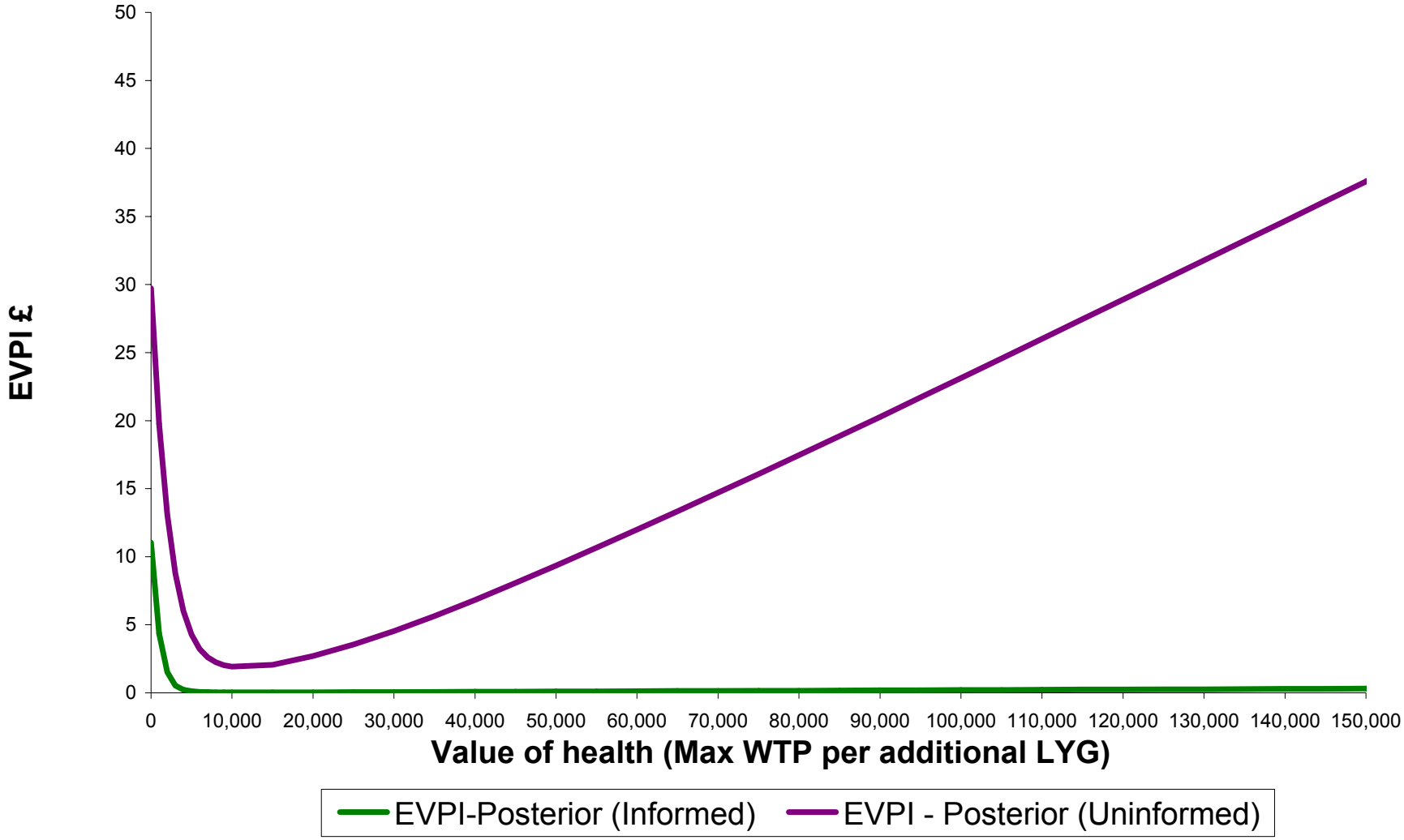


Figure 10: Value of information analysis comparison (informed and uninformed posterior analysis)



References:

1. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JGF, Horowitz JD, Massie BM, et al. Comparative effects of low and high does of the angiotensin-converting enzyme inhibitor, lisonpril, on morbidity and mortality in chronic heart failure. *Circulation* 1999;100:2312-2318.
2. Sculpher M, Poole L, Cleland JGF, Drummond M, Armstrong PW, Horowitz JD, et al. Low doses vs. high doese of the angiotensin converting-enzymme inhibitor lisinopril in chronic heart failure: an assessment of treatment with lisinopril and survival (ATLAS) study. *European Journal of Heart Failure* 2000????
3. Ader R, Chatterjee K, Ports T, Brundage B, Hiramtsu H, Parmley W. Immediate and sustained hemodynamic and clinical improvement in chronic heart failure by oral angiotensin-converting enzyme inhibitor. *Circulation* 1980;61:931-937.
4. DiCarlo L, Chatterjee K, Parmley W, Swedberg K, Atherton B, Curran D, et al. Enalapril: a new angiotensin-converting enzyme inhibitor in chronic heart failure: acute and chronic hemodynamic evaluations. *J Am Coll Cardiol* 1983;2:865-871.
5. Uretsky B, Shaver J, Liang C-S, Amin D, Shah P, Levine T, et al. Modulation of hemodynamic effects with converting enzyme inhibitor: acute hemodynamic dose-response relationship of a new angiotensin converting enzyme inhibitor, lisinopril, with observation on long-term clinical, functional and biochemical responses. *American Heart Journal* 1988;116:480-488.
6. Riegger GAJ. Effects of quinapril on exercise tolerance testing in patients with mild to moderate congestive heart failure. *European Heart Journal* 1991;12:705-711.
7. Pacher R, Stanek S, Globits S, Berger R, Hussman M, Wutte M, et al. Effects of two different enalapril dosages on clinical, haemodynamic and neurohormonal response of patients with severe congestive heart failure. *European Heart Journal* 1996;17:1223-1232.
8. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA* 1995;273:1450-1456.
9. Barabino A, Galbariggi G, Pizzorni C, Lotti G. Comparative effects of long-term therapy with captopril and ibopamine in chronic congestive heart failure in old patients. *Cardiology* 1991;78:289-296.
10. Bussman WD, Storger H, Hadler D. Long-term treatment of severe chronic heart failure with captopril: a double-blind randomised, placebo-controlled long-term study. *Journal of Cardiovascular Pharmacology* 1987;9:S50-S60.
11. Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. *JAMA* 1988;259:539-544.
12. Cleland JGF, Dargie HJ, Ball SG. Effects of enalapril in heart failure: a double blind study of effects on exercise performance, renal function, hormones, and metabolic state. *British Heart Journal* 1985;54:305-311.
13. Colfer HT, Ribner HS, Gradman A, Hughes V, Kapoor A, Laideau JC. Effects of once-daily benazepril therapy on exercise tolerance and manifestations of chronic congestive heart failure. *American Journal of Cardiology* 1992;70:354-358.
14. Dickstein K, Barvik S, Aarsland T. Effect of long-term enalpril therapy on cardiopulmonary exercise performance in men with mild heart failure and previous myocardial infarction. *J Am Coll Cardiol* 1991;18:596-602.
15. Drexler H, Banhardt BS, Meinertz T, Wollschlager H, Lehmann M, Just H. Contrasting peripheral short-term and long-term effects of converting enzyme inhibition in patients with congestive heart failure: a double blind, placebo controlled trial. *Circulation* 1989;79:491-502.
16. Enalapril CHF Investigators. Long-term effects of enalapril in patients with congestive heart failure: a multicenter, placebo-controlled trial. *Heart Failure* 1987;1987:102-107.

17. Giles TD. Lisinopril treatment of congestive heart failure-results of a placebo controlled trial. *Circulation* 1990;82:III-323.
18. Gordon M. Evaluation of the efficacy and safety of ramipril (HOE 498) in patients with congestive heart failure in a double blind placebo controlled trial. Frankfurt: Germany: Hoechst Aktiengesellschaft, 1991:Unpublished report.
19. Kleber FX, Niemoller L, Doering W. Impact of converting enzyme inhibition on progression of chronic heart failure: results of the Munich mild heart failure trial. *British Heart Journal* 1992;67:289-296.
20. Lemarie JC. Multicenter double-blind placebo controlled study of the efficacy and safety of ramipril administered orally for 24 weeks in the treatment of stable chronic congestive cardiac failure. Paris: France: Laboratories Hoeschst, 1992:Unpublished report.
21. Maass L. Evaluation of the effect of ramipril (HOE 498) on exercise duration, invasive cardia haemodynamics profiles, and safety in patients with congestive heart failure. Frankfurt: Germany: Hoechst Aktiengesellschaft, 1991:Unpublished Report.
22. Maass L. Efficacy and safety of ramipril (HOE 498) in patients with congestive heart failure in a double blind placebo controlled trial. Frankfurt: Germany: Hoechst Aktiengesellschaft, 1991:Unpublished Report.
23. Maass L. Double blind comparative trial with ramipril and placebo in patients with heart failure (NYHA Class III-IV) stabilized on digitalis and furosemides. Frankfurt: Germany: Hoechst Aktiengesellschaft, 1991:Unpublished report.
24. Magnani B, Magelli C. Captopril in mild hear failure: preliminary observations of a long-term double-blind, placebo-controlled multicentre trial. *Postgraduate Medical Journal* 1986;62:153-158.
25. McGarry R. Randomized, double blind, multicenter study comparing benazepril to digoxin and to placebo as add on therapy to diuretic in patients with CHF, NYHA Class II-III During a 12 week treatment period, GHBA-194 (Unpublished Report), 1992.
26. Newman TJ, Maskin CS, Dennick LG, Meyer JH, Hallows BG, Cooper WH. Effects of captopril on survival in patients with heart failure. *American Journal of Medicince* 1988;84:140-144.
27. Northridge DB, Rose E, Elder A. A multicenter, double-blind, placebo-controlled trial of quinapril in mild chronic heart failure. *European Heart Journal* 1991;12 (Suppl):184.
28. Riegger GAJ. The effects of ACE inhibitors on exercise capacity in the treatment of congestive heart failure. *Journal of Cardiovascular Pharmacology* 1990;15:41-46.
29. Rucinska EJ. Lisinopril first line therapy in CHF. *Circulation*. West Point, Pa: Merck Sharpe & Dohme Research Laboratories, 1991:Unpublished report.
30. Rucinska EJ. Enalapril vs placebo in previously untreated patients with CHF. West Point, Pa: Merck Sharpe & Dohme Research Laboratories, 1991:Unpublished Report.
31. Rucinska EJ. A double-blind placebo controlled study to evaluate the effects of enalapril in patients with chronic heart failure. West point, Pa: Merck Sharpe & Dohme Research Laboratories, 1991:Unpublished Report.
32. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *New England Journal of Medicine* 1991;325:293-302.
33. Swedberg K, Amtorp O, Gundersen T, Remes J, Nilsson B. Is maximal exercise testing a useful method to evaluate treatment of moderate heart failure? *Circulation* 1991;57:226.
34. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. *New England Journal of Medicine* 1987;316:1429-1435.
35. Zwehl W, Rucinska E. Long-term effects of lisinopril in patients with chronic heart failure: a multicenter, placebo-controlled trial. In: Nicholls MG, editor. *A focus on the clinical effects of a long acting ACE-Inhibitors/Heart Failure*. New York: Raven Press, 1990:31-40.

36. Hart W, Rhodes G, McMurray J. The cost-effectiveness of enalapril in the treatment of chronic heart failure. *British Journal of Medical Economics* 1993;6:91-98.
37. Paul S, Kuntz K, Eagle K, Weinstein M. Costs and effectiveness of angiotensin converting enzyme inhibition in patients with congestive heart failure. *Archives of Internal Medicine* 1994;154:1143-1149.
38. Glick H, Cook J, Kinosian B, Bourassa M, Pouleur H, Gerth W. Costs and effects of enalapril therapy in patients with symptomatic heart failure: An economic analysis of the studies of left venticular dysfunction (SOLVD) treatment trial. *Journal of Cardiac Failure* 1995;1:371-380.
39. Department of Health. *Policy Appraisal and Health*: London: Department of Health, 1995.
40. *British National Formulary, Number 36*: London: British Medical Association and the Royal Pharmaceutical Society of Great Britain, 1998.
41. Department of Health. *National Service Framework for Coronary Heart Disease*: Department of Health, 2000.
42. Government Actuary's Department. 2000-based population projections, 2000.
43. Gilks W, Thomas A, Spiegelhater D. A language and program for complex Bayesian modelling. *The Statistician* 1994;43:169-178.
44. Gilks W, Richardson S, Spiegelhalter D. *Markov Chain Monte Carlo in practice*: Chapman & Hall, 1996.
45. Billingham L, Abrams K, Jones D. Methods for the analysis of quality-of-life and survival data in health technology assessment. *Health Technol Assess* 1999;3.
46. Lin D, Feuer E, Etzioni R, Wax Y. Estimating medical costs from incomplete follow-up data. *Biometrics* 1997;53:419-434.

Part II

A Bayesian approach to cost-effectiveness and value of information analysis: Application to a policy of pre-operative optimisation employing dopexamine or adrenaline for patients undergoing major elective surgery

Tissue hypoxia is the fundamental physiological event, which leads to organ failure and death in critically ill patients. Hence, optimisation of tissue oxygen delivery and consumption are essential for reducing mortality and morbidity amongst these patients. In 1959, cardiac output was identified as the critical determinant of patient survival (Boyd et al. 1959), and in 1960, it was reported that the cardiac output and oxygen delivery associated with survivors of major surgery was considerably higher than for patients who died. As a result, it was suggested that the higher values of cardiovascular flow, observed in survivors, should become additional goals for peri-operative treatment for surgical patients (Bland et al. 1978).

In 1988, a randomised trial compared standard patient management with a deliberate policy of pre-operative management using dopexamine in high-risk patients in the U.S. (Shoemaker et al. 1988). Such pre-operative management involves admitting high-risk elective patients to intensive care; inserting a pulmonary artery catheter to monitor cardiac index; and administering inotropes to achieve target oxygen delivery before surgery. The results illustrated mortality and morbidity benefits associated with a deliberate policy of pre-operative management. These results were replicated in a U.K. trial in 1993 (Boyd et al. 1993) (see Table 1 for details of the results of the studies). In addition, the trials provided some evidence that the use of pre-operative management reduced hospital costs (Shoemaker et al. 1988; Guest et al. 1997) and constituted a cost-effective method of managing high-risk surgery (Guest et al. 1997). However, the results of these trials have not had a major influence on surgical management in the U.K.

In 1999, a further trial was undertaken comparing pre-operative management, employing the inotropes dopexamine or adrenaline, with standard methods of management for high-risk patients undergoing major elective surgery. The results of the 1999 trial confirm the mortality and morbidity benefits identified by the previous trials.

The objective of this project was to examine the information, concerning pre-operative optimisation (pre-op) that was in existence before and after the 1999 trial, in order to address the two decisions of interest to health-care decision-makers: (i) whether, given the evidence, a

policy of pre-operative management should have been adopted; and (ii) whether the collection of further information through research is potentially worthwhile.

I. PRE-TRIAL ANALYSIS

1. INTRODUCTION

The initial stage of the analysis involved assessing the information, concerning pre-operative optimisation (pre-op) in existence before the 1999 trial commenced, in order to address the following issues: (i) whether, given the evidence, a policy of pre-operative management should have been adopted at that time; (ii) whether the 1999 trial was potentially worthwhile; and if so (iii) how that trial should have been designed. This assessment required us to assume a position before the 1999 trial commenced and examine the information that was available to decision makers at that time – that is to take a "retrospectively prospective" view.

2. METHODS

The initial stage of the process involved the construction and population of a model to represent the information position available to decision makers before the 1999 trial. The model was constructed within the Excel ™ computer package, incorporating the add-in programme Crystal Ball ™.

2.1 Structuring the model

Both of the original trials (Shoemaker et al. 1988; Boyd et al. 1993) compared pre-operative optimisation (employing the inotropic agent dopexamine to enhance oxygen delivery) with standard patient management for high-risk patients undergoing major elective surgery.

However, before the 1999 trial, there was debate concerning whether or not to include the use of adrenaline as an inotropic agent to enhance oxygen delivery; this was subsequently reflected in the design of the 1999 trial. Therefore, a full analysis of the pre-trial uncertainty concerning the patient management decision required the inclusion of a strategy of pre-operative optimisation with adrenaline within the pre-trial model.

As such, the pre-trial model incorporated three strategies for patient management – pre-operative optimisation with dopexamine (*pre-opd*), pre-operative optimisation with adrenaline (*pre-opa*), and standard patient management. The initial node in the decision model represents the surgical team's choice of management strategy when undertaking major elective surgery with a high-risk patient (see figure 1).

Each patient management strategy was incorporated as a separate branch following this decision node (see figure 2). Each branch represented the sequence of events that a patient might experience with each strategy, according to the assumptions of the model 1.

For each treatment group, a proportion of those who undergo surgery will develop a complication as a result. Each patient management strategy was modelled by splitting the patient population according to the emergence of complications, within 28 days of surgery. Irrespective of the patient's complication status, a proportion of patients will die following surgery. Within the model we have split mortality into surgical mortality, that occurring within 28 days of surgery (the usual end-point employed within intensive care trials), and other mortality (occurring after 28 days post surgery). The other mortality is further split into three specific end-points: mortality within six months; mortality within 1 year; and mortality 2 years post-surgery. These end-points were chosen to fit with the data from the 1999 trial thus simplifying the post-trial informed analysis (see below)2.

2.2 Populating the model

As previously stated, the aim of the analysis was to model the information position that existed and was available to decision-makers before the recent trial commenced. This required us to take a 'retrospectively prospective' view. This information was identified through a search of the literature and, in consultation with clinical colleagues, three articles were identified as relevant to the decision question being addressed (see Appendix 1 for details of the search strategy)(Shoemaker et al. 1988; Boyd et al. 1993; Guest et al. 1997).

Shoemaker et al (Shoemaker et al. 1988) detail the results of a randomised trial of pre-op employing dopexamine versus standard patient management in high-risk patients in the US, and provide a basic cost analysis. Boyd et al (Boyd et al. 1993) detail the results of a randomised

1 Note that whilst each management strategy has an identical sequence of possible pathways, the probability of the individual events occurring varies according to the strategy employed.

2 Six months corresponds to the period to which the cost data relates, 1 year is a natural end-point, and 2 years

trial of pre-op employing dopexamine versus standard patient management in high-risk patients in the UK. Guest et al (Guest et al. 1997) provide a detailed analysis of the cost of resources associated with the management strategies encountered within the UK trial. See Table 1 for a summary of the results from the 2 trials and the cost analysis.

Due to the similarity of the setting (UK) and the pre-operative procedure employed, the UK studies (Boyd et al. 1993; Guest et al. 1997) were identified as the most appropriate sources of information. Hence, whilst populating the pre-trial model priority was given to data that originated from these studies (Boyd et al. 1993; Guest et al. 1997).

Unless otherwise stated, the following methods were applied to both *pre-opd* and standard patient management branches of the model. Since the identified literature did not include any information about pre-operative optimisation with adrenaline, other methods had to be employed to populate the *pre-opa* branch of the model. These methods are detailed in a separate section below.

2.2.1 Probabilities

Decision analysis requires a probability to be associated with every possible event that patients might experience, conditional on the other events that occur before it. As a result, the model required the following probabilities:

- probability of developing a complication, given management strategy;
- probability of 28-day mortality, given complication status and management strategy3;
- probability of 6 month mortality, given complication status and management strategy[2];
- probability of 1 year mortality, given complication status and management strategy[2];
- probability of 2 year mortality, given complication status and management strategy[2];

Beta distributions (Gelman et al. 1995; Berry and Stangl, 1996) were used to represent the uncertainty concerning each of the probabilities within the model. Beta distributions are specified by two parameters - alpha and beta, which represent the number of successes (α) and failures (β) within the sample (n). Thus, beta distributions can be populated directly from trial data.

The size of the sample (n) is the number of patients who are exposed to the event of interest. The number of successes (α) is the number of patients who actually experience the event. The

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corresponds to the period to which the survival data relates.

3 Note that the mortality probabilities are conditional on being alive at the start of the period.

number of failures (β) is the remaining patients (n-α), those that don't experience the event. The probability of interest (p) is given by the proportion of successes in the exposed population (α/n), and is therefore restricted to a value between 0 and 1. To characterise the beta distribution any two of these elements (α,β,n, p) are all that is required.

Probability of complication

In order to characterise the uncertainty surrounding the probability of a patient developing complications for each management strategy, data was required concerning either the number (α) or probability (p) of patients experiencing at least one complication; or the number (β) or probability (1-p) of patients not experiencing any complications.

Data is available from Shoemaker et al (Shoemaker et al. 1988) in the form of the number and proportion of patients, in each treatment group, experiencing 0,1,2,3 and 4^{+} complications (Table 2). However, data from Boyd et al (Boyd et al. 1993) illustrated differences in the average number of complications per patient in each treatment group (Table 3), with both groups experiencing more complications on average compared with the U.S. trial. Employing the assumption that the proportions experiencing 1,2,3 or 4+ complications, given at least one complication is experienced, are similar in the two trials, the data can be combined to determine the number of patients not experiencing a complication (β) subject to the constraint that the average number of complications is equivalent to that of the U.K. trial.

Probability of 28-day mortality given complication status

The structure of the model required the probability of 28-day mortality given management strategy and complication status. In order to characterise the uncertainty surrounding these probabilities, data was required concerning either the number (α) or probability (p) of patients dying within 28-days; or the number (β) or probability (1-p) of patients surviving to 28-days for each complication status and management strategy combination.
This data was not readily available within the identified literature. However, Boyd et al (Boyd et al. 1993) detail the probability of 28-day mortality for all patients in each treatment group (not conditioned according to complication status) and data about the occurrence of complications conditioned upon survival status. The probability of 28-day mortality (1-p) given complication status can be determined from this information through the application of Bayes rule (see appendix 2).

Probability of longer term mortality given complication status

The standard period for analysis in intensive care trials, is 28-days post-surgery and this is the time-frame used in both the U.S. and U.K. trials (Boyd et al. 1993). This implies that after 28-days post-surgery, patients were expected to experience the same outcomes irrespective of complication status and treatment group.

However, the 1999 trial had a follow-up of two years post surgery. For the purposes of the post-trial analysis (see below), this was split into 4 time periods – 28-days; six months; 1 year and 2 years[2]. In order to incorporate the longer time horizon into the model, standard mortality rates (Office for National Statistics, 1998) have been used to determine the probability of mortality in each of the remaining time periods. The published annual rates are converted to take account of the different time periods over which they apply using equation 1:

$$1 - (1 - SMR)^{(\text{no of months in period of interest/no of months in original data})} \qquad \textit{Equation 1}$$

The application of standard mortality rates within the model implies that after 28-days post-surgery (i) the probability of mortality returns to the standard rate for a population of the same age, and (ii) the probability of mortality is independent of the complication status.

The specification of the Beta distributions for all of the probability parameters is detailed in Table 4.

2.2.2 Survival

In order to determine the expected survival duration associated with each management strategy, it is necessary to specify survival duration for every possible pathway. This is then used in combination with the probability associated with each pathway, to determine the expected survival. The process requires the derivation of a distribution of survival duration for each treatment group, complication status and mortality status/period combination.

Where possible, patient level data has been identified and used as input into a Bayesian bootstrap procedure 4 (Rubin, 1981) to generate a distribution of mean survival duration. Where

4 The principles of Bayesian bootstrapping are similar to that of standard bootstrapping, except the draws are from the posterior distribution.

patient level data is not available, assumptions have been applied to define the distribution of survival duration.

28 day mortality

Boyd et al (Boyd et al. 1993) provide patient level data for survival duration measured up to 28-days post-surgery. The survival duration of patients dying within 28-days post-surgery can be isolated from this data (Table 5). This data is then used within a Bayesian bootstrap procedure (1000 iterations) to provide a distribution of mean survival duration for pathways involving mortality within 28 days post-surgery, for both treatment groups. An empiric distribution formed from the bootstrap replicates provides the distribution of mean survival duration for the 28-day mortality pathways within the model, for each treatment group.

It must be noted that all of the deaths, within the UK trial, occurred in patients who had developed complications post-surgery. As such, it was not possible to generate a separate distribution of mean survival duration for the 28-day mortality without complication pathways within the model. Under the assumption that survival duration (at 28-days) is identical irrespective of complication status, the empiric distribution generated from the patient level data can be applied to 28-day mortality pathways irrespective of complication status. The impact of this assumption on the model is negligible because the probabilities associated with 28-day mortality given no complication are small 5, precisely because the event had not been witnessed in the clinical trials (Table 4).

Longer period mortality

As noted above, the published trials (Shoemaker et al. 1988) (Boyd et al. 1993) only incorporate patient outcomes up to 28-days post-surgery whilst the 1999 trial has patient follow-up to two years post-surgery.

In order to incorporate the longer timeframe into the model, it was necessary to determine the distribution of expected survival duration for each of the pathways involving mortality between 28-days and 2 years. This required the application of an assumption concerning the distribution of deaths over these time periods (i.e. 28 days to 6 months, 6 months to 1 year and 1 year to 2 years). The assumption was made that the probability of dying on any particular day, within the period, was equal, and hence the survival duration was uniformly distributed over the time

5 For dopexamine the probability was calculated to be 0.005 and for standard treatment it was 0.01.

period. The uniform distribution is parameterised by the minimum; maximum and mean value. In the case of survival duration the minimum value of the distribution is taken as the last day of the previous period; the maximum value of the distribution is taken as the last day of this period of interest; and the mean of the distribution is the mid-point. For example, for pathways involving mortality within six months the survival duration is represented by a distribution with a minimum value of 28 days, a maximum value of 183 days and a mean of 105.5 days.

The timeframe of the analysis is restricted to 2 years, which requires the assumption that all surviving patients die on the third anniversary of surgery (day 731). Hence the survival duration for all of these patients is 730 days.

2.2.3 Costs

In order to determine the expected cost associated with each patient management strategy, it was necessary to specify a distribution of cost for every possible pathway. This required the derivation of a distribution of cost for each treatment group, complication status and mortality status/period combination.

The aim was to use patient level cost data within a Bayesian bootstrap (Rubin, 1981) in order to generate an empiric distribution of mean patient cost for each of these pathways. However, the patient level data for costs was not available. As a result, the patient level data was simulated from the data that was available, using Monte Carlo Simulation. This process involved segmenting the patient costs into the various elements of importance: (a) pre-operative cost; (b) intra-operative cost; (c) post-operative cost; and (d) complication cost. A distribution was assigned to each of the elements of patient cost, using the available data. Monte Carlo simulation was then used to simulate per patient cost for each element using these distributions. With each individual patient represented by an iteration, in the simulation, the draws from each distribution represented the individual patient cost for each element. The total patient cost was determined by summing the cost elements across an iteration.

It was not possible to distinguish between costs for survivors and non-survivors, due to the lack of available data. As such, the Monte Carlo simulation was used to generate cost distributions for each treatment group and complication status combination only. This required an assumption that costs were not affected directly by mortality status, although an indirect link remained through complications6.

6 This is because upto 28 days post-surgery cost; mortality and survival are all modelled separately for those with

(a) ***pre-operative cost*** – these costs represent the costs of resources used to manage patients prior to surgery. These costs include, where applicable, the costs of admitting, monitoring and optimising patients prior to surgery. Given the protocol for pre-operative management of patients, the resources employed pre-operatively are not considered to be uncertain7. Hence a fixed amount is specified for the pre-operative costs for each treatment, taken from the available literature (Guest et al. 1997).

(b) ***intra-operative cost*** – this element relates solely to the cost of inotropes given during surgery. These costs are not uncertain[7], hence a fixed amount is specified for the intra-operative cost for *pre-opd*. These costs were included at the price applicable during the recent trial (dopexamine = £24.67) for each patient who received *pre-opd*.

(c) ***post-operative cost*** – these costs represent the costs of resources used to manage patients following surgery. The resources employed post-operatively are dependant upon the recovery of the patient and the patient management decisions made by the clinical team. Hence the post-operative costs are considered to be uncertain. For each management strategy the post-operative cost was modelled as a lognormal distribution, due to the positive nature and positive skew of costs. These distributions were specified by the appropriate median and interquartile range reported in Guest et al (Guest et al. 1997).

(d) ***complication cost*** – these costs represent the costs of resources used to manage complications following surgery. The resources employed to manage complications are dependant upon the nature and severity of the complication, the recovery of the patient and the patient management decisions made by the clinical team. As such, the complication costs are considered to be uncertain. For each management strategy, the complication cost was modelled as a lognormal distribution, due to the positive nature and positive skew of costs. Data was not readily available to specify the parameters of these distributions. However, trial data was available concerning the numbers of each type of complication for each management strategy (Boyd et al. 1993 Table 3) and the median costs (and range) associated with managing these complications (Guest et al. 1997 Table 4). This data was used to simulate the patient level cost of managing complications, through Monte Carlo simulation. Within the process, each type of complication was simulated separately, with the number of simulations determined by the number of each type of complication in each group (Boyd et al. 1993). The cost of managing each type of complication, in each group, was specified as a log-normal

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complications.

7 Although they may be variable and hence a candidate for sensitivity analysis.

distribution using data presented by Guest et al (Guest et al. 1997). Once all of the complications are simulated, the data for each group provides the average (and standard deviation) cost of managing complications in each treatment group. This data is used to specify the parameters of the lognormal distribution of complication cost.

Following the Monte Carlo simulation, the cost profile was created for each patient. For those not experiencing a complication, the cost profile was derived from the summation of the pre and post-operative costs and, where applicable, the appropriate intra-operative cost (see equation 2).

$$\text{Total cost}_{\text{no comp}} = \text{pre-op cost} + \text{post-op cost} (+ \text{intra-op cost}) \qquad \textit{Equation 2}$$

For those patients who experienced a complication, the cost profile included an additional cost, representing the average cost of managing complications in those that experience them for the treatment group of interest (see equation 3).

$$\text{Total cost}_{\text{comp}} = \text{total cost}_{\text{no comp}} + \text{complication cost} \qquad \textit{Equation 3}$$

For each patient this complication cost was a combination of the average cost of complications for the treatment group (derived as above) and the average number of complications suffered by a patient with at least one complication for the treatment group (as reported in Boyd et al (Boyd et al. 1993) (equation 4).

$$\text{Complication cost}_{\text{tx group}} = \text{average complication cost}_{\text{tx group}} * \text{av number of complications}_{\text{tx group}} \qquad \textit{Equation 4}$$

This process provided simulated total cost data for each patient in each treatment group, which could be used as the basis for a Bayesian bootstrap of mean cost. However, due to the size of the patient groups being simulated, the Monte Carlo simulation used to get the cost profiles involved few iterations. As such the starting value and the sequence of random numbers used within the simulation could potentially have a major impact upon the results8. In order to lessen

8 Monte Carlo simulation picks values randomly from the specified distributions. When enough iterations are undertaken the values selected should correspond to the probability assigned to each value. However, when the number of iterations undertaken is small there is a possibility that, purely by chance, all of the values picked at random are from one section of the distribution.

the impact of the starting value on the process of generating the patient cost profiles, the process was undertaken twenty times. Each simulation employed a different starting (seed) value (determined from a table of random numbers) and provided a different per patient cost profile (see Table 6 for an example). Each set of per patient cost profiles was then used as the basis of a Bayesian bootstrap (70 iterations per set) to generate mean patient costs for each treatment group, given complication status. The overall set of bootstrap replicates (1400) formed the empiric distribution of expected cost employed within the respective pathways of the model.

2.2.4 Incorporating Pre-op employing adrenaline

The studies identified, by the literature search, compared pre-operative optimisation (with dopexamine) to standard patient management. No published information was identified that provided details of pre-operative optimisation with adrenaline. Therefore, in order to incorporate this strategy into the decision model, it was necessary to make a series of assumptions to represent how the available data concerning pre-opd and/or standard patient management might be translated to reflect the impact of the pre-opa strategy.

Probabilities

Whilst the *pre-opa* strategy had not been used in practice, in order to obtain ethical approval for the trial, a case must have been established that suggested that the use of adrenaline, as an inotrope, was no worse than dopexamine. In addition, the recent clinical trial reasoned that adrenaline should be included within the trial because '*inotropic agents….have different effects on circulation to the gut, which may possibly affect post-operative morbidity'* (Wilson et al. 1999).

As such the assumptions are made that the choice of inotrope: (i) has no direct affect upon mortality; and (ii) may affect the probability of complications. The impact on complications is modelled through the use of an adjustment factor, which determines the probability of complications associated with *pre-opa* by scaling the probability of complications associated with *pre-opd* (equation 5).

$$\text{Probability (complications with adrenaline)} = \frac{\text{probability (complications with dopexamine)}}{\text{adjustment factor}}$$

Equation 5

Within the model, a sceptical prior is placed on the impact of adrenaline upon the probability of complications. This is represented by a normal distribution with an unitary mean (*pre-opa* is expected to be associated with the same probability of complications as *pre-opd*); and a 5% chance that the adjustment factor is at or below the level which would give the same probability of complications as standard patient management. This equates to a 5% chance that the probability of complications with *pre-opa* is less than ¾ or more than 1.5 times that associated with *pre-opd*.

Costs and Effects

The use of this adjustment factor directly impacts upon the proportion of patients experiencing each of the patient pathways. This, in turn, indirectly impacts upon the expected cost and expected survival duration associated with the patient management strategy.

In addition, previous trials have illustrated that *pre-opd* is associated with a different profile of complications to standard patient management (Shoemaker et al. 1988; Boyd et al. 1993). Thus the choice of inotrope may have a direct impact upon the outcomes for patients experiencing a complication. In order to incorporate this impact within the model, the assumption is made that when the probability of complications for *pre-opa* is equal to or better (less) than that of *pre-opd* (i.e. the adjustment factor used was =>1), the profile of complications is similar to that associated with dopexamine. In this case, the assumption is made that the probability of 28-day mortality and the pathway survival duration for *pre-opa* patients, are equivalent to the values for *pre-opd*. When the probability of complications is worse (higher) than that for dopexamine (i.e. the adjustment factor used was < 1), the assumption made is that the profile of complications and patient outcomes are similar to those associated with standard patient management.

Similar logic is used to specify the pathway costs for *pre-opa* patients. However, in order to incorporate the appropriate intra-operative cost into the pathway costs for *pre-opa*, it is not possible to use the raw pathway costs for standard patient management or *pre-opd*. Instead, two extra bootstrap distributions have to be created: one for the adrenaline patients who are considered to be similar to dopexamine patients; and a second for those who are considered to be similar to standard care patients. This involves revising the patient cost profiles and bootstrapping. The profiles are revised either by replacing the dopexamine cost (£24.67) with the cost of adrenaline (£2.35), for those patients who are considered similar to dopexamine patients, or by adding in the adrenaline cost, for those considered similar to standard care patients. These two bootstrap distributions, constructed in the same way as for *pre-opd* and

standard patients, form the cost distributions for the *pre-opa* pathways and are applied according to the adjustment factor.

3. COST-EFFECTIVENESS ANALYSIS

3.1 a priori

Following the construction and population of the pre-trial model, the next stage of the process involved determining the distribution of expected cost and expected life years associated with each patient management strategy. As stated in section 2, this probabilistic analysis involved Monte Carlo simulation using Crystal Ball™.

In order to compare standard patient management with a policy of pre-operative patient management employing either inotrope (*pre-opo*), a fourth pair of distributions (expected cost and expected survival duration) were generated. These distributions were created from those associated with *pre-opd* and *pre-opa*, under the assumption that patients would be assigned between inotropes equally.

The mean values of the distributions of expected cost and expected survival duration were reported for each patient management strategy and the *pre-opo* strategy. The *a priori* for the decision between standard care and a policy of pre-operative optimisation (*pre-opo*), and for the decision between the three distinct methods of patient management were identified. Where appropriate, the ICER was calculated for the different methods of patient management in comparison with the next less effective, non-dominated alternative (Karlsson and Johannesson, 1996).

3.2 Uncertainty

An initial assessment of the uncertainty surrounding the expected costs and expected survival durations associated with each strategy was provided by plotting the individual values of incremental cost and effect on incremental cost-effectiveness planes. For simplicity, and to address the two level *a priori* decision, *pre-opo* was compared to standard care, and *pre-opa* was compared to *pre-opd*.

The uncertainty surrounding the adoption of each strategy was quantified and presented as a cost-effectiveness acceptability curve, and cost-effectiveness acceptability frontiers (Fenwick et al. 2001) were presented to illustrate the uncertainty surrounding the *a priori* decision.

3.3 Expected value of perfect information (EVPI)

The final stage of the analysis involved the use of value of information analysis to provide a formal assessment of the uncertainty surrounding the *a priori* decision. The EVPI was calculated for the decision between standard care and a policy of pre-operative optimisation employing either inotrope (*pre-opo*), and for the decision between the three patient management strategies. In addition, the cost of uncertainty was assessed for the uncertainty surrounding the cost; short-term and long-term survival probabilities; short-term survival duration; and the probability of complications associated with each patient management strategy. Finally, the EVPI was calculated for various combinations of parameters (e.g. economic; clinical) to assess the potential worth of different types of research.

The EVPI per surgical procedure was translated into a population value through reference to the estimated number of qualifying surgical procedures9 over the expected lifetime of the decision, discounted at 6%. It was estimated that 0.4% of all surgical procedures undertaken in the UK (3.3 million per annum) could be considered to be qualifying procedures. The lifetime of the decision was assumed to be 15 years 10.

9 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.

10 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 6 years at least.

4. RESULTS

4.1 Costs

The mean expected cost associated with patients receiving pre-operative optimisation was £9,412 (£10,847 adrenaline, £7,976 dopexamine) whilst the mean expected cost for patients receiving standard management was £11,885.

4.2 Life expectancy

Mortality at 2 years was 29% for patients receiving standard care, compared with 16% in the pre-op group (19% - adrenaline, 13% - dopexamine). Translating 2-year mortality into survival duration generated a mean of 1.74 years post-surgery for patients in the pre-op group (1.68 - adrenaline, 1.80 - dopexamine), compared with 1.48 for patients receiving standard care.

4.3 Cost-effectiveness

Figure 3a illustrates the simulated values of expected incremental costs and survival for the comparison between *pre-opo* and standard patient management. Each point represents one iteration from the simulation of incremental expected cost and incremental expected survival duration. Based upon the mean of these points, *pre-opo* dominated standard patient management – as, on average, it was both cheaper (saving of £2,473) and more effective (additional life-years of 0.26). The majority of the points were located below the horizontal axis (negative incremental cost), indicating that the probability that pre-optimisation was cost-saving was high (75%). In addition, a considerable proportion of the points were located within quadrant II, where pre-op involved both reduced costs and higher survival duration than standard care, indicating a reasonable probability that pre-op dominated standard patient management (74%).

Figure 3b illustrates the simulated values of incremental expected cost and expected survival duration for the comparison between the inotropes. Based upon the mean of these points, *pre-opa* was dominated by *pre-opd* – as, on average, it was both more expensive (£2,871) and less effective (reduction in life-years of 0.12). The majority of the points were located within quadrant IV, where adrenaline involves higher costs and lower survival duration than dopexamine, indicating a reasonable probability that *pre-opd* dominates *pre-opa* (42%).

Figure 4a illustrates the cost-effectiveness acceptability curve for *pre-opo* compared with standard patient management. The figure shows that the probability that a policy of pre-

operative optimisation (either inotrope) was optimal when the decision-maker was unwilling to pay anything for an additional life-year (i.e. the probability that it was less costly than standard care) was 75%. At a willingness-to-pay of £20,000 per life-year gained, the probability that *pre-opo* was optimal is 95.5% (hence the probability that standard patient management is optimal was 4.5%). Whilst if the decision-maker was willing to pay £30,000 per life-year gained, the probability that *pre-opo* was optimal was 97.3% (hence the probability that standard patient management is optimal is 2.7%). The cost-effectiveness frontier for the decision between pre-operative optimisation with either inotrope traces the cost-effectiveness curve for pre-opo, due to it's being dominant.

Figure 4b illustrates the cost-effectiveness acceptability curves for the comparison between the three patient management strategies. When the decision-maker was unwilling to pay anything for an additional life-year, the probability that *pre-opd* was optimal (i.e. dopexamine is cost saving) was 71%. If the decision-maker was willing to pay £20,000 per life-year gained, the probability that *pre-opd* was optimal is 80%, compared with probabilities of 19% and 1% for *pre-opa* and standard patient management respectively. Whilst if the decision-maker was willing to pay £30,000 per life-year gained, the probability that *pre-opo* was optimal was 79.7%, compared with probabilities of 20% and 0.3% for *pre-opa* and standard patient management respectively. The cost-effectiveness frontier for the decision between the three patient management strategies traces the cost-effectiveness curve for *pre-opd*, due to it's being dominant.

4.4 Expected value of perfect information

For the *a priori* decision between standard patient management and a policy of pre-operative optimisation (either inotrope) the EVPI was £78 per surgical procedure given a λ value of £20,000 per life year, or £50 per surgical procedure given a λ value of £30,000 per life year. This translated into a population EVPI of £11 million or £7 million for λ value of £20,000 or £30,000 per life year respectively.

The EVPI for the comparison between the three patient management strategies was calculated to be £345 per surgical procedure, £48.5m for the population, given a λ value of £20,000 per life year. At a λ value of £30,000 per life year, the EVPI was calculated to be £374 per surgical procedure, £53 million for the population. Figure 5 illustrates the population EVPI over the full range of values of λ.

Figures 6 and 7 illustrate the EVPI per surgical procedure, for individual parameters and groups

of parameters, assuming a λ value of £20,000 or £30,000 per life year. This analysis illustrates that, given a λ value of £20,000 per life year, the EVPI for costs was £20 per surgical procedure (£2.8 million for the population), whilst that for short-term survival (probability and duration) was £0.50 per surgical procedure (£ 70,000 for the population). It is of particular interest that the partial EVPI was maximised for the combination of short-term survival and economic parameters. For a λ value of £20,000 per life year, the EVPI associated with short-term, economic parameters was £345 per surgical procedure (£48 million for the population).

5. DISCUSSION

5.1 Results from the pre-trial model

5.1.1 a priori

The analysis presented here suggests that, before the 1999 trial was undertaken, a policy of pre-operative optimisation (either inotrope) was expected to dominate standard management (probability 74%). In addition, regardless of the value placed upon a life year gained, the probability that *pre-opo* was optimal, compared with standard care, was high (>75%).

However, this comparison does not inform the decision-maker as to which inotrope to employ. Whilst the use of adrenaline as an inotrope had not been investigated or compared with the use of dopexamine within a trial environment, it was considered a possible alternative. This strategy was included within the model through the incorporation of several assumptions reflecting prior views concerning the clinical and cost impact of *pre-opa*. This enabled the three strategies to be compared, according to information available before the recent trial was undertaken. This comparison suggested that *pre-opd* dominated both standard patient management and *pre-opa* (probability 39%*)*. In addition, regardless of the value placed upon a life year gained, the probability that *pre-opd* was optimal, compared with standard care, was high (>71%).

Hence, this study showed that, given the levels of information that existed before the 1999 trial, a policy of pre-operative optimisation was the optimal choice for managing high-risk surgical patients undergoing major elective surgery. The study also showed that decision-makers should employ dopexamine, to achieve optimisation.

5.1.2 Uncertainty

The analysis shown in Figure 4b indicates that there was considerable uncertainty surrounding

the *a priori* decision involving the choice between the three methods of patient management. The extent of the uncertainty depends upon the decision-makers willingness-to-pay for a life year gained. If decision-makers are only interested in costs, and they do not value improvement in patients' life expectancy, the uncertainty (i.e. error probability) associated with the choice of *pre-opd* was 29%. At a λ value of £20,000 per additional life year the uncertainty associated with the choice of *pre-opd* was 20%. This was much higher than would be acceptable by standard conventions of significance. However, not implementing *pre-opd* on the basis of adherence to 'statistical significance' would result in the continuation of standard patient management practices, which had a much lower probability of being optimal (1%). Continuing to use standard patient management would result in an expected loss of £10,251 per surgical procedure, an estimated £138 million annually.

5.1.3 Value of information analysis

The VOI analysis formally valued the uncertainty in the decision and generated explicit valuations that could be compared to the cost of further investigation to determine whether additional research was potentially worthwhile. The EVPI for the whole decision was found to be £345 per surgical procedure, or £48m for the whole population, 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, at this value of λ. Figure 8 illustrates the relationship between the level of uncertainty (as represented by the cost-effectiveness frontier) and the expected value of perfect information. As the value of λ increases, the valuation of the consequences associated with the uncertainty increases, but the uncertainty (as represented by the cost-effectiveness acceptability frontier) falls. The two effects work in opposing directions. Here the increased value of the consequences (λ) outweighs the reduction in the uncertainty and the value of information increases. Assuming a λ value of at least £30,000 per life year, the EVPI for the whole decision was found to be £374 per surgical procedure, or £53m for the whole population.

In addition, the partial EVPI analysis identified that the cost of uncertainty was greatest surrounding the short-term clinical and economic parameters. Thus a short-term trial, incorporating economics, would have the largest potential worth (£48 million). The majority of this worth 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.

5.2 Limitations

The absence of data to populate important aspects of the model meant that several assumptions were required to complete the analysis. The most important of these is the absence of any pre-trial data concerning the cost and effectiveness of *pre-opa*. In order to include this strategy, it was necessary to make assumptions concerning the relationship between the available data and the required data. The probability of complications for *pre-opa* was modelled using an adjustment factor; the probability of mortality was assumed to be unaffected by the inotrope employed; whilst the costs and effects were modelled as equivalent to either *pre-opd* or standard care depending upon the value of the adjustment factor. The use of these assumptions had a major impact upon the results of the analysis. The distinctive shape observed in figure 3b is due to the use of the adjustment factor, in combination with the switch values for cost and effect, which collaborate to produce a bi-modal distribution of expected costs and expected survival duration for *pre-opa*. However, the absence of any data concerning *pre-opa* requires that such assumptions are made, and the assumptions used here are considered reasonable given the beliefs that existed pre-trial.
Where early stage modelling is not undertaken, decisions concerning the worth of further research, and design issues relating to such research, are necessarily made on the basis of assumptions. Although in this situation, these assumptions are implicit.

The second major aspect of the model where assumptions were required to overcome the absence of data, was the modelling of long-term outcomes. The use of standard mortality statistics to proxy the probability of mortality beyond 28-days post-surgery regardless of the complication status and the treatment group restricts the uncertainty incorporated into the long-term section of the model. Whilst the use of these assumptions can be justified on the basis that they are equivalent to the assumptions that are implicit in a short-term trial, the effect on the results of the model, in particular the EVPI calculations, must be acknowledged.

In addition, the absence of patient level data concerning cost required the use of Monte Carlo simulation to recreate such data. It is hoped that the potential biases introduced by this process were overcome by the use of several simulations to generate a series of sets of patient level data.

Finally, the absence of data separating the resource use and unit costs has required the use of a composite measure. This reduces the flexibility, and restricts the generalisability, of the model.

II. TRIAL ANALYSIS WITH VAGUE PRIORS

The pre-trial analysis of the information available to decision-makers before the 1999 trial showed that pre-operative optimisation was cost-effective (probability > 75%), and that a policy of pre-operative optimisation employing dopexamine was the optimal decision for high-risk patients undergoing major elective surgery in the UK (probability > 71%). Failure to implement the policy, in favour of continuation of a policy of standard patient management, was estimated to cost the UK in excess of £111 million per annum. In addition, the analysis showed that further research to reduce the uncertainty surrounding the decision was potentially worthwhile, and suggested that the potential worth of research was greatest for a short term clinical trial incorporating economic endpoints for all three patient management strategies (£48 million for the UK population, over 15 years).

The next stage in the project involved establishing an estimate of the cost-effectiveness of pre-operative optimisation for high-risk patients undergoing major elective surgery based upon the results of the 1999 trial.

1. INTRODUCTION

The 1999 trial compared standard peri-operative patient management with pre-operative optimisation, in high-risk patients undergoing major elective surgery (Wilson et al. 1999). In addition, the trial assessed the relative performance of the inotropes - adrenaline and dopexamine - given to enhance oxygen delivery. The study randomised 138 patients to receive standard management (n=46); pre-operative optimisation employing adrenaline (n=46) or pre-operative optimisation employing dopexamine (n=46) (Figure 9). The results showed a significant reduction in hospital mortality associated with pre-op (3%) compared with standard patient management (17%) and a reduction in morbidity associated with pre-op employing dopexamine (30%) compared with that employing adrenaline (53%) and standard patient management (61%) (Wilson et al. 1999). This trial did not include a formal study of the cost-effectiveness of pre-op, although it did identify some important differences in resource consumption between the three arms (Wilson et al. 1999). In particular, the use of dopexamine was associated with a significantly lower length of hospital stay (Wilson et al. 1999).

The second stage of the analysis involves an economic analysis of the 1999 clinical trial (Wilson et al. 1999). The analysis identifies the cost-effectiveness of the three methods of pre-operative patient management and details the uncertainty surrounding the policy decision, based purely upon the trial results. However, in order to provide a foundation for the next stage of the iterative

process, where the trial data is combined with the pre-trial information to provide a fully informed analysis of the trial, this analysis was undertaken using Bayesian methods. To allow for the possibility of non-conjugate prior beliefs, in the fully informed analysis, the analysis of the trial data was conducted within WinBUGS ™. Hence, in addition to detailing the cost-effectiveness results of the trial, in isolation, the analysis provides the model structures that are to be used for the informed analysis.

2. METHODS

2.1 Trial design

The design, baseline characteristics and clinical results of the study have been published elsewhere (Wilson et al. 1999). In brief, the trial included patients undergoing major elective surgical procedures in general surgery, vascular surgery or urology who had been identified as being at high risk of developing peri-operative complications. This prognosis was based upon surgical criteria or the presence of coexisting medical conditions. Whilst it was not possible to blind either patients or clinicians to the standard care versus pre-op status, double-blinding was employed within the pre-op group concerning the actual inotrope received. The randomisation was stratified by three surgical sub-groups: vascular surgery (30%); surgery for upper gastrointestinal malignancy (20%); and other abdominal surgery (50%) (Wilson et al. 1999). See Figure 9 for a summary of the patient flows through the original study.

All patients randomised to receive pre-operative optimisation (with either inotrope) were admitted to either an intensive care or high dependency care unit at least 4 hours prior to surgery. They received haemodynamic monitoring, fluid optimisation and inotrope optimisation (employing either adrenaline or dopexamine). The inotropic support was continued for 12-24 hours post surgery. Patients randomised to receive standard care received standard peri-operative patient management, as determined by the surgeon and anaesthetist. At hospital discharge, the mortality in the pre-op group was 3% compared with 17% in the standard management group (p=0.007). There was a significant reduction in both morbidity and length of hospital stay within the pre-op group that received dopexamine (30% morbidity, 13 days per patient), compared with both the adrenaline (53%, 19 days per patient) and standard management (61%, 22 days per patient) groups.

2.2 Data

2.2.1 Resource-use measurement

The measurement of resource consumption of all patients in the trial was central to the process of estimating the differential cost associated with pre-operative optimisation, compared to standard patient management, and of pre-optimisation with dopexamine compared to adrenaline. Detailed resource-use data were not collected prospectively as part of the original trial protocol, hence it was necessary to interrogate, retrospectively, the trial case record forms and clinical notes to identify each patient's NHS resource-use.

The study focused on two key areas of resource-use that were expected to drive cost differences: that employed within the initial hospital stay; and that employed in the management of subsequent related events. For the initial hospital stay, the resource-use was fully detailed in clinical notes. For each patient, data were collected on the length and type of in-patient stay, and usage of drugs, interventions, infusions and investigations. Drugs that patients were taking on admission, analgesics and drugs given to help patients sleep were excluded from the resource-use profile. For patients randomised to pre-operative optimisation (either inotrope), the resource-use profile included the length of the period of optimisation and the fluid employed in the process.

Some patients were re-admitted subsequent to the initial hospitalisation. Two independent clinicians, blinded to the initial randomisation, assessed whether subsequent admissions were related to the initial surgical procedure. For those that were, resource-use was measured at an aggregate level, based upon length of stay. These data related to the period of 6 months following initial surgery, because beyond this period, it was assumed that re-admissions related to the original procedure would be minimal. Any additional healthcare resources used over the lifetime of those patients who survive are excluded from the analysis.

Mean resource-use data are presented (with standard deviations), by study group, for the period of six months following initial surgery.

2.2.2 Valuing resource-use

The cost of managing each individual patient was estimated by applying the relevant unit cost data to the detailed resource profile compiled for each patient in the study. The unit costs were obtained from the NHS hospital where the study was undertaken, in 1999-2000 prices. All drugs, including any consumables required to administer them, were based on the British National Formulary (British National Formulary, 2000). The costs for all infusions, investigations and interventions, included overheads and all consumables required to administer them. Hotel costs for the intensive care unit, the high dependency unit and the surgical ward, included fixed costs, staff costs, estate costs, overheads and the cost of monitoring equipment. The costs of all other equipment were converted into hourly rates, based on their purchase and re-sale prices, annual maintenance cost, expected useful life and estimated usage per annum. These were included separately on a per patient basis (Drummond et al. 1997). The additional cost of optimisation was calculated for each patient in the adrenaline and dopexamine arms, using patient specific length of hospital stay and use of fluid, together with use of drugs and disposables set by the study protocol.

Given that the aim of the study was to cost different methods of pre-operative patient management, the cost of the original surgery was excluded from the analysis. However, the cost of any further surgery required to manage a complication or related event, was included. The cost of subsequent admissions related to initial surgery was calculated on a per diem basis, using the cost of a standard surgical ward including overheads, drugs, infusions, interventions and investigations.

Mean costs (with standard deviations) are presented, by study group, for hospitalisation (in each type of ward), drugs, interventions, infusions, investigations, pre-operative optimisation and related events. In addition, the median cost and interquartile range are provided to highlight any skewness in the cost distribution. The mean and standard error, median and interquartile range are presented for the total cost for each patient management strategy.)

2.2.3 Survival

Estimates of the mean survival duration in the three arms of the trial are required for the cost-effectiveness analysis. These were based upon the area between the survival curves over the two-year follow up11 .

11 This involves censoring all surviving patients at two years.

3. ANALYSIS

3.1 Bayesian analysis

The economic analysis was undertaken using Bayesian methods. The Bayesian approach starts with prior information, concerning the element of interest. As new information becomes available the prior information is 'updated' with the new data to provide a posterior information position. The fundamental difference of this type of analysis to standard methods is the formal inclusion of prior information. An estimate of the cost-effectiveness of pre-operative management based purely upon the results of the 1999 clinical trial (Wilson et al. 1999) is obtained through the use of vague priors. This allows the data "to speak for itself" (Fryback et al. 2001) and ensures that the trial results have a larger influence upon the analysis than the prior beliefs.

The Bayesian analysis was undertaken within the WinBUGS ™ (Windows-based Bayesian Inference Using Gibbs Sampling) computer package.

3.2 Cost-effectiveness analysis

As with a Frequentist trial analysis incorporating bootstrapping, the aim of the Bayesian analysis is to use the patient level trial data concerning cost and effect to generate a distribution of mean cost and mean survival for each treatment group. These distributions are used to address the *a priori* decision; to assess the level of uncertainty and to address the decision concerning whether to fund further research to reduce uncertainty.

4. MODEL STRUCTURES

Each of the WinBUGS ™ models incorporates patient level data concerning total cost and survival in order to generate posterior distributions of mean cost and mean survival for each treatment group. In order to model the results for pre-operative optimisation (with either inotrope), a further analysis was undertaken incorporating patient level data for both pre-operative groups.

4.1 Standard model

4.1.1 Survival

The simplest model of survival data is the exponential distribution. For this distribution the hazard/failure rate (*evrate*) is assumed to be constant with respect to time. That is, the individual has the same probability of dying at time (*time)*, given that they survived up to that point in time, regardless of *time*. Thus the survival function is given by equation 6:

S(*t*) = exp (-*evrate* * *time*) **Equation 6**

The mean survival duration over the period is derived from the area under the curve (equation 7).

Mean survival duration = $\int_0^t S(time)dtime$ **Equation 7**

However, the assumption of a constant hazard rate over the period of follow-up was perceived to be unrealistic for this example, where the probability of survival during the first 28 days is much lower than for the remaining period. Instead, here the patient level survival data was modelled using a piecewise exponential distribution. This involved splitting the duration of follow-up (2 years) into a number of distinct periods and approximating the survival function in each period using a separate exponential function. This required that the hazard rate was constant over the period rather than the full timescale. In this analysis, the survival period is split into four distinct periods (*timegp*) (see Figure 10). The first period covers the initial 28 days post surgery (the standard length of time used to report outcomes in intensive care). The second period extends to six months post surgery (the interval for which complication data and costs were available). The third period extends to one year post surgery, and the final period covers the entire second year post-surgery. The mean survival (*msurv*) in each period is derived from the area under the survival curve for the relevant interval, and these are summed to provide the overall mean survival duration (*tmsurv*).

In WinBUGS ™, priors are attached to the log hazard rate (*lambda*) rather than the hazard/failure rate (*evrate*). Hence, a log hazard rate (*lambda*) is defined for each time period for each treatment group. Each of the log hazard rates (*lambda*) is modelled as a normal

distribution specified by a mean and precision12. In the analysis of the trial data, vague priors are specified for the mean (-10) and the precision (1.0 E-2).

$$lambda = \log(evrate) \qquad \textbf{Equation 8}$$

The model updates using patient data on the survival time in each period (*time*). Table 7 gives an example of the structure of the patient data. Where the patient (*subject*) survives the period (*event* = 0), the survival time equals the full length of the period. Where the patient dies within the period (*event* = 1), the survival time equals the number of days spent within the period before death.

Posterior distributions are calculated for the hazard rate (*evrate*); probability of survival to the end of each period (*surv*) and the mean survival time during each period (*msurv*). See equations 9 - 11 respectively for these calculations for the first period (upto 28 days post-surgery).

$$evrate = e^{lambda} \qquad \textbf{Equation 9}$$

$$surv = e^{-evrate*t} \qquad \textbf{Equation 10}$$

$$msurv = (1/evrate)*(1-surv) \qquad \textbf{Equation 11}$$

In addition, posterior distributions are generated for the overall survival duration, which is outcome of interest for the economic study (equation 12).

$$tmsurv_{tx} = \Sigma\, msurv_{tx\,j} \qquad \textbf{Equation 12}$$

The appropriateness of the piecewise exponential approximation for survival can be tested, following the analysis, by comparing the results with a bootstrap of actual trial data.

4.1.2 Costs

The patient level cost data is assumed to follow a log normal distribution, due to its' positive nature and positive skew. However, the current version of WinBUGS ™ does not include a log-normal distribution. As a result, the patient level costs were logged and the log costs, for each treatment group, were modelled as normally distributed with a mean (*nu.trt*) and a precision (*tau.trt*) (equation 13).

12 Note that WinBUGS uses the precision (inverse of the variance) to specify a normal distribution.

Log cost ~ N (*nu.trt*, *tau.trt*) **Equation 13**

Mean of the log cost (nu.trt)

The mean of the distribution of log cost (*nu.trt*) is, in turn, specified by a normal distribution. This distribution represents the second order uncertainty in the log costs, that is the variation in the mean log cost. Priors are specified for the mean and the standard deviation of the distribution of mean log cost (*nu.trt*). In the analysis of the trial results, vague priors are specified for the mean (0) and precision (1.0E-6) for each treatment group (equation 14).

nu.trt ~ N (0, 1.0E-6) **Equation 14**

Precision of the log cost (tau.trt)

The precision of the log cost (*tau.trt*) represents the first order uncertainty in the prior data, and provides an estimate of the extent of variation within the likelihood. In the standard model, the standard deviation of the distribution of log cost (*sigma.trt*) is modelled as a half normal distribution specified by a mean and precision 13. This is then converted to give the precision of the log cost (see equation 15).

$tau.trt = 1/(sigma.trt)^2$ **Equation 15**

Priors are specified for the specified for the mean and precision of the distribution of the standard deviation of the log cost. In this analysis of the trial results, vague priors are specified for the mean (0) and precision (0.01) for each treatment group (see equation 16).

sigma.trt ~ N (0, 0.01)I(0,) **Equation 16**

The model updates using per patient data on the total cost logged (*logcost*). However, the outcome of interest for the economic analysis is the mean cost for each treatment group. In order to generate this distribution, it is necessary to transform back from log costs to the original monetary scale. This back transformation involves the mean cost (*nu.trt*) and the variance of the log cost (*sigmasqd.trt*) (see equation 17).

$\text{mean cost (£)} = e^{[nu.trt + (sigmasqd.trt/2)]}$ **Equation 17**

13 The use of the half normal truncates the distribution at zero and prevents the occurrence of negative values

Note that the back transformation only provides a reasonable estimate of the mean cost if the data are log-normally distributed. If this assumption is inappropriate, the back transformation will generate inaccurate results.

The WinBUGS ™ code for the standard model is given in Appendix 3.

4.2 Additional model structures

Within the process of updating, WinBUGS ™ handles each node in the model separately and independently. Therefore, any relationships between nodes have to be specified within the model. Unless defined within the model, there is no opportunity for relationships to be taken into account within the analysis.

Within the standard model there is no allowance for a relationship between costs and survival, hence the results of this analysis will be uncorrelated.

During the model development process several different approaches to enhance the standard model to allow for the incorporation of a relationship between cost and survival were considered. These approaches included:

1) Incorporating the relationship with net benefits
2) Modelling the causal relationship with a regression equation
3) Modelling the statistical relationship with a frailty term

4.2.1 Incorporating the relationship – the Net Benefit model

One solution to the problem of allowing for the existence of a relationship between cost and survival, is to combine the two into one measure, and 'trap' the relationship. This can be achieved through the use of the net benefit statistic in monetary terms ( ) which is calculated from the combination of costs and effects, re-scaled into monetary terms through reference to society's willingness-to-pay for health effect (λ) (see equation 18) (Phelps and Mushlin, 1988; Claxton and Posnett, 1996; Stinnett and Mullahy, 1998; Tambour et al. 1998; Claxton, 1999).

$$ t = (\lambda * QALY_t) - Cost_t \qquad \textbf{Equation 18} $$

Converting the patient level data into a measure of net benefit captures any relationship that exists between the two. Thus enabling the relationship to be incorporated without the need to specify the nature of that relationship.

However, this solution does require that the model be re-specified in terms of net benefits, rather than cost and effect. This may be difficult in itself, as there is little guidance as to the distributional form of net benefits. Information will be lost during the data translation process and it will become impossible to return to the original data. As a result, it will not be possible to calculate expected value of information concerning cost and effect separately, and the loss of health effect data will make extrapolation within WinBUGS ™ impossible. In addition, the combination of the cost and effect data into one measure removes WinBUGS ™ capability for applying different weights to the prior evidence for cost and effect. This will not impact upon the analysis of the trial results, where vague priors are used, however this restriction will impact upon the results of a fully informed analysis, where priors are informed by levels of current information.

A further complication, is that the net benefits data is specific to the societal value (λ) used to re-scale the health effects. In an environment where the societal willingness to pay for health effects is known and explicit this would pose no problem. However, where this is not the case analysis should be presented to the decision-maker for a range of values for the societal willingness to pay for health effects. In these circumstances, the data will need to be translated, the model constructed, and the analysis undertaken for every value of λ that is to be considered by the decision-maker. In these circumstances, the net benefits solution will be computationally cumbersome.

Due to the complexities and limitations associated with the net benefits solution and the availability of other (superior) solutions, this solution will not been pursued here.

4.2.2 Modelling the causal relationship – the regression model

The next solution to be considered involved considering the structure and cause of the relationship between cost and health effects. In this solution, the factor(s) that the analyst expects to affect both cost and health effects (the source(s) of correlation) are identified ex ante14. The dataset is then partitioned according to the existence of these factors, with data for patients exhibiting the factor(s) analysed separately from data for patients not exhibiting the

14 These factors are often likely to be related to the occurrence of particular events e.g. hospitalisation.

factor(s). In this way, the solution maintains some element of the correlation between cost and effect. This method is equivalent to the methods for handling correlation within standard decision analytic modelling, where correlation between costs and effects is maintained for each patient pathway (sequence of events).

Within the modelling of pre-operative optimisation, the development of post-surgical complications was considered to be an event that would impact upon both costs and survival. As such the dataset was partitioned according to patients' complication status.

In order to analyse the datasets separately whilst retaining mean cost and mean survival results for the treatment group as a whole, the model was structured like a regression equation with the addition of a new term to both the survival (*beta1 * comp.e*) and cost (*beta2 * comp.c*) equations of the standard model. Within the survival equation, the *beta1* term for each treatment group represented the difference in the overall log hazard rate for those who do and do not experience a complication. For the cost equation, the *beta2* term for each treatment group represented the difference in the mean log cost for those who do and do not experience a complication. Both of the *beta* terms are modelled as normal distributions, specified by a mean and a precision, thus allowing flexibility in the impact of complication status upon costs and survival duration. The *comp.e* and *comp.c* terms act like dummy variables, representing the existence of complications. However, unlike a standard regression equation with dummy variables these terms did not take the values zero and one15. Instead, those patients for whom the post-surgical experience was complication free, were assigned a dummy variable value equal to the probability of experiencing no complications in that treatment group. Whilst those patients who experienced at least one complication, were assigned a dummy variable value equal to minus the probability of experiencing at least one complication, in that treatment group. These values were used, in place of the usual values of zero and one, to reduce the time to convergence.
In addition to the priors specified for the standard model (see section 4.1), the regression model requires the specification of prior values for the parameters of the distributions of *beta1* and *beta2*. In the analysis of the trial results, both are specified by vague priors for the mean (0) and the precision (1.0E-4) for each treatment group.
As with the standard model, the regression model updates with patient level data concerning total costs logged and survival, and generates distributions of mean cost and mean survival for each treatment group.

This solution incorporates the important relationships between cost and survival whilst ignoring

15 Although the values of the dummy variables still sum to 1.

spurious correlations which would not be expected in repeated samples. Although the solution and results will only be as useful as the ex ante identification of the sources of correlation between cost and effect.

4.2.3 Modelling the statistical relationship – the frailty model

The next solution to be considered involved the use of a statistical model of the relationship between cost and survival. Within the modelling of pre-operative optimisation, this solution was implemented through the incorporation of a 'frailty' term to both the survival (*gamma1*) and cost (*gamma2*) equations of the standard model.

For each treatment group, the frailty terms were modelled as a bivariate normal distribution with a mean (*mu.gamma*) and a precision matrix (*gamma.T*). The mean values of these distributions were all set equal to zero, whilst the precision matrices were modelled as Wishart distributions (see equation 19).

$$\begin{pmatrix} R1,1 & R1,2 \\ R2,1 & R2,2 \end{pmatrix} \qquad \textbf{Equation 19}$$

Where: R1,1 = precision of survival
R1,2 = R2,1 = 1/covariance between cost and effect
R2,2 = precision of cost

Within WinBUGS ™, the parameters of a Wishart distribution cannot be specified by prior distributions and must instead be specified directly and entered as if they were data. For the pre-operative optimisation model estimates, based upon the trial data, were used for each element of the matrix for each (see equation 20).

$$\begin{pmatrix} 0.5 & 0.01 \\ 0.01 & 0.005 \end{pmatrix} \qquad \textbf{Equation 20}$$

Modelling the frailty terms using the bivariate normal distribution provides a link between the cost and survival elements of the model, enabling each to influence the updating of the other. In addition, investigation of the frailty terms provides information on the correlation between the

cost and the survival (see equations 21 and 22).

Covariance(cost and survival) = 1/ precision(cost and effect) **Equation 21**

$$\text{Correlation (cost and survival)} = \frac{\text{Covariance(cost and survival)}}{\sqrt{\text{Variance(cost)} * \text{variance(survival)}}} \quad \textbf{Equation 22}$$

As with the standard model, the frailty model updates with patient level data concerning total costs and survival, and generates distributions of mean cost and mean survival for each treatment group.

4.2.4 Bivariate regression model

The final solution to be considered involved combining the statistical and the modelling solutions within one WinBUGS ™ model. This solution allows the main sources of the correlation to be incorporated within the model, using the regression equation format specified in section 4.2.2, whilst any residual correlation is incorporated through the use of the frailty term, as specified in section 4.2.3.

As this model is a hybrid of the other models it incorporates the structure and prior values specified for all of those models.

As with the other solutions, the model updates with patient level data concerning total costs and survival, and generates distributions of mean cost and mean survival for each treatment group. The results of the combination model can be used to compare the appropriateness of the modelling solution and the statistical solution in isolation. If the modelling solution incorporates all of the important elements of the relationship between cost and survival then the results should compare to those from the combination solution, and the correlation term within the combination solution should be negligible.

The WinBUGS ™ code for each of the alternative model structures are given in Appendix 4.

5. RESULTS

5.1 Resource-use

Table 8 gives a summary of the key resource-use within the alternative arms of the trial. One patient (pre-op with adrenaline, other abdominal sub-group) was excluded from the analysis due to the absence of any data concerning resource-use. Patients who received pre-op spent an average (sd) of 16 days (12) in hospital at the time of surgery (19 in the adrenaline group, 13 in the dopexamine group) compared to 22 days (26) in the standard care group. In addition, patients who received pre-op tended to have lower usage of key resources (with those randomised to dopexamine having the lowest usage overall).

5.2 Costs

The unit costs of key resources are detailed in Table 9. Table 10 details the costs for the standard care group and the pre-op patients, both for the entire group and separately for each inotrope. The additional costs of administering pre-op were more than offset by reductions in the costs of the initial in-patient stay and in the costs of resources used in post-operative patient care. The mean cost (sd) associated with patients receiving *pre-opo* was £7,261 (£7,390), whilst for *pre-opa* and *pre-opd* the mean cost (sd) was £8,706 (£8,907) and £5,847 (£5,246) respectively. The mean cost (sd) for patients receiving standard management was £10,297 (£12,039).

5.3 Survival

In the paper reporting the clinical results of the study (Wilson et al. 1999), an 8% lower absolute risk of in-hospital mortality was reported in the pre-op group at hospital discharge. At two years post surgery, standard patient management is associated with a mortality of 33% (15 deaths) compared with 26% in the pre-optimisation group (24 deaths - 11 adrenaline, 13 dopexamine) (see Figure 10).

The mean survival duration for patients in the pre-op group is 1.68 years (1.74 - adrenaline, 1.62 - dopexamine), compared with 1.47 years for patients receiving standard care. , compared with 1.68 in the pre-op group. This compares favourably (<1% difference) with the results of a bootstrap analysis of the survival data, which gives a survival of 1.68 years for the pre-op patients (1.73 – adrenaline, 1.63 – dopexamine) and a survival of 1.47 years for patients receiving standard care.

5.4 Cost-effectiveness

For each of the models a total of 20,000 iterations were run, with a burn-in of 10,000 iterations. The Bayesian analysis generated a distribution (10,000 values) of mean costs and mean survival durations for each of the methods of patient management. These distributions were used to address the *a priori* decision; assess the level of uncertainty surrounding the decision; and provide a valuation for further research to reduce the level of uncertainty surrounding the decision. As for the pre-trial stage, the analysis was undertaken for the comparison between standard patient management and pre-operative optimisation (with either inotrope) and for the choice between the three methods for patient management.

5.4.1 Standard model

Figure 11a illustrates the simulated values of mean incremental costs and life years for the comparison between pre-op (using either inotrope) and standard care. Based upon the mean of these points, *pre-opo* dominates standard patient management – as, on average, it is both cheaper (saving of £3,571) and more effective (additional life-years of 0.21). The majority of the points are located below the horizontal axis (negative incremental cost), indicating that the probability that pre-optimisation is cost-saving is high (98%). In addition, a considerable proportion of the points are located within quadrant II, where pre-op involves both reduced costs and higher survival duration than standard care, indicating a reasonable probability that pre-op dominates standard patient management (94%).

Figure 11b illustrates the simulated values of mean incremental cost and effect pairs for the comparison between the inotropes. The majority of the points are located within quadrant I, where adrenaline involves higher costs and higher survival duration than dopexamine. Based upon the mean of these points, pre-op employing adrenaline is associated with an ICER of £23,936 per life-year gained when compared to pre-op employing dopexamine (incremental cost = £2,865; incremental effect =0.12 life-years).

Figure 12a illustrates the cost-effectiveness acceptability curves for *pre-opo* and standard patient management. The figure shows that the probability that pre-op is optimal when the decision-maker is unwilling to pay anything for an additional life-year (i.e. the probability that it is less costly than standard care) is 98%. If the decision-maker is willing to pay £20,000 per life-year gained, the probability that pre-op is optimal is 99.3%, hence the probability that standard patient management is optimal is 0.7%. This probability falls slightly to 98.8% if the decision-maker is willing to pay £30,000 per life-year gained. The cost-effectiveness frontier for the

decision between pre-operative optimisation and standard patient management, traces the cost-effectiveness curve for *pre-opo* due to it being the dominant strategy.

Figure 12b illustrates the cost-effectiveness acceptability curves for the choice between all three patient management strategies. When the decision-maker is unwilling to pay anything for an additional life-year, the probability that pre-op with dopexamine is optimal (i.e. dopexamine is cost saving) is 99.6%. If the decision-maker is willing to pay £20,000 per life-year gained, the probability that pre-op with dopexamine is optimal is 57%, compared with probabilities of 42.8% and 0.2% for pre-op with adrenaline and standard patient management respectively. However, if the decision-maker is willing to pay £30,000 per life-year gained, the optimal choice switches to pre-op with adrenaline, with a probability that it is optimal of 57%, compared with probabilities of 42.7% and 0.3% for pre-op with dopexamine and standard patient management respectively. The cost-effectiveness frontier (not shown) for the choice between the three methods of patient management, follows the CEAcc curve for dopexamine up to the point where the *a priori* switches to *pre-opa* (λ value of £23,936) and then follows the CEAcc curve for *pre-opa.*

5.4.2 Alternative model structures

Table 11 details the expected mean cost and expected mean survival (with standard errors) for each of the different model structures employed for the trial analysis. 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, whilst the expected mean survival duration (and standard error) increases. These results hold across all of the model structures employed, and concord with the empirical evidence that there is a small, negative correlation between cost and survival (-0.1).

For all of the models, pre-operative optimisation (either inotrope) dominates standard care. Hence the *a priori* choice is *pre-opo* regardless of the model structure employed. For the decision between the three methods of patient management, standard care is dominated by both methods of pre-operative optimisation, and *pre-opa* is more costly and more effective than *pre-opd* in all of the models. Although, the incremental cost-effectiveness ratio associated with *pre-opa* varies between the models – from £12,366 for the regression and frailty model to £32,851 for the frailty model. Hence, the *a priori* choice, between *pre-opa* and *pre-opd*, depends upon the willingness-to-pay for life-years gained and the model structure employed.

Figures 13 and 14 illustrate how the different model structures impact upon the level of uncertainty surrounding the decision.

5.5 Expected value of perfect information

For the decision between standard patient management and a policy of pre-operative optimisation (either inotrope) the EVPI was £7.66 per surgical procedure given a λ value of £20,000 per life year, or £16.51 per surgical procedure, given a λ value of £30,000 per life year. These values were translated into population values using the same assumptions as specified for the pre-trial analysis, with the exception that the lifetime of the decision was reduced to 9 years, to take account of the advancement of time between the pre-trial model and the analysis of the trial results. The results for the population are £0.78 million and £1.7million respectively.

For the choice between the three methods of patient management, the EVPI is £871 per surgical procedure (£89 million for the population) at a λ value of £20,000 per life year, and £1,203 per surgical procedure (£123 million for the population) for a λ value of £30,000 per life year (see Figure 15).

6. DISCUSSION

6.1 Results from the trial analysis

6.1.1 a priori

The analysis of the trial data suggests that pre-operative optimisation (either inotrope) is expected to dominate standard management (probability 94%). In addition, regardless of the value placed upon a life year gained, the probability that *pre-opo* is optimal, compared with standard care, is high (>97%).

However, this comparison does not inform the decision-maker as to which inotrope to employ within the optimisation process and so, decision-makers will be interested in a comparison of the three methods of patient management. For this comparison, standard management was expected to be dominated by both pre-op management strategies, whilst pre-op employing adrenaline was expected to be both more effective and more expensive than pre-op employing dopexamine (with each additional life year costing £23,936).

Hence, the analysis suggests that, given the data available from the trial, a policy of pre-operative optimisation was the optimal choice for managing high-risk patients undergoing major elective surgery. Whilst the choice as to which inotrope to employ to achieve optimisation,

depends crucially upon the value that the decision-maker is willing-to-pay for additional life-years in this patient group. Decision-makers should adopt pre-op employing dopexamine if their willingness-to-pay for life years is below the incremental cost-effectiveness ratio associated with pre-op employing adrenaline (£23,936), and pre-op employing adrenaline otherwise.

6.1.2 Uncertainty

The analysis shown in Figure 12b indicates that there was considerable uncertainty surrounding the *a priori* decision involving the choice between the three methods of patient management. The extent of the uncertainty depends upon the decision-makers willingness-to-pay for a life year gained. If decision-makers are only interested in costs, and they do not value improvement in patients' life expectancy, the uncertainty associated with the choice of *pre-opd* was 0.4%. However, at a λ value of £20,000 per additional life year the uncertainty (error probability) associated with the choice of *pre-opd* was 43%. This was much higher than would be acceptable by standard conventions of significance. However, not implementing *pre-opd* on the basis of statistical significance would result in the continuation of standard patient management practices, that had a much lower probability of being optimal (0.1%). Continuing to use standard patient management would result in an expected loss of £7,937 per surgical procedure (an estimated £104 million annually). If decision-makers are willing-to-pay £30,000 per life year, the *a priori* decision is to adopt *pre-opa*, reflecting the fact that as decision-makers are willing to pay more for a life-year gained pre-op employing adrenaline (which is both more expensive and more effective than dopexamine) becomes more attractive to them. At this value of λ, the uncertainty associated with the choice of *pre-opa* is 43%, and the expected loss associated with continual use of standard patient management is £10,217 per surgical procedure (an estimated £134 million annually).

6.1.3 Value of information analysis

The VOI analysis formally valued the uncertainty in the decision and generated explicit valuations that could be compared to the cost of further investigation to determine whether additional research was potentially worthwhile. Assuming a λ value of £20,000 per life year, the EVPI for the whole decision was found to be £871 per surgical procedure, or £89m for the whole population. This provides an absolute limit on the worth of further research concerning all elements of the decision, at this value of λ. Figure 16 illustrates the relationship between the level of uncertainty (as represented by the cost-effectiveness frontier) and the expected value of perfect information. As the value of λ increases, upto a value of £23,936, both the uncertainty

(as represented by the cost-effectiveness acceptability frontier) and the valuation of the consequences associated with the uncertainty increase. The two effects work in the same direction to provide a maximum EVPI of £1,265 per surgical procedure (£130 million for the population) at the point where the *a priori* decision switches from *pre-opd* to *pre-opa*. As the value of λ increases beyond this point, the valuation of the consequences associated with the uncertainty continues to increase but the uncertainty falls. The two effects work in opposing directions. Initially, the reduction in uncertainty outweighs the increased value of the consequences (λ), and the value of information falls. However, as the value of λ continues to increase, the reduction in uncertainty becomes outweighed by the increased value of the consequences (λ). Hence the value of information starts to increase again.

6.2 Comparisons between the model structures

Table 12 details the expected mean cost and expected mean survival (with standard errors) for the bootstrap analysis of the trial data (Frequentist analysis). Since a Bayesian analysis employing vague priors is equivalent to a Frequentist analysis of trial data, these results can be used as the standard by which to compare the results of the different model structures. Overall, the standard model gives results that are closer to those of the Frequentist analysis, although other model structures may give closer results for particular management strategies. This seemingly obtuse result reflects the fact that the correlation between cost and effect is quite low and attempting to model it gives 'worse' results.

The results of the regression model show, as postulated, that those patients who experience a complication post-surgery are expected to have a lower survival (*beta1* is negative) and a higher cost (*beta2* is positive) than those patients whose post-surgical experience is complication free. The results of the frailty model suggest a negative correlation (-0.6) between cost and survival that exceeds the correlation identified in the trial data. Closer examination of these results shows that the standard model and regression model give lower survival duration than the models incorporating a frailty element, whilst the standard model and the frailty model give higher costs than the models incorporating a regression equation.

Comparison with the results of the Frequentist analysis suggests that the frailty model tends to over-estimate the survival duration, whilst the regression model tends to under-estimate the costs. Examination of the trial data suggests that this is due to the existence of a complex relationship between cost and survival. Where patients die early (within six months) there is a positive relationship between cost and survival. However, for patients that survive the initial six

months post-surgery, there is a slight negative relationship between cost and survival. This reflects the fact that the early deaths are pre-dominantly due to complications, hence prolonging survival increases the costs of managing those complications. This effect is compounded by the collection of cost data only to six months post-surgery. It appears that the relationship between cost and survival is not adequately picked up by either model.

The results of the regression model incorporating the frailty element illustrate that those patients who experience a complication post-surgery are expected to have a lower survival (*beta1* is negative) and a higher cost (*beta2* is positive) than those patients whose post-surgical experience is complication free. The extent of the relationship is similar to that of the regression model. In addition, the results of the regression model with frailty indicate a smaller negative correlation (-0.5) between cost and survival than the frailty model. However, this attempt to capture the complex relationship between cost and survival results in 'worse' results than any of the other models.

In addition, there were convergence problems with the models incorporating the frailty, as exist with most variance component models. These problems affected the covariance slightly, and had a large impact upon the correlation calculation, which is a function of the co-variance. In addition, these models had high autocorrelation between the log hazard rates. There are a number of ways that could be investigated to provide a solution to these problems. Firstly, the model could be re-parameterised. Here the Wishart prior on the precision matrix, which is notoriously sensitive to the prior values, would be replaced by a product normal formulation. Secondly, the Markov chain could be thinned. Here a longer chain is run and only one value in every x iterations is maintained for the posterior, the remaining values are discarded. Finally, if the problem is perceived to be due to the chain getting stuck in a particular area of the distribution, then the problem may be resolved through the use of multiple chains with different starting values.

Regardless of the differences in the expected results, the CEAcc curves associated with *pre-opo* for the standard model and the regression model are almost identical over the whole range of values of λ. Both are similar to the CEAcc curve created from the Frequentist analysis, with the curves converging as λ increase, reflecting the higher proportion of points where *pre-opo* is more costly and more effective than standard care. The CEAcc curves associated with the models incorporating the frailty term diverge as λ increases, reflecting the higher proportion of points where *pre-opo* is less effective and less costly than standard care.

For the choice between the three methods of patient management, the CEAcc frontiers illustrate the different ICERs, for *pre-opa* in comparison with *pre-opd,* associated with the different model structures. Again, the CEAcc frontiers associated with the standard model and the regression model are the most similar to that associated with the Frequentist analysis.

Despite the difficulties associated with the different models, the decision was taken to undertake the informed analysis for each of the model structures presented here. Although the emphasis will be placed upon the results of the standard model and the regression model.

6.3 Limitations of the study

The study has attempted to capture the life-years gained associated with pre-operative patient management through the survival duration data, although in the current analysis these have been censored at 2 years post surgery. This is a limitation of the study because it underestimates the life expectancy of patients in all of the different patient management arms. There are other limitations to this study. Firstly, it concentrates upon the health care costs that directly affect the hospital, and ignores costs that fall upon other sectors, either directly or indirectly. For example, earlier discharge from hospital may impact upon resource use at a general practitioner or patient level as patients receive care at home rather than in hospital. Secondly, the study utilised local costs that apply in one centre that may not be representative of costs at other UK hospitals, hence the study may not be generalisable to other settings without some modification. Thirdly, retrospective collection of resource data can be a limitation to studies. However, in this study the patient notes had been well maintained and over 70% of the costs related to in-patient stay about which hospital information systems are generally accurate and complete. Finally, the structure of the models used to analyse the trial results have required the use of a composite measure of total cost, rather than separation of the resource use from the unit costs. This reduces the flexibility and restricts the generalisability of the model, as well as restricting the amount of information available for the calculation of parameter EVPI. As a result, EVPI could only be calculated for the whole decision and for the uncertainty surrounding costs and survival duration.

6.4 Comparison to the results of previous studies

The results of our study corroborate the cost and cost-effectiveness analyses undertaken in previous studies (Shoemaker et al. 1988; Guest et al. 1997). Shoemaker (Shoemaker et al. 1988) concluded that average hospital charges and patient expenditures were reduced for patients receiving pre-op, but did not undertake a formal cost-effectiveness analysis. Guest et al

(Guest et al. 1997) provided a detailed analysis of the cost of resources associated with pre-operative optimisation and standard patient management pre-operatively, intra-operatively, post-operatively and employed in treating complications. They concluded that the median cost per patient and per survivor was lower for the group receiving pre-op (Guest et al. 1997). However, the use of medians rather than means reduces the impact of any extreme values on the results, and where data are likely to be highly skewed (as costs typically are) the use of medians will not facilitate an estimate of the total cost impact across a sample of patients (Briggs and Gray, 1998). In addition, the use of the number of survivors, at 28 days post-surgery, as the measure of effectiveness limits the analysis through the implicit assumption that life expectancy for survivors is identical between the groups.

III. INFORMED TRIAL ANALYSIS

The results of an economic analysis of the 1999 trial confirmed those of the pre-trial analysis, adding to the weight of evidence in support of a policy of pre-operative optimisation. On the basis of the 1999 trial pre-operative optimisation was found to be cost-effective (probability > 97%), although the decision over which inotrope to employ to achieve optimisation was dependent upon the value that the decision-maker was willing-to-pay for additional life years in this patient group. Where the societal willingness to pay for life years was above £23,367 pre-op with adrenaline was cost-effective, otherwise dopexamine was the optimal choice for achieving optimisation. In addition, the value of information analysis concluded that further research was likely to be good value for money, with a potential worth of £89 million for the UK population, given a λ value of £20,000 per life year. Whilst this analysis "adds" to the weight of evidence in support of pre-operative optimisation it does not provide any formal indication of the impact of the recent trial on the body of evidence and does not allow any assessment of the overall information position following the recent trial.

The final stage of the project involves formally combining the data from the 1999 trial with the pre-trial information to produce a 'post-trial' information position, which incorporates all of the identified information. This process generates a new information position from which the decision-maker can re-address the *a priori* decision and the decision whether to undertake further research.

1. INTRODUCTION

The informed trial analysis involves re-analysing of the recent trial data in the light of the other information that was available before the trial commenced. For this analysis, the results of the pre-trial model were used to generate informative priors for the identified model structures. The results of the informed re-analysis are then used to re-address the policy decisions regarding pre-operative management of high-risk patients undergoing major elective surgery. The results are used to determine (i) whether, given the evidence, a policy of pre-operative management should be adopted and (ii) whether the collection of further information through research is potentially worthwhile. In this case, these decisions will be based upon all information available to decision-makers following the recent trial.

2. COST-EFFECTIVENESS ANALYSIS

2.1 Treatment group

The Bayesian analysis uses patient level trial data concerning cost and effect to generate posterior distributions of mean cost and mean survival duration for each treatment group. These distributions are used to address the *a priori* decision; to assess the level of uncertainty and to address the decision concerning whether to fund further research to reduce uncertainty.

2.2. Sub-group analysis

In addition to generating posterior distributions for each treatment group, the use of Bayesian methods allows the completion of additional analyses of the trial information, for example an analysis according to patient sub-group (Spiegelhalter et al. 2000). This is because, unlike in a Frequentist analysis where multiple testing increases the chance of a type I error leading to problems with power and significance 16, the nature of Bayesian statistics (probability of hypothesis given data) lends itself to multiple testing and unplanned analyses (Spiegelhalter et al. 2000). These types of analyses may be of interest to decision makers through the provision of additional information concerning which, if any, patient groups should be targeted.

In the 1999 trial of pre-operative optimisation the randomisation procedure was stratified by surgical sub-group (vascular surgery (*v*); surgery for upper gastro-intestinal malignancy (*u*); and other abdominal surgery (*o*)), although the trial did not plan or power for analysis on this basis. The use of Bayesian methods for the economic evaluation enabled a sub-group analysis to be undertaken on the basis of surgical procedure. As such, posterior distributions of mean cost and mean survival duration were also generated for each of the treatment and sub-group combinations. Thus enabling the *a priori* decision and the decision whether to fund further research to be addressed at a surgical sub-group level.

3. MODEL STRUCTURES

The models used for the informed re-analysis have the same structures as those used for the trial analysis with vague priors. As with the trial analysis with vague priors, each of the WinBUGS ™ models incorporated patient level data concerning total cost and total survival

16 In order to maintain the overall type I error, adjustments can be made to the type I error employed within the individual hypothesis tests (for example the Bonferroni adjustment).

duration in order to generate posterior distributions of mean cost and mean survival duration for each treatment group, plus a pre-operative optimisation (with either inotrope) group.

The difference is the replacement of the vague priors with informed priors, specified in accordance with the data and results of the pre-trial model. Table 13 provides a summary of the informative priors used within each of the model structures.

3.1 Standard model

3.1.1 Survival

Within the standard model, survival data was modelled using a piecewise exponential distribution, with four distinct time periods 17. A log hazard rate (*lambda*) was defined for each time period for each treatment group, and each of the log hazard rates (*lambda*) was modelled as a normal distribution specified by a mean and precision. The mean of this distribution represents the expected value of the log hazard rate, whilst the precision represents the second order uncertainty i.e. the uncertainty surrounding the mean value. For the informed re-analysis, the prior estimates of the mean and precision were constructed from the results of the pre-trial model.

Whilst the pre-trial model did not include the hazard rate or log hazard rate, it did incorporate the probability that survivors at time t survive the period of interest. This probability can then be converted to a log hazard rate (see equation 23):

$$lambda_i = \log[-\log(1-P_i)/time_i] \qquad \textbf{Equation 23}$$

where: P_i = probability of death during interval $_i$,

$time_l$ = length of interval $_i$

The Monte Carlo simulation of the pre-trial model generated distributions for each conditional survival probability. Each iteration was converted to a log-hazard rate (using equation 23) to give a distribution of *lambda* values. This distribution was then used to provide the mean and

17 The first period covers the initial 28 days post surgery (the standard length of time used to report outcomes in intensive care). The second period extends to six months post surgery (the interval for which complication data and costs were available). The third period extends to one year post surgery, and the final period covers the entire second year post-surgery.

precision required by the WinBUGS ™ model.

As with the trial analysis with vague priors, the model updates using patient data on the survival time in each period (*time*) and generates posterior distributions for the hazard rate (*evrate*); probability of survival to the end of each period (*surv*); mean survival time during each period (*msurv*) and the overall mean survival duration (*tmsurv*).

3.1.2 Costs

Within the standard model the logged patient level cost data was modelled using a normal distribution, specified by a mean (*nu.trt*) and precision (*tau.trt*).

$$\text{Log cost} \sim N(nu.trt, tau.trt) \qquad \textbf{Equation 24}$$

Mean of the log cost (nu.trt)

The mean of the log cost is itself modelled as a normal distribution, specified by a mean and precision. This distribution represents the second order uncertainty in the log costs (i.e. the variation in the mean log cost). Priors were specified for the mean and precision of the distribution of mean log cost.

A distribution of mean log cost was generated during the Monte Carlo simulation of the pre-trial model and this distribution was used to directly determine the prior values for the distribution of the mean log cost (*nu.trt*) required by WinBUGS.

Precision of the log cost (tau.trt)

The distribution of the precision of the log cost (*tau.trt*) represents the first order uncertainty in the prior data, and provides an estimate of the extent of variation within the likelihood. This distribution is not modelled directly, but rather through the standard deviation of the log cost (*sigma.trt*) 18. This is then converted to give the precision of the log cost (see equation 25).

$$\text{tau.trt} = 1/(\text{sigma.trt})^2 \qquad \textbf{Equation 25}$$

18 The reason for this indirect modelling of the precision of the log cost is that it has been found to speed up time to convergence.

The distribution of the standard deviation of the log cost (*sigma.trt*) was modelled using a half normal distribution, specified by a mean and precision 19. Prior values were specified for the mean and precision parameters of the distribution.

Specification of the priors for this distribution required estimates of the standard deviation in the prior data. One such estimate could be obtained direct from the original trial data used to populate the pre-trial model, if this data were available. In this case, the original pre-trial data was not available. However, this data was recreated in order to produce the bootstrap distributions of the mean cost required for the pre-trial model, enabling an estimate of the standard deviation to be made. The Monte Carlo simulation used to recreate the patient data was employed several (20) times, so as to avoid the bias associated with starting values when simulations involve small numbers of iterations. This process provided a distribution of estimates of standard deviation that was used to derive the prior values of the parameters of the distribution of standard deviation of the log cost (*sigma.trt*).

As for the trial analysis with vague priors, the model updates using per patient data on the total cost logged (*logcost*) and generates a posterior distribution for the mean monetary cost for each treatment group, through the use of a back transformation.

3.2 Additional model structures

3.2.1 The regression model

Within the regression model the dataset was partitioned according to each patient's complication status, whilst a term was added to both the survival (*beta1 * comp.e*) and cost (*beta2 * comp.c*) equations of the standard model. Within the survival equation, the *beta1* term for each treatment group represented the difference in the overall log hazard rate for those who do and do not experience a complication. For the cost equation, the *beta2* term for each treatment group represented the difference in the mean log cost for those who do and do not experience a complication. Both of the beta terms are modelled as normal distributions, specified by a mean and a precision, thus allowing flexibility in the impact of complication status upon costs and survival duration. The *comp.e* and *comp.c* terms act like dummy variables, representing the existence of complications.

In addition to the priors specified for the standard model (see section 3.1), the regression model

19 The use of the half normal truncates the distribution at zero and prevents the occurrence of negative values.

requires the specification of prior values for the parameters of the distributions of *beta1* and *beta2*.

To specify the priors for the *beta1* distribution, estimates were required of the difference in overall log hazard rate (*olambda*) between those who did and did not suffer complications post-surgery. Whilst the pre-trial model did not include the overall hazard rate or log hazard rate, it did incorporate the probability of surviving the period of follow-up, for both those with and without complications. These probabilities were then converted to overall log hazard rates (see equation 26):

$$olambda = \log[-\log(B)/\text{length of follow-up}] \qquad \textbf{Equation 26}$$

where: B = probability of survival till end of follow-up,

For each iteration, the difference between the overall log hazard rates (*olambda*) for those with and without complications was taken, and this distribution was then used to provide the prior values of mean and precision for the distribution of *beta1*, required by the WinBUGS ™ model.

To specify the priors for the *beta2* distribution, estimates were required of the difference in mean log cost between those who did and did not suffer complications post-surgery. A distribution of mean log cost for those with and without complications was generated during the Monte Carlo simulation of the pre-trial model, and the difference between these values was calculated for each iteration. This distribution of the difference in mean log costs was then used to directly determine the prior values for the mean and precision of the distribution of *beta2*.

As with the trial analysis with vague priors, the regression model updates with patient level data concerning total costs logged and survival duration, and generates posterior distributions of mean cost and mean survival duration for each treatment group.

3.2.2 The frailty model

The frailty model provided a statistical model of the relationship between cost and survival, through the incorporation of a 'frailty' term to both the survival (*gamma1*) and cost (*gamma2*) equations of the standard model.

For each treatment group, the frailty terms were modelled as a bivariate normal distribution with

a mean (*mu.gamma*) and a precision matrix (*gamma.T*). The mean values (*mu.gamma*) of these distributions were all set equal to zero, whilst the precision matrices (*gamma.T*) were modelled as Wishart distributions (see equation 27).

$$\begin{pmatrix} R1,1 & R1,2 \\ R2,1 & R2,2 \end{pmatrix}$$ **Equation 27**

Where: R1,1 = precision of survival
R1,2 = R2,1 = 1/covariance between cost and effect
R2,2 = precision of cost

In addition to the priors specified for the standard model (see section 3.1), the frailty model requires information about the prior values of the parameters of the Wishart distribution. These parameters cannot be specified by prior distributions and must instead be specified directly and entered as if they were data. The informed analysis employed the same estimates for the elements in precision matrix as used in the analysis of the trial data with vague priors.

As with the trial analysis with vague priors, the frailty model updates with patient level data concerning total costs and survival duration, and generates posterior distributions of mean cost and mean survival duration for each treatment group.

3.2.3 Bivariate regression model

The bivariate regression model involved combining the statistical and the modelling solutions within one WinBUGS ™ model. This solution allows the main sources of the correlation to be incorporated within the model using the regression equation format whilst any residual correlation is incorporated through the use of the frailty term.

As this model is a hybrid of the other models it incorporates the structure and prior values specified for all of those models.

As with the trial analysis with vague priors, the bivariate regression model updates with patient level data concerning total costs and survival, and generates distributions of mean cost and mean survival for each treatment group.

3.3 Sub-group analysis

The informed sub-group analysis was undertaken using the standard model structure. The difference was that the updating process for each sub-group analysis only incorporated the data for patients in the sub-group of interest.

The prior values specified for each sub-group analysis were identical to those specified for the standard model incorporating all sub-groups (see section 3.1 for details). This represents a prior belief that the sub-groups are similar, and exchangeable, in terms of cost and effect, and allows the analyses to borrow power across the sub-groups.

4. RESULTS

4.1 Costs

Table 14 summarises the expected costs (mean and standard error) for each treatment group for each of the WinBUGS ™ models.

For the standard model, the mean cost (se) associated with patients receiving *pre-opo* was £7,075 (£482), whilst for *pre-opa* and *pre-opd* the mean cost (se) was £8,589 (£983) and £5,958 (£469) respectively. The mean cost (se) for patients receiving standard management was £10,180 (£1,342).

4.2 Survival

Table 14 summarises the expected survival duration (mean and standard error) for each treatment group for each of the WinBUGS ™ models.

For the standard model, the mean survival duration (se) associated with patients receiving *pre-opo* was 1.66 years (0.06), whilst for *pre-opa* and *pre-opd* the mean survival duration (se) was 1.71 years (0.077) and 1.62 years (0.085) respectively. The mean survival duration (se) for patients receiving standard management was 1.39 years (0.1).

4.3 Cost-effectiveness

For each of the models a total of 20,000 iterations were run, with a burn-in of 10,000 iterations. The Bayesian analysis generated a distribution (10,000 values) of mean costs and mean survival durations for each of the methods of patient management. These distributions were used to address the *a priori* decision; assess the level of uncertainty surrounding the decision; and provide a valuation for further research to reduce the level of uncertainty surrounding the decision. As with the pre-trial analysis and the trial analysis with vague priors, the analysis was undertaken for the comparison between standard patient management and pre-operative optimisation (with either inotrope) and for the choice between the three methods for patient management.

4.3.1 Standard model

Figure 17a illustrates the simulated values of mean incremental costs and life years for the comparison between pre-op (using either inotrope) and standard care. Based upon the mean of these points, *pre-opo* dominates standard patient management – as, on average, it is both cheaper (saving of £3,105) and more effective (additional life-years of 0.27). The majority of the points are located below the horizontal axis (negative incremental cost), indicating that the probability that pre-optimisation is cost-saving is high (99.4%). In addition, a considerable proportion of the points are located within quadrant II, where pre-op involves both reduced costs and higher survival duration than standard care, indicating a reasonable probability that pre-op dominates standard patient management (98%).

Figure 17b illustrates the simulated values of mean incremental cost and effect pairs for the comparison between the inotropes. The majority of the points are located within quadrant I, where adrenaline involves higher costs and higher survival duration than dopexamine. Based upon the mean of these points, pre-op employing adrenaline is associated with an ICER of £29,577 per life-year gained when compared to pre-op employing dopexamine (incremental cost = £2,631; incremental effect =0.09 life-years).

Figure 18a illustrates the cost-effectiveness acceptability curve for *pre-opo* compared with standard patient management. The figure shows that the probability that pre-op is optimal when the decision-maker is unwilling to pay anything for an additional life-year (i.e. the probability that it is less costly than standard care) is 99.4%. If the decision-maker is willing to pay £20,000 per life-year gained, the probability that pre-op is optimal is 99.94%, hence the probability that standard patient management is optimal is 0.06%. This probability falls slightly to 99.88% if the

decision-maker is willing to pay £30,000 per life-year gained. The cost-effectiveness frontier for the decision between pre-operative optimisation and standard patient management, traces the cost-effectiveness curve for *pre-opo* due to it's being dominant.

Figure 18b illustrates the cost-effectiveness acceptability curves for the choice between all three patient management strategies. When the decision-maker is unwilling to pay anything for an additional life-year, the probability that pre-op with dopexamine is optimal (i.e. dopexamine is cost saving) is 99.73%. If the decision-maker is willing to pay £20,000 per life-year gained, the probability that pre-op with dopexamine is optimal is 62.55%, compared with probabilities of 37.42% and 0.03% for pre-op with adrenaline and standard patient management respectively. However, if the decision-maker is willing to pay £30,000 per life-year gained, the optimal choice switches to pre-op with adrenaline, with a probability that it is optimal of 50.59%, compared with probabilities of 49.34% and 0.07% for pre-op with dopexamine and standard patient management respectively. The cost-effectiveness frontier (not shown) for the choice between the three methods of patient management, follows the CEAcc curve for dopexamine up to the point where the *a priori* switches to *pre-opa* (λ value of £29,577) and then follows the CEAcc curve for *pre-opa.*

4.3.2 Alternative model structures

Table 14 details the expected mean cost and expected mean survival duration (with standard errors) for each of the different model structures employed for the trial analysis. 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, whilst the expected mean survival duration (and standard error) increases. These results hold across all of the model structures employed, and concord with the empirical evidence that there is a small, negative correlation between cost and survival (-0.1).

For all of the models, pre-operative optimisation (either inotrope) dominates standard care (see Table 15), with a probability in excess of 98% for each of the model structures. Hence the *a priori* choice is *pre-opo* regardless of the model structure employed

For the decision between the three methods of patient management, standard care is dominated by both methods of pre-operative optimisation, and *pre-opa* is more costly and more effective than *pre-opd* in all of the models. Although, the incremental cost-effectiveness ratio associated with *pre-opa* varies between the models – from £22,738 for the frailty model to £34,139 for the regression model. Hence, the *a priori* choice, between *pre-opa* and *pre-opd*,

depends upon the willingness-to-pay for life-years gained and the model structure employed.

Figures 19 and 20 illustrate how the different model structures impact upon the level of uncertainty surrounding the choice between standard management and pre-operative optimisation and the choice between the three methods of patient management respectively.

4.4 Expected value of perfect information

For the decision between standard patient management and a policy of pre-operative optimisation (either inotrope) the EVPI was £0.91 per surgical procedure given a λ value of £20,000 per life year, or £1.98 per surgical procedure, given a λ value of £30,000 per life year. These values were translated into population values using the same assumptions as used for the trial analysis with vague priors20. The results for the population are £0.09 million and £0.2 million respectively.

For the decision between the three methods of patient management, the EVPI is £652 per surgical procedure (£67million for the population) at a λ value of £20,000 per life year, and £1441 per surgical procedure (£148 million for the population) for a λ value of £30,000 per life year (see Figure 21).

4.5 Sub-groups

4.5.1 Cost-effectiveness

Tables 14 and 15 summarise the expected cost and expected survival duration (mean and standard errors) and the incremental cost effectiveness ratios associated with each treatment and sub-group combination.

Figures 22 (a, b and c) and 23 (a, b and c) illustrate the simulated values of mean incremental cost and life years for the comparison between pre-op (using either inotrope) and standard care, and between the inotropes for each of the sub-groups respectively. A comparison across the figures highlights the differences in the mean estimates and in the uncertainty surrounding these

20 Note that the lifetime of the decision used in the re-analysis is 9 years. This is because the re-analysis employing informed priors should be undertaken at the same time as the original trial analysis, hence there is no advancement of time between these analyses, unlike between the analysis of the pre-trial model and the analysis of the trial results.

estimates across the three surgical sub-groups. For other abdominal surgery (*o*) and vascular surgery (*v*) *pre-opo* dominates standard management (probabilities are 78% and 99% respectively), whilst for surgery for upper gastrointestinal malignancy (*u*) *pre-opo* is less costly and marginally less effective than standard management. However, the incremental cost-effectiveness ratio associated with standard management exceeds 1.4 million per life year gained. In addition, the uncertainty surrounding the estimates is much less for sub-groups *o* and *v* (see figure 22).

For the choice between the inotropes (figure 23), *pre-opa* dominates for sub-group *o* and *pre-opd* dominates in sub-group *v*. Whilst for sub-group *u*, *pre-opd* is less costly and less effective than *pre-opa*, which has an associated ICER of £40,787 per life year gained. Again there are marked differences in the extent of the uncertainty surrounding the estimates, with less uncertainty associated with sub-groups *v* and *o* (see figure 23).

Figure 24 illustrates the decision uncertainty associated with the choice between pre-operative optimisation and standard patient management, through the cost-effectiveness acceptability curve for *pre-opo* for each surgical sub-group. When the decision-maker is unwilling to pay anything for an additional life year the probability that *pre-opo* is optimal (i.e. probability that pre-opo is cost-saving) is 80%; 96% and 99% for sub-groups *o*, *u* and *v* respectively. If the decision-maker were willing to pay 20,000 per life-year gained, this probability increases for sub-groups *o* and *v* (to 98.5% and 99.99% respectively), but falls dramatically for sub-group *u* (to 73%). If the decision-maker were willing to pay 30,000 per life year gained this probability levels off for sub-groups *o* and *v*, but continues to fall for sub-group *u* (to 66%).
Figure 25 illustrates the decision uncertainty associated with the choice between the three methods of patient management, through the cost-effectiveness acceptability frontier for each surgical sub-group. Due to dominance, the cost-effectiveness frontier traces the cost-effectiveness curve for *pre-opa* for sub-group *o*, and traces the cost-effectiveness curve for *pre-opd* for sub-group *v*. Whilst for sub-group *u* the cost-effectiveness frontier traces the follows the CEAcc curve for *pre-opd* up to the point where the a priori switches to *pre-opa* (λ value of £40,787 per life year gained) and then follows the CEAcc curve for *pre-opa*.

4.5.2 Expected value of perfect information

Figure 26 illustrates the expected value of perfect information associated with the decision between the three methods of patient management for each of the surgical sub-groups. It can be seen that the discrepancy in the levels of decision uncertainty is translated into a considerable difference in the EVPI between the three sub-groups, with the EVPI for sub-group

u dwarfing that for sub-groups *o* and *v*. Given a λ value of £20,000 per life year the EVPI per surgical procedure is £1,922 (£39 million for the population21) for sub-group *u* compared to £79, £326 (£2 million and £17 million) for sub-groups *v and o* respectively. At a λ value of £30,000 per life year the EVPI per surgical procedure is £3,727 (£75 million for the population) for sub-group *u* compared to £253, £463 (£8 million and £24 million) for sub-groups *v and o* respectively (see Table 16).

5. DISCUSSION

5.1 Results from the re-analysis of the trial

5.1.1 a priori

The analysis of the trial data suggests that pre-operative optimisation (either inotrope) is expected to dominate standard management (probability 98%). In addition, regardless of the value placed upon a life year gained, the probability that *pre-opo* is optimal, compared with standard care, is very high (>99%).

For the comparison between the three methods of patient management, standard management was expected to be dominated by both pre-op management strategies, whilst pre-op employing adrenaline was expected to be both more effective and more expensive than pre-op employing dopexamine (with each additional life year costing £29,577).

Hence, the analysis suggests that, given all of the available data, a policy of pre-operative optimisation was the optimal choice for managing high-risk patients undergoing major elective surgery. Whilst the choice as to which inotrope to employ to achieve optimisation, depends crucially upon the value that the decision-maker is willing-to-pay for additional life-years in this patient group. Decision-makers should adopt pre-op employing dopexamine if their willingness-to-pay for life years is below the incremental cost-effectiveness ratio associated with pre-op employing adrenaline (£29,577).
If the decision-maker were able to differentiate policy on the basis of surgical sub-group, the results of the sub-group analysis suggest that pre-operative optimisation should be adopted for all patients, with dopexamine employed to achieve optimisation for those undergoing vascular

21 The population values for the sub-groups have been calculated in the same proportions as the trial data, on the assumption that the occurrence of each surgical specialty in the population is as it is within the trial data (50% sub-group *o*; 20% sub-group *u* and 30% sub-group *v*).

surgery, and adrenaline used for those undergoing other abdominal surgery. For those patients undergoing surgery for upper gastrointestinal malignancy the inotrope employed to achieve optimisation depends crucially upon the decision-makers willingness to pay for additional life years. If this exceeds the ICER associated with *pre-opa* (£40,787 per life year) then adrenaline should be employed in this patient group, otherwise dopexamine is the optimal choice.

5.1.2 Uncertainty

The analysis shown in Figure 18b indicates that there was considerable uncertainty surrounding the *a priori* decision involving the choice between the three methods of patient management. The extent of the uncertainty depends upon the decision-makers willingness-to-pay for a life year gained. If decision-makers are only interested in costs, and they do not value improvement in patients' life expectancy, the uncertainty associated with the choice of *pre-opd* was 0.3%. However, at a λ value of £20,000 per additional life year the uncertainty associated with the choice of *pre-opd* was 37%. This was much higher than would be acceptable by standard conventions of significance. However, not implementing *pre-opd* on the basis of statistical significance would result in the continuation of standard patient management practices, that had a much lower probability of being optimal (0.03%). Continuing to use standard patient management would result in an expected loss of £8,693 per surgical procedure (an estimated £114 million annually). If decision-makers are willing-to-pay £30,000 per life year, the *a priori* decision is to adopt *pre-opa*, reflecting the fact that as decision-makers are willing to pay more for a life-year gained pre-op employing adrenaline (which is both more expensive and more effective than dopexamine) becomes more attractive to them. At this value of λ, the uncertainty associated with the choice of *pre-opa* is 48%, and the expected loss associated with continual use of standard patient management is £10,966 per surgical procedure (an estimated £144 million annually).

Figures 22 and 23 illustrate that the extent of the uncertainty surrounding the estimates of mean cost and mean survival duration varies considerably between the surgical sub-groups. The uncertainty surrounding estimates is greatest for sub-group *u*, for which there is the least trial data (27 patients). Figures 24 and 25 illustrate the extent of the decision uncertainty surrounding the choice between pre-operative optimisation and standard treatment, and between the three methods of patient management respectively. The figures show that there is a reasonable amount of uncertainty associated with the *a priori* decision in each of the sub-groups, in particular sub-group *u*. For the choice between the three methods of patient management, if decision-makers are only interested in costs, and they do not value improvement in patients' life

expectancy, the uncertainty associated with the *a priori* choice was 47%, 3% and 0.05% for sub-groups *o*, *u* and *v* respectively. However, at a λ value of £20,000 per additional life year this uncertainty becomes 21%, 46% and 5% respectively. These values are much higher than would be acceptable by standard conventions of significance. However, not implementing the *a priori* choice on the basis of statistical significance would result in the continuation of standard patient management practices, that had a much lower probability of being optimal (0.3%, 12% and 0% respectively). Continuing to use standard patient management would result in an expected annual loss of £45 million, £14 million and £72 million respectively. Whilst, if decision-makers are willing-to-pay £30,000 per life year, the uncertainty associated with the *a priori* choice increases to 21%, 60% and 9% respectively, and the expected annual losses associated with continual use of standard patient management increases to an estimated £63 million, £15 million and £94 million respectively.

For sub-group *o* the *a priori* decision was to adopt pre-operative optimisation employing adrenaline. However, if the decision-maker failed to implement the differential policy for this sub-group, in favour of a universal policy of pre-operative optimisation with dopexamine for all sub-groups, the expected loss would be £3,136 per surgical procedure, an estimated £20 million per annum.

Comparison of figures 22 and 23 with figures 24 and 25 shows that whilst the uncertainty surrounding the estimates is greater for sub-group *v* than sub-group *o*, the uncertainty surrounding the decision is greater for sub-group *o*. This illustrates the difference between the two types of uncertainty, and reflects the positioning of the mean estimates within the two-dimensional decision space (incremental costs vs incremental effects).

5.1.3 Value of information analysis

The VOI analysis formally valued the uncertainty in the decision and generated explicit valuations that could be compared to the cost of further investigation to determine whether additional research was potentially worthwhile. Assuming a λ value of £20,000 per life year, the EVPI for the whole decision was found to be £652 per surgical procedure, or £67m for the whole population. This provides an absolute limit on the worth of further research concerning all elements of the decision, at this value of λ. Figure 27 illustrates the relationship between the level of uncertainty (as represented by the cost-effectiveness frontier) and the expected value of perfect information. As the value of λ increases, upto a value of £29,577, both the uncertainty (as represented by the cost-effectiveness acceptability frontier) and the valuation of the consequences associated with the uncertainty increase. The two effects work in the same

direction to provide a maximum EVPI of £1,441 per surgical procedure (£148 million for the population) at the point where the *a priori* decision switches from *pre-opd* to *pre-opa*. As the value of λ increases beyond this point, the valuation of the consequences associated with the uncertainty continues to increase but the uncertainty falls. The two effects work in opposing directions. Initially, the reduction in uncertainty is large and the value of information rises slightly. However, as the value of λ continues to increase, the reduction in uncertainty slows and the increased value of the consequences (λ) leads VOI to rise more sharply.

The formal valuation of the uncertainty surrounding the *a priori* decision in each of the sub-groups provided an explicit valuation of the cost of uncertainty that could be compared to the cost of further investigation within the sub-group to determine whether additional research was potentially worthwhile. The results indicate that the EVPI per surgical procedure was greatest for sub-group *u* for λ values in excess of £7,000, for λ values below £7,000 the EVPI was greatest for sub-group *o*. This result is maintained for the estimates of population EVPI despite sub-group *u* having the smallest population of patients, and reflects the considerable uncertainty surrounding the *a priori* choice between the three methods of patient management in sub-group *u*.

5.2 Comparison between the model structures

As in the trial analysis with vague priors, the results of the regression model show, as postulated, that those patients who experience a complication post-surgery are expected to have a lower survival (beta1 is negative) and a higher cost (beta2 is positive) than those patients whose post-surgical experience is complication free. The results of the frailty model suggest a negative correlation (-0.37) between cost and survival that exceeds the correlation identified in the trial data, but is lower than that identified for the trial analysis with vague priors. The results of the regression model incorporating the frailty element also illustrate that those patients who experience a complication post-surgery are expected to have a lower survival (beta1 is negative) and a higher cost (beta2 is positive) than those patients whose post-surgical experience is complication free. The extent of the relationship is similar to that of the regression model. In addition, this model indicates a negative correlation between cost and survival that is smaller (-0.3) than that indicated by the frailty model. This is to be expected, as the frailty element in this model is simply used to ‘mop up’ any correlation between cost and effect not explained by the regression element of the model. If the frailty term were larger for this model than for the standard frailty model it would suggest that the regression model were having a negative effect upon the modelling of the correlation.

Closer examination of the results shows that the standard model and regression model continue to yield a lower survival duration than the models incorporating a frailty element, whilst the standard model and the frailty model continue to yield higher costs than the models incorporating a regression equation. It is postulated that this is due to the existence of a complex relationship between cost and survival within the trial data. Where patients die early (within six months) there is a positive relationship between cost and survival. However, for patients that survive the initial six months post-surgery, there is a slight negative relationship between cost and survival. This reflects the fact that the early deaths are pre-dominantly due to complications. Hence prolonging survival increases the costs of managing those complications. This effect is compounded by the collection of cost data only to six months post-surgery. As with the trial analysis with vague priors, the relationship between cost and survival is not adequately picked up by either model. However, the incorporation of prior information into the analysis has tempered the results of the models, bringing the estimates from the models closer together.

The convergence problems associated with the models incorporating a frailty element, which were experienced within the trial analysis with vague priors continued to occur within the informed analysis. These problems affected the covariance slightly, and had a large impact upon the correlation calculation, which is a function of the co-variance. In addition, these models had high autocorrelation between the log hazard rates. As with the trial analysis with vague priors, there are a number of ways that could be investigated to provide a solution to these problems.

Regardless of the differences in the expected results, the CEAcc curves associated with *pre-opo* are almost identical between the models over the whole range of values of λ (figure 19).

For the choice between the three methods of patient management, the CEAcc frontiers (figure 20) illustrate the different ICERs, for *pre-opa* in comparison with *pre-opd,* associated with the different model structures. Again, the CEAcc frontiers are very similar.

5.3 Limitations of the study

The informed re-analysis suffers from the same limitations as discussed for the trial analysis with vague priors, including the censoring of survival duration data and use of a composite measure for costs. In addition, the re-analysis involves the incorporation of prior information from the pre-trial model into the analysis. As such, the re-analysis relies heavily upon the structure and results of the pre-trial model. Any limitations within the pre-trial model become

limitations for the informed re-analysis e.g. absence of data to model longer term outcomes.

THE VALUE OF THE ITERATIVE FRAMEWORK

The impact and value of an iterative framework for managing the process of health technology assessment can be determined through comparison of the various stages of the analysis. A comparison of the results and conclusions from the pre-trial model with those of the informed Bayesian re-analysis illustrates the impact that the data from the 1999 trial had upon the available information position and how this affected decision-making. Whilst, a comparison of the results and conclusions from the trial analysis with and without informative priors illustrates the impact of formally incorporating the prior information position within the trial analysis rather than discarding the information or relying upon informal methods to incorporate it.

1. '*A PRIORI*' DECISION

For the choice between a policy of pre-operative optimisation employing either inotrope (*pre-opo*) or standard patient management, the pre-trial analysis; trial analysis with vague priors and informed Bayesian re-analysis of the trial all give the same result – a policy of pre-operative optimisation employing either inotrope is expected to dominate standard patient management. Although, the certainty attached to this statement varies between the analyses – 74% for the pre-trial model; 94% for the trial analysis; and 98% for the informed reanalysis. For the choice between the three methods of patient management, the estimate of the cost and effect associated with *pre-opd* and the cost associated with *pre-opa* are higher for the pre-trial model in comparison with the trial data (analysed both with and without the influence of prior evidence), whilst the estimate of the effect associated with *pre-opa* is lower. Hence, for the pre-trial analysis *pre-opd* is expected to dominate *pre-opa*. Whilst, the results of the uninformed trial analysis conclude that *pre-opa* is more costly and more effective than *pre-opd*, with an associated ICER of £23,936. For the informed Bayesian re-analysis, the larger uncertainty surrounding the prior estimates for *pre-opa* results in the priors exerting less influence within the updating process than those for *pre-opd*. As a result, the estimates of mean cost and mean survival duration for *pre-opa* and *pre-opd* are driven further apart within the informed Bayesian re-analysis, and the ICER associated with the use of *pre-opa* increases to £29,577.

Hence, whether the *a priori* decision is affected by the incorporation of prior information depends upon the decision-makers willingness-to-pay for life years. If the decision-maker were willing to pay below £20,000 or above £30,000 per life year gained the *a priori* decision resulting from the two analyses would be identical. However, if the decision-makers willingness to pay fell between the ICERs generated by the two analyses then the incorporation of pre-trial data would affect the *a priori* decision.

2. UNCERTAINTY

Whilst the new trial data and the iterative framework had limited impact upon the *a priori* decision, they had considerable impact upon the extent of the uncertainty surrounding both the estimates and the decision.

Table 17 summarises the expected costs and expected survival duration (mean and standard error) for each treatment group for each stage in the iterative process. The standard errors illustrate that in all cases the uncertainty surrounding the estimates from the pre-trial model exceeded those from the analysis of the trial data. As expected, the incorporation of the

information available from the pre-trial model into the informed Bayesian re-analysis served to further reduce the uncertainty surrounding the estimates of expected cost and expected survival duration. Figure 28 provides a graphical illustration of the reduction in the estimate uncertainty, between the stages of the framework, for the comparison between the expected cost and survival duration of *pre-opa* and *pre-opd* 22. Each figure is plotted on the same scale to illustrate the shrinking of the uncertainty surrounding the estimates.

However, reductions in estimate uncertainty do not necessarily translate into reductions in decision uncertainty. This is due to the presence of two factors that influence the decision uncertainty – 1) the estimate uncertainty; and 2) the position of the mean estimates within the two-dimensional decision space. For the choice between *pre-opo* and standard patient management the extent of the decision uncertainty falls between the pre-trial model (25%); the trial analysis (3%) and the informed Bayesian re-analysis (2%), regardless of the value of λ. However, for the choice between the three methods of patient management the shift in the position of the mean estimates for *pre-opa* and *pre-opd*, due to the differential weightings attached to the prior evidence, results in increased decision uncertainty for the informed Bayesian re-analysis, over a specific range of values of λ (λ > £13,000 for comparison with the pre-trial model, λ > £26,500 for comparison with the trial analysis). This is illustrated in Figure 29 through the CEAcc frontiers associated with each stage of the framework. For the pre-trial analysis *pre-opd* is expected to dominate, hence the CEAcc frontier follows the shape of the CEAcc curve for *pre-opd*. For the trial analyses the CEAcc frontier follows the shape of the CEAcc curve for *pre-opd* up to the point where *pre-opa* becomes cost-effective (λ = £23,936 for the trial analysis, and λ = £29,577 for the informed Bayesian re-analysis). The figure illustrates the range of values for λ over which the a priori decision is affected by the inclusion of prior information, as well as indicating the decision uncertainty surrounding the *a priori* for each stage of the framework.

3. DECISION CONCERNING WHETHER TO FUND FURTHER INFORMATION

Figure 30 illustrates the EVPI (per surgical procedure) for each stage of the framework for a range of λ values. It can be seen that the shift in the position of the mean estimates for *pre-opa* and *pre-opd*, due to the differential weightings attached to the prior evidence, which resulted in increased decision uncertainty for the informed Bayesian re-analysis, leads to an increase in the EVPI, over a specific range of values of λ. Hence, for λ values in excess of £16,000, the EVPI is

22 Note that the strange distribution of estimates for the pre-trial model results from the use of the adjustment factor to model the cost and effects associated with *pre-opa* (see chapter 5 for details).

larger than for the pre-trial model, whilst for λ values in excess of £27,500 discarding prior information leads to an underestimate of the EVPI. However, the valuations are such that additional research looks potentially worthwhile at each stage of the framework (Table 18).

CONCLUSIONS

The results of the Bayesian re-analysis with informative priors suggest that, given all the information available to them, decision-makers can be confident that pre-operative optimisation is a cost-effective method of managing high-risk surgical patients undergoing major elective surgery. Whilst the decision concerning which inotrope to employ, to achieve optimisation, depends crucially upon the value that the decision-maker is willing to pay for additional life years, in this patient group. In addition, there is more uncertainty surrounding the choice between inotropes. The value of information analysis has shown that further research to reduce the uncertainty is potentially worthwhile.

In addition, the informed Bayesian re-analysis has illustrated that it is only by formally incorporating all of the information available to decision makers through the use of informed priors that the proper estimates of cost-effectiveness, upon which appropriate decisions can be made, are attained.

Table 1 Summary of clinical trial results

	UK trial published 1993 (cost analysis published 1996)	(Boyd et al. 1993) (Guest et al. 1997)	US trial published 1988	(Shoemaker et al. 1988)
	Protocol	Control	Protocol	Control
Number of patients	53	54	28	30
Age, yr	69 (61, 77) *	72.5 (66, 80) *	56.4+/-3.1 #	53.4+/-2.5 #
Sex, males/females (%)	74/26	61/39	75/25	39/61
ICU days	1.67 (0.79, 5) *	1.8 (0.83, 4.1) *	10.2+/-1.6 #	15.8+/-3.1 #
Hospital days	12 (7, 40) *	14 (7, 37) *	19.3+/-2.4 #	25.2+/-3.4 #
Complications	0.68 +/- 0.16 #	1.35 +/- 0.20 #		
Post-operative death no (%)	3 (5.7%)	12 (22.2%)	1 (4%)	10 (33%)
Patient cost	£ 6,525 (£ 4201,£ 17469)*	£ 7,525 (£ 4660,£ 16156)*	£ 19,127 a$	£ 39,300 a$

* median (interquartile range)
\# mean +/- standard error of the mean
a average patient cost
$ Converted to £UK using an exchange rate of $1.50 to £1

Table 2 Frequency of multiple complications from (Shoemaker et al. 1988)

Frequency of multiple complications	Dopexamine	Standard Treatment
No of patients	28	30
No of complications	11	31
No of complications per patient	0.39	1.03
No of patients with complications	8 (28%)	15 (50%)
Patients with 0 complications	20 (71%)	15 (50%)
Patients with 1 complication	5 (18%)	7 (23%)
Patients with 2 complications	3 (11%)	3 (10%)
Patients with 3 complications	0	2 (7%)
Patients with 4 or more complications	0	3 (10%)

Table 3 Summary of data concerning events from (Boyd et al. 1993)

	No. of patients	No. of comps	No. of comps per patient – all	No. of comps per patient – survivors	No. of deaths	% deaths
Dopexamine	43	30	0.7	0.48	3	7%
Standard management	38	55	1.45	0.93	9	23.7%

Table 4 Beta distributions for pathway probabilities

	alpha	beta	probability
Dopexamine			
Probability of complication	22	21	0.5116
Probability of 28 day mortality|complication	3	19	0.1364
Probability of 28 day mortality|no complication	0.1	21	0.0048
Control			
Probability of complication	27	11	0.7105
Probability of 28 day mortality|complication	9	18	0.3333
Probability of 28 day mortality|no complication	0.1	11	0.0091
Probability of longer term survival			
Probability of mortality (6 months post-surgery)	0.26	18.74	0.0138
Probability of mortality (1 year post-surgery)	0.31	18.43	0.0166
Probability of mortality (2 years post-surgery)	0.6	17.82	0.0328

Table 5 Survival duration for non-survivors (at 28 days)

	Dopexamine	**Control**
1	3	3
2	6	5
3	8	7
4	-	8
5	-	11
6	-	13
7	-	17
8	-	24
9	-	25

Table 6 Cost profiles per patient

	Dopexamine		Control		Adrenaline as dopexamine		Adrenaline as control	
	Complications	No Complications	Complications	No Complications	Complications	No Complications	Complications	No Complications
	9,726.09	6,982.57	9,218.33	11067.18271	6,797.34	8,873.94	9,974.45	9,121.13
1	6,551.59	9,911.87	6,181.98	11789.21205	4,694.78	11,587.28	16,286.09	10,454.15
2	19,591.49	9,209.72	30,055.58	27926.88691	9,592.09	3,516.15	8,610.64	7,340.63
3	5,449.95	2,564.54	26,061.99	13026.33768	2,601.97	4,139.47	15,862.33	4,660.19
4	6959.324455	4,056.09	9,210.87	20956.12793	5,557.30	2,236.11	4,654.19	2,201.90
5	2421.258375	17,025.02	3,783.34	6846.252628	13,672.27	12,346.97	3,417.04	7,510.07
6	5609.907813	2,966.94	7,950.69	7134.031829	8,985.05	9,566.31	7,954.73	21,867.55
7	17616.39569	3,749.88	3,437.55	19024.21857	6,742.21	9,133.99	9,337.12	18,301.36
8	4802.775846	1,706.26	6,860.85	3012.703921	8,092.28	6,978.26	15,423.41	8,126.67
9	1913.504895	11,251.12	10,399.05	7693.23545	4,966.80	27,400.56	13,335.17	5,229.80
10	9092.920575	4,091.27	8,072.05	2351.769487	3,607.37	1,834.26	9,938.91	5,518.93
11	7461.260783	7,853.63	12,729.83	1978.233375	6258.656062		4,899.33	
12	14772.50531	4,400.08	3,082.82					
13	9777.273587	3,720.07	5,571.11					
14	5244.493753	14,604.65	3,392.02					
15	5427.302957	5,129.39	2,825.50					
16	5872.798249	4,692.43	2,772.28					
17	1785.526339	16,222.57	16,218.88					
18	8186.835963	4,726.95	7,095.53					
19	42036.37275	6,346.63	8,389.74					
20	11521.83329	4692.401403	19,550.37					
21	16263.71226	7712.38111	4,625.06					
22	5614.960068		11362.56009					
23			19,018.44					
24			9875.602807					
25			3917.916835					
26			4241.547334					
27			2211.662004					

Table 7 Structure of the survival data for the piecewise exponential

subject	event	time	timegp	trt
1	0	28	1	1
1	0	155	2	1
1	0	182	3	1
1	0	365	4	1
2	0	28	1	1
2	0	155	2	1
2	0	182	3	1
2	0	365	4	1
3	0	28	1	1
3	0	155	2	1
3	0	182	3	1
3	0	365	4	1
4	0	28	1	1
4	0	155	2	1
4	1	65	3	1
5	0	28	1	1
5	0	155	2	1
5	0	182	3	1
5	0	365	4	1

Table 8 Details of the key resource-use collected on patients

	Standard		Adrenaline		Dopexamine		Pre-op (either inotrope)	
Resource	**Mean (sd) *n***	**Median (IQR)**	**Mean (sd) *n***	**Median (IQR)**	**Mean (sd) *n***	**Median (IQR)**	**Mean (sd) *n***	**Median (IQR)**
Length of stay								
Initial hospitalisation								
Ward (hrs)	437.33 (588.03) *44*	271.00 (168.25,379)	387.67 (317.21) *45*	286.00 (212,401)	248.59 (147.39) *45*	196.50 (172.75,285.75)	317.36 (254.84) *90*	235.00 (190,313)
ICU (hrs)	66.91 (137.49) *21*	0.00 (0.00,36.25)	42.91 (97.94) *21*	0.00 (0.00,27)	35.57 (93.03) *17*	0.00 (0.00,24.00)	39.20 (95.03) *38*	0.00 (0.00,25.00)
HDU (hrs)	25.15 (53.51) *21*	0.00 (0.00,27.75)	25.38 (28.93) *33*	21.00 (0.00,25.00)	24.30 (18.35) *36*	23.00 (15.00,30.50)	24.84 (24.04) *69*	22.00 (2.00,26.50)
Total	529.39 (624.71) *46*	323.00 (216.25,500.75)	455.96 (363.17) *45*	311.00 (239,505)	308.46 (194.30) *46*	249.00 (211.25,330)	381.40 (298.09) *91*	287.00 (213,392)
Subsequent in-patient stay								
Related to surgery (days)	0.70 (3.10) *3*	0.00 (0.00,0.00)	3.18 (11.63) *4*	0.00 (0,0)	0.11 (0.74) *1*	0.00 (0.00,0.00)	1.63 (8.29) *5*	0.00 (0.00,0.00)

Table 8 continued

	Standard		Adrenaline		Dopexamine		Pre-op (either inotrope)	
Resource	Mean (sd) n	Median (IQR)	Mean (sd) n	Median (IQR)	Mean (sd) n	Median (IQR)	Mean (sd) n	Median (IQR)
Main Drugs								
Cefotaximine 1g iv	10.33 (10.50) 18	6.50 (3.00,15.00)	9.52 (5.56) 23	9.00 (7.00,14.50)	8.11 (5.56) 18	7.00 (5.25,11.00)	8.90 (5.54) 41	8.00 (6.00,12.00)
Fragmin 2500 iu sc	15.92 (12.36) 38	12.00 (8.00,20.00)	13.76 (11.38) 37	11.00 (7.00,15.00)	9.66 (3.70) 41	9.00 (8.00,12.00)	11.60 (8.48) 78	9.00 (8.00,13.00)
Metronidazole 500 mg iv	11.65 (8.88) 20	11.50 (3.00,17.25)	8.29 (5.84) 21	9.00 (3.00,12.00)	9.20 (7.44) 20	7.00 (4.50,12.25)	8.73 (6.60) 41	8.00 (3.00,12.00)

	Standard		Adrenaline		Dopexamine		Pre-op (either inotrope)	
Resource	Mean (sd) n	Median (IQR)	Mean (sd) n	Median (IQR)	Mean (sd) n	Median (IQR)	Mean (sd) n	Median (IQR)
Main Infusions								
Blood (units)	5.25 (7.15) 32	3.00 (2.00,6.00)	5.57 (12.27) 23	2.00 (2.00,4.00)	3.62 (3.28) 26	2.00 (1.25,4.75)	4.53 (8.69) 49	2.00 (2.00,4.00)
Altracurium	2.00 (n/a) 1	2.00 (2.00,2.00)	n/a (n/a) 0	n/a (n/a,n/a)	n/a (n/a) 0	n/a (n/a,n/a)	n/a (n/a) 0	n/a (n/a,n/a)
Albumin 4.5% 250 mls	12.22 (14.46) 18	7.50 (3.00,15.00)	5.63 (6.15) 19	3.00 (1.50,7.00)	5.41 (3.97) 27	4.00 (3.00,8.00)	5.50 (4.92) 46	4.00 (2.00,8.00)

Table 8 continued

Platelets	8.00 (n/a) 1	8.00 (8.00,8.00)	5.50 (2.12) 2	5.50 (4.75,7.25)	3.50 (3.54) 2	3.50 (2.25,4.75)	4.50 (2.65) 4	5.00 (3.25,6.25)
Cryoprecipitate	4.00 (2.83) 2	4.00 (3.00,5.00)	10.00 (n/a) 1	10.00 (10.00,10.00)	4.00 (n/a) 1	4.00 (4.00,4.00)	7.00 (4.24) 2	7.00 (5.50,8.50)

	Standard		Adrenaline		Dopexamine		Pre-op (either inotrope)	
Resource	Mean (sd) n	Median (IQR)	Mean (sd) n	Median (IQR)	Mean (sd) n	Median (IQR)	Mean (sd) n	Median (IQR)
Main investigations								
Full blood count	9.13 (8.25) 46	6.00 (3.00,12.75)	8.71 (8.32) 45	6.00 (4.00,10.00)	6.51 (4.92) 45	5.00 (3.00,8.00)	7.61 (6.89) 90	5.00 (3.00,9.00)
Clotting studies	7.06 (8.26) 34	4.00 (1.00,9.00)	5.40 (7.31) 40	2.50 (1.00,5.25)	4.00 (5.31) 36	2.50 (1.00,4.00)	4.74 (6.44) 76	2.50 (1.00,4.00)
Cross match	3.70 (4.48) 46	2.00 (2.00,3.75)	3.23 (4.92) 43	2.00 (1.00,3.00)	2.48 (2.03) 44	2.00 (1.00,3.00)	2.85 (3.75) 87	2.00 (1.00,3.00)
Urea and Electrolytes	9.87 (8.77) 45	7.00 (4.00,13.00)	9.00 (8.87) 45	6.00 (3.00,11.00)	6.60 (5.17) 45	5.00 (3.00,8.00)	7.80 (7.32) 90	5.00 (3.00,9.00)

Table 8 continued

	Standard		Adrenaline		Dopexamine		Pre-op (either inotrope)	
Resource	Mean (sd) n	Median (IQR)	Mean (sd) n	Median (IQR)	Mean (sd) n	Median (IQR)	Mean (sd) n	Median (IQR)
Main interventions								
Surgery (hrs)	2.67 (0.82) 6	2.50 (2.00,3.00)	3.67 (0.58) 3	4.00 (3.50,4.00)	2.75 (0.96) 4	2.50 (2.00,3.25)	3.14 (0.90) 7	3.00 (2.50,4.00)
Arterial blood gas (no. given)	25.73 (33.91) 26	10.50 (2.25,36.75)	14.13 (21.79) 32	6.00 (2.75,11.00)	11.67 (13.45) 30	7.50 (4.00,13.75)	12.94 (18.13) 62	6.00 (3.00,11.00)
TPN *	9.25 (4.86) 8	11.00 (4.00,12.50)	6.50 (3.15) 6	5.00 (4.25,8.75)	8.50 (9.19) 2	8.50 (5.25,11.75)	7.00 (4.47) 8	5.00 (4.00,10.25)
Pre-operative optimisation								
Length of stay (hrs)	n/a (n/a) n/a	n/a (n/a,n/a)	9.18 (6.89) 45	5.00 (4.00,16.00)	10.30 (7.17) 46	6.00 (4.00,17.75)	9.75 (7.02) 91	5.00 (4.00,17.00)

Table 9 Unit costs of the key resources used within the trial

Resource	Unit cost
Length of stay:	
Ward (per hour)	£ 10.30
ICU (per hour)	£ 35.50
HDU (per hour)	£ 25.50
Related stay (per day)	£ 257.00
Main drugs (per dose):	
Cefotaximine 1g iv	£ 7.01
Fragmin 2500 iu sc	£ 2.29
Metronidazole 500 mg iv	£ 5.19
Main infusions:	
Blood (per unit)	£ 79.79
Altracurium infusion (mls/hr)	£ 36.15
Albumin 4.5% 250 mls (per dose)	£ 20.93
Platelets (per unit)	£ 141.93
Cryoprecipitate (per unit)	£ 24.13
Main investigations (per test):	
Full blood count	£ 4.05
Clotting studies	£ 7.28
Cross match	£ 8.72
Urea and electrolytes	£ 3.53
Pre-operative optimisation	
Adrenaline (per patient)	£ 2.35
Dopexamine (per patient)	£ 24.67
Hotel costs (per hour)	£ 21.00
Disposables (per patient)	£ 221.64
Cost of fluid (per unit)	£ 19.93

(see text for source of data)

Table 10 Costs in the trial groups – 1999 £ UK

	Standard		Adrenaline		Dopexamine		Pre-op (either inotrope)	
Resource	**Mean (sd)**	**Median (IQR)**	**Mean (sd)**	**Median (IQR)**	**Mean (sd)**	**Median (IQR)**	**Mean (sd)**	**Median (IQR)**
Length of stay:								
Ward	4504 (6057)	2791 (1733,3904)	3993 (3267)	2946 (2184,4130)	2560 (1518)	2024 (1779,2943)	3269 (2625)	2421 (1957,3224)
ICU	2375 (4881)	0 (0,1287)	1523 (3477)	0 (0,959)	1263 (3302)	0 (0,852)	1392 (3374)	0 (0,888)
HDU	641 (1364)	0 (0,708)	647 (738)	536 (0,638)	620 (468)	587 (383,778)	633 (613)	561 (51,676)
Total excl related	7521 (8326)	4413 (2439,8066)	6163 (5634)	4061 (2957,6463)	4443 (4060)	3372 (2518,4668)	5294 (4950)	3594 (2636,5569)
Related in-patient stay	371 (2072)	0 (0,0)	817 (2989)	0 (0,0)	28 (189)	0 (0,0)	418 (2132)	0 (0,0)
All drugs	225 (304)	104 (38,288)	149 (188)	77 (31,156)	132 (181)	63 (37,147)	140 (184)	70 (32,154)
All Infusions	689 (1219)	245 (99,674)	477 (1158)	157 (61,338)	374 (603)	182 (47,335)	425 (916)	176 (60,342)
All Investigations	255 (257)	164 (77,338)	211 (233)	129 (72,200)	150 (135)	106 (79,171)	180 (191)	113 (77,196)
All Interventions	525 (1080)	55 (0,618)	291 (658)	28 (7,180)	206 (524)	32 (0,80)	248 (592)	28 (0,126)
Total cost	10,297 (12,039)	5,373 (2749,11257)	8,706 (8,907)	5,976 (3875,7765)	5,848 (5246)	4,179 (3371,6191)	7,261 (7390)	4,623 (3394,7363)

Table 11 Cost and survival results for the different model structures – mean and standard error

	Standard	Regression	Frailty	Regression & Frailty
Pre-opo	£6,941 (£538)	£6,426 (£386)	£6,823 (£532)	£6,331 (£407)
	612 (22)	618 (23)	639 (27)	643 (26)
Standard	£10,512 (£2,140)	£9,527 (£1,695)	£10,237 (£2,051)	£9,369 (£1,697)
	535 (43.3)	534 (45)	599 (59)	576 (54)
Pre-opd	£5,685 (£533)	£5,392 (£408)	£5,584 (£525)	£5,383 (£408)
	592 (34.4)	602 (36)	637 (39)	627 (40)
Pre-opa	£8,551 (£1,119)	£7,823 (£821)	£8,394 (£1,111)	£7,688 (£780)
	635 (28.1)	647 (29)	668 (33)	695 (31)

Table 12 Cost and survival results for the Frequentist analysis of trial data mean (standard error)

	Cost - mean (standard error) Survival – mean (standard error)
Pre-opo	£ 7,282 (£ 775) 613 (22.2)
Standard	£ 10,314 (£1,748) 536 (43.5)
Pre-opd	£ 5,844 (£ 760) 594 (34.2)
Pre-opa	£ 8,693 (£1,310) 632 (28.5)

Table 13 Prior values used within the informed analysis

	Pre-op	Standard	Adrenaline	Dopexamine
Standard model				
Mean log-cost	N (9, 44)	N (9,28)	N (9,14)	N (9,49)
Precision log-cost	N (0.5, 118) I(0,)	N (0.6, 52) I(0,)	N (0.6, 42) I(0,)	N (0.4, 97) I(0,)
Lambda 1	N (-5.8, 2.7)	N (-4.7, 8.7)	N (-5.5, 1.4)	N (-6.1, 2.7)
Lambda 2	N (-11.9, 0.07)	N (-11.9, 0.07)	N (-11.9, 0.07)	N (-11.9, 0.07)
Lambda 3	N (-11.5, 0.09)	N (-11.5, 0.09)	N (-11.5, 0.09)	N (-11.5, 0.09)
Lambda 4	N (-10.3, 0.29)	N (-10.3, 0.29)	N (-10.3, 0.29)	N (-10.3, 0.29)
Regression model				
Beta1	N (0.16, 5.85)	N (-0.5, 7.54)	N (0.18, 1.97)	N (0.12, 6.78)
Beta2	N (0.36, 0.38)	N (3.85, 0.58)	N (0.49, 0.19)	N (0.23, 0.57)

N = Normal distributed

N.B. Within WinBUGS™ the Normal distribution is expressed by the mean and the precision (the inverse of the variance).

Table 14 Mean cost and mean survival duration results for the different model structures and sub-groups – mean (standard error)

Costs (£) Survival Duration (days)	Pre-op with adrenaline		Pre-op with dopexamine		Standard management		Pre-op with either	
Standard model	8,589	(983)	5,958	(469)	10,180	(1,342)	7,075	(482)
	623	(28)	591	(31)	509	(38)	606	(22)
Regression model	7,951	(784)	5,667	(393)	9,568	(1,202)	6,600	(383)
	628	(28)	591	(32)	503	(39)	607	(22)
Frailty model	8,534	(960)	5,904	(466)	10,094	(1,348)	7,008	(483)
	641	(28)	613	(32)	521	(40)	620	(22)
Bivariate regression model	7,911	(772)	5,656	(394)	9,487	(1,220)	6,566	(383)
	640	(27)	607	(33)	513	(41)	622	(23)
Surgical Sub-groups:								
Other abdominal	5,807	(735)	5,979	(572)	6,824	(1,125)	5,799	(459)
	661	(29)	625	(38)	555	(39)	645	(25)
Upper GI malignancy	11,079	(2005)	7,424	(873)	12,635	(2,032)	8,921	(975)
	461	(78)	428	(70)	423	(81)	422	(54)
Vascular	11,194	(2025)	5,721	(664)	12,917	(2,044)	7,918	(848)
	649	(38)	657	(37)	461	(65)	660	(27)

Table 15 ICERs for the different model structures and sub-groups

ICER - £/life year	Pre-op with adrenaline	Pre-op with dopexamine	Standard management	Pre-op with either
Standard model	29,577	LC	D	LC
Regression model	34,139	LC	D	LC
Frailty model	22,738	LC	D	LC
Bivariate regression model	25,439	LC	D	LC
Surgical Sub-groups:				
Other abdominal	LC	D	D	LC
Upper GI malignancy	40,787	LC	D / 1,421,569 *	LC
Vascular	D	LC	D	LC

LC = strategy with the lowest cost
D = strategy is dominated
* The standard management strategy is dominated by the pre-operative optimisation with dopexamine strategy, but has a ICER of 1,421,569 when compared with the pre-operative optimisation with either inotrope

Table 16 Expected value of perfect information results for the different model structures and sub-groups – per surgical procedure and for the UK population

EVPI – (£)	per surgery λ = £20,000	per surgery λ = £30,000	population λ = £20,000	population λ = £30,000
Standard model	652	1441	67 million	148 million
Regression model	849	1088	87 million	111 million
Frailty model	588	1333	60 million	137 million
Bivariate regression model	764	1234	78 million	126 million
Surgical Sub-groups:				
Other abdominal	326	463	17 million	24 million
Upper GI malignancy	1922	3727	39 million	75 million
Vascular	79	253	2 million	8 million

Table 17 Mean cost and mean survival duration results for the different stages of the iterative framework – mean (standard error)

	Cost – mean (se)	Survival duration – mean (se)
Pre-trial analysis		
Pre-opo	£9,412 (£1,949)	636 (42)
Standard	£11,885 (£3,477)	541 (50)
Pre-opd	£7,976 (£1,407)	657 (35)
Pre-opa	£10,180 (£3,644)	615 (64)
Trial analysis		
Pre-opo	£6,941 (£538)	612 (22)
Standard	£10,512 (£2,140)	535 (43)
Pre-opd	£5,685 (£533)	592 (34)
Pre-opa	£8,551 (£1,119)	635 (28)
Informed Bayesian re-analysis		
Pre-opo	£7,075 (£482)	606 (22)
Standard	£10,180 (£1,342)	509 (38)
Pre-opd	£5,958 (£469)	591 (31)
Pre-opa	£8,589 (£983)	623 (28)

Table 18 Expected value of perfect information results for the different stages of the iterative framework – per surgical procedure and for the UK population

EVPI – (£)	per surgery λ = £20,000	per surgery λ = £30,000	population λ = £20,000	population λ = £30,000
Pre-trial analysis	£ 345	£ 374	£48 million	£53 million
Trial analysis	£ 857	£ 1203	£89 million	£123 million
Informed Bayesian re-analysis	£ 652	£ 1441	£67 million	£148 million

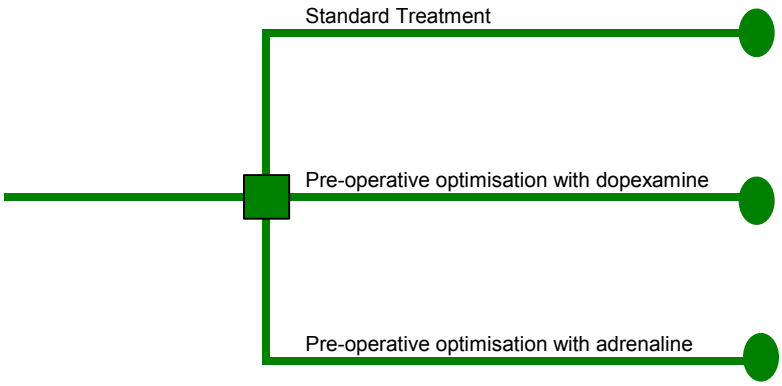


Figure 1 The patient management decision

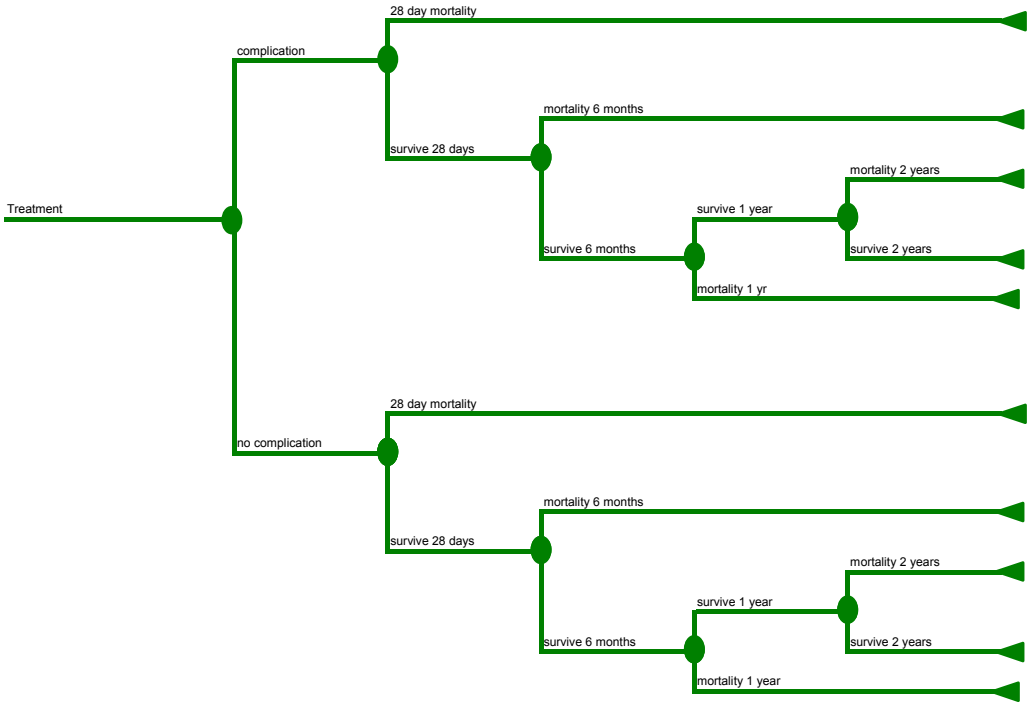


Figure 2 Decision tree for each management strategy

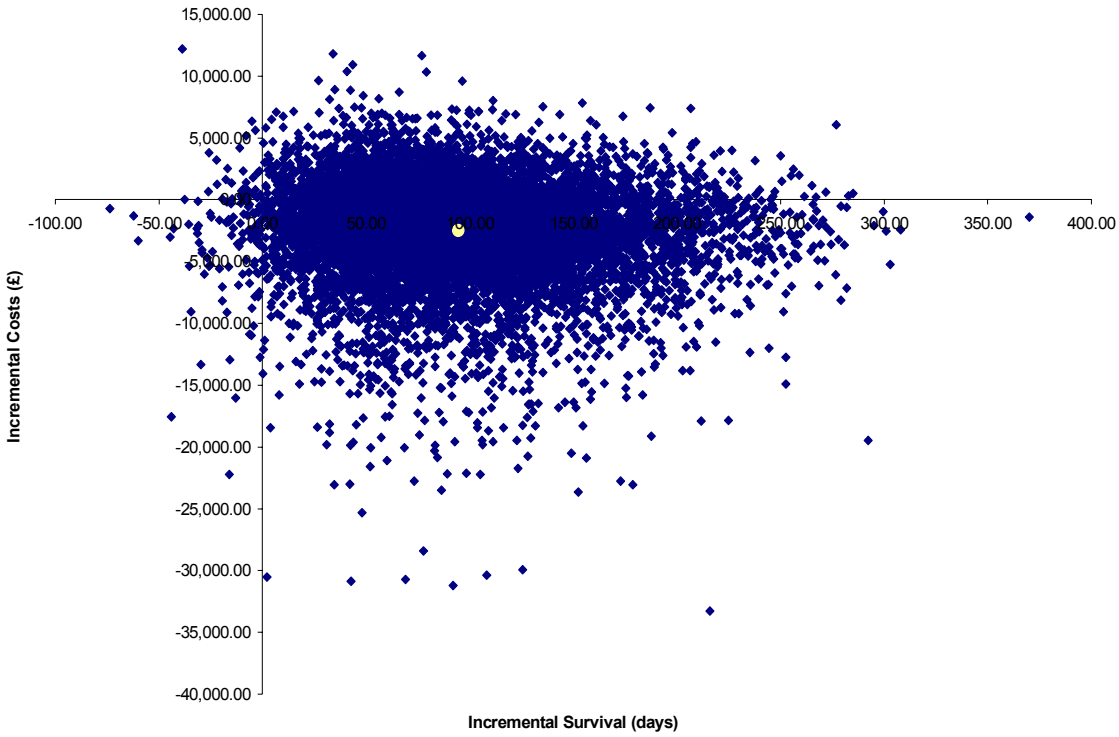


Figure 3a Cost-effectiveness plane for pre-operative optimisation vs standard treatment

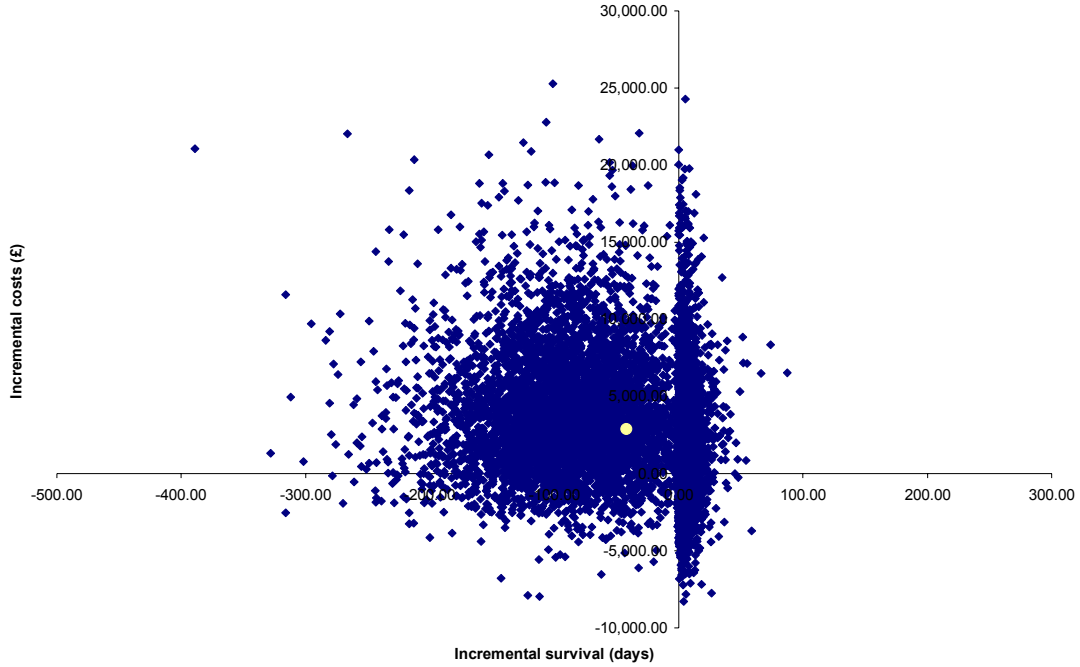


Figure 3b **Cost-effectiveness plane for pre-operative optimisation with adrenaline vs pre-operative optimisation with dopexamine**

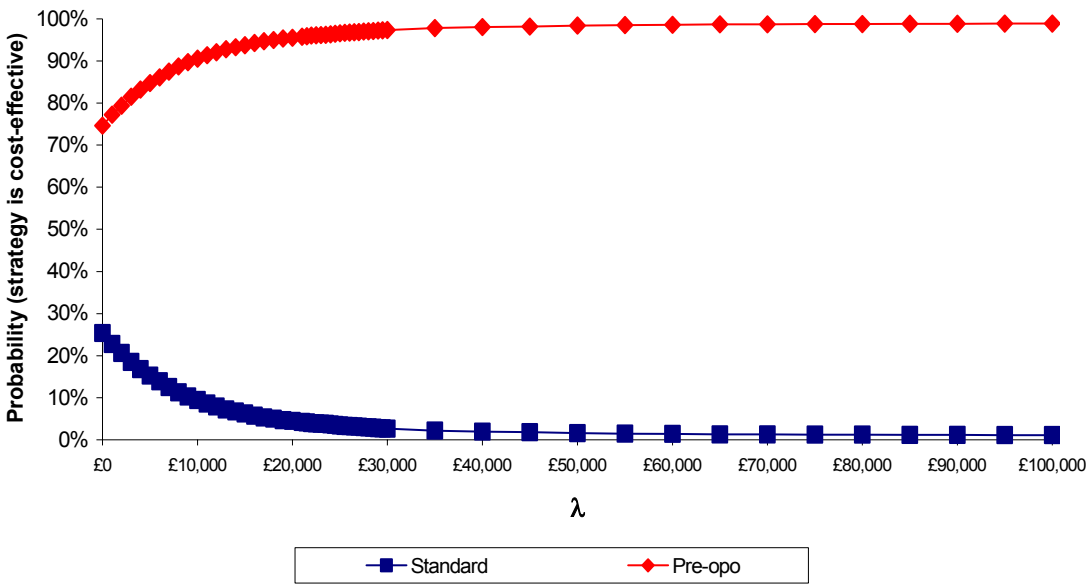


Figure 4a **Cost-effectiveness acceptability curves showing the probability that pre-operative optimisation (either inotrope) is optimal, compared with standard patient management, for a given willingness to pay for an additional life year (λ)**

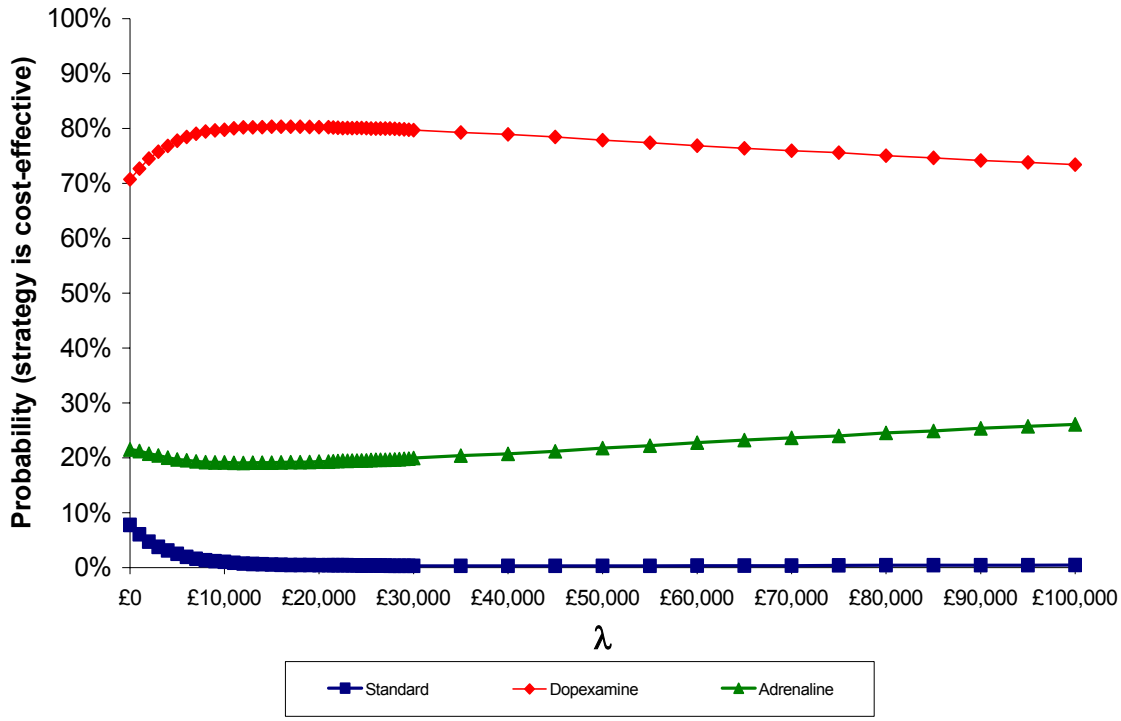


Figure 4b **Cost-effectiveness acceptability curves showing the probability that each strategy is cost-effective, for a given willingness to pay for an additional life year (λ)**

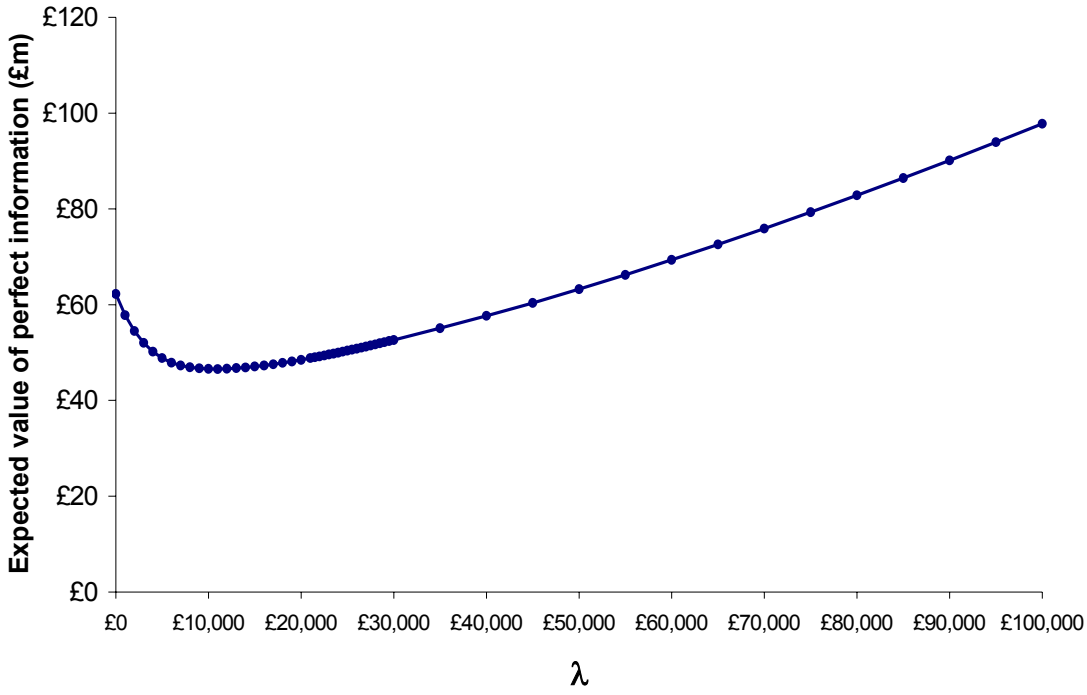


Figure 5 **Expected value of perfect information for the decision between three patient management strategies – £ population**

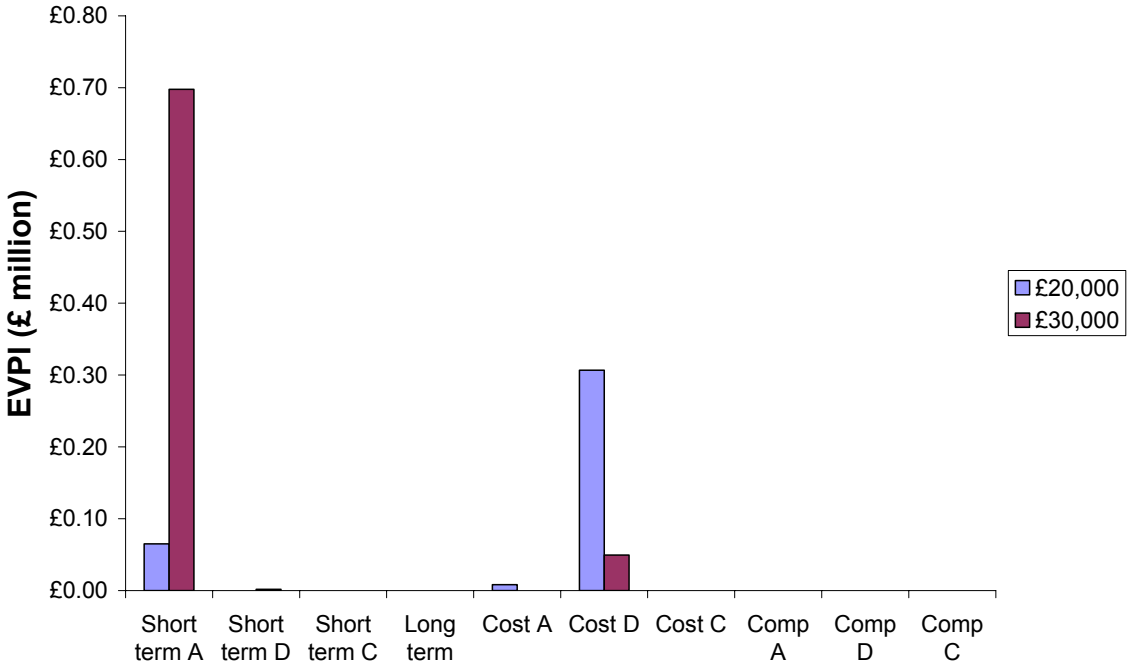


Figure 6 **Population expected value of perfect information for specific parameters of the decision at λ = £20k and £30k - £ million**

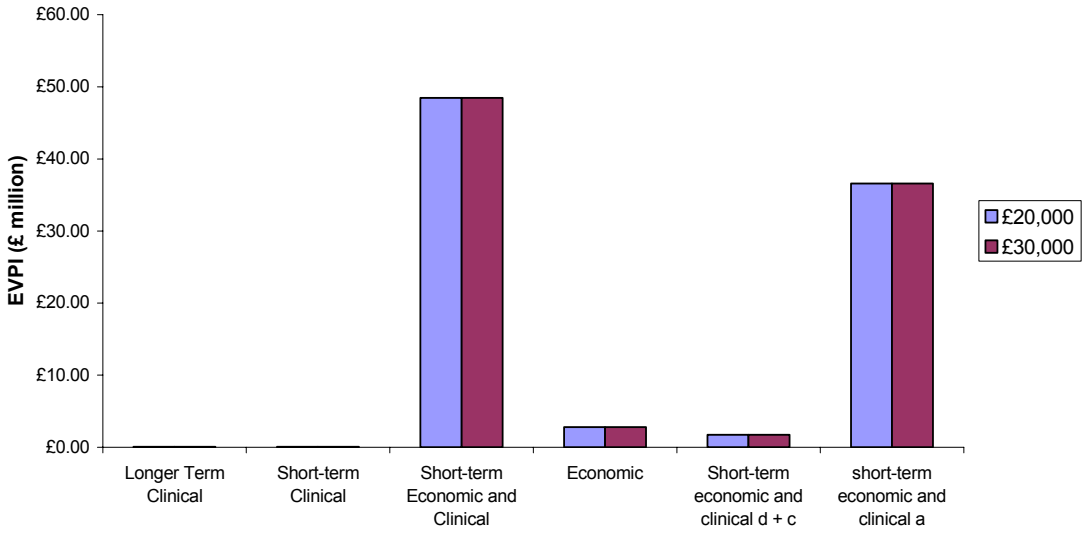


Figure 7 Population expected value of perfect information for particular types of trials λ = £20k and £30k - £ million

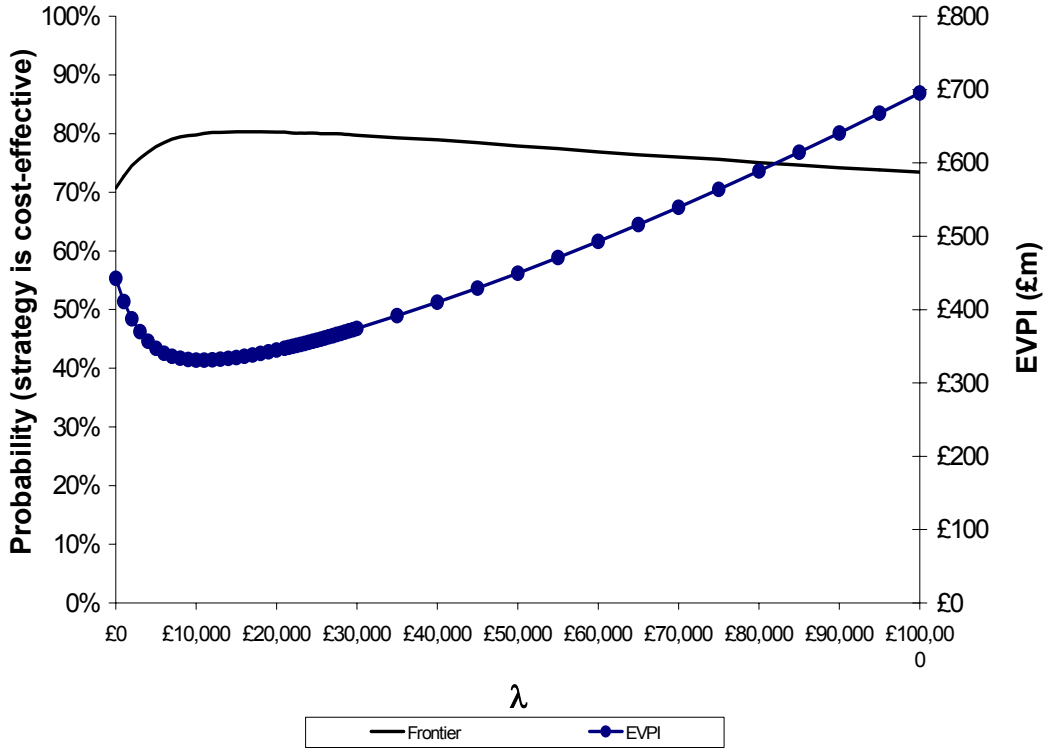
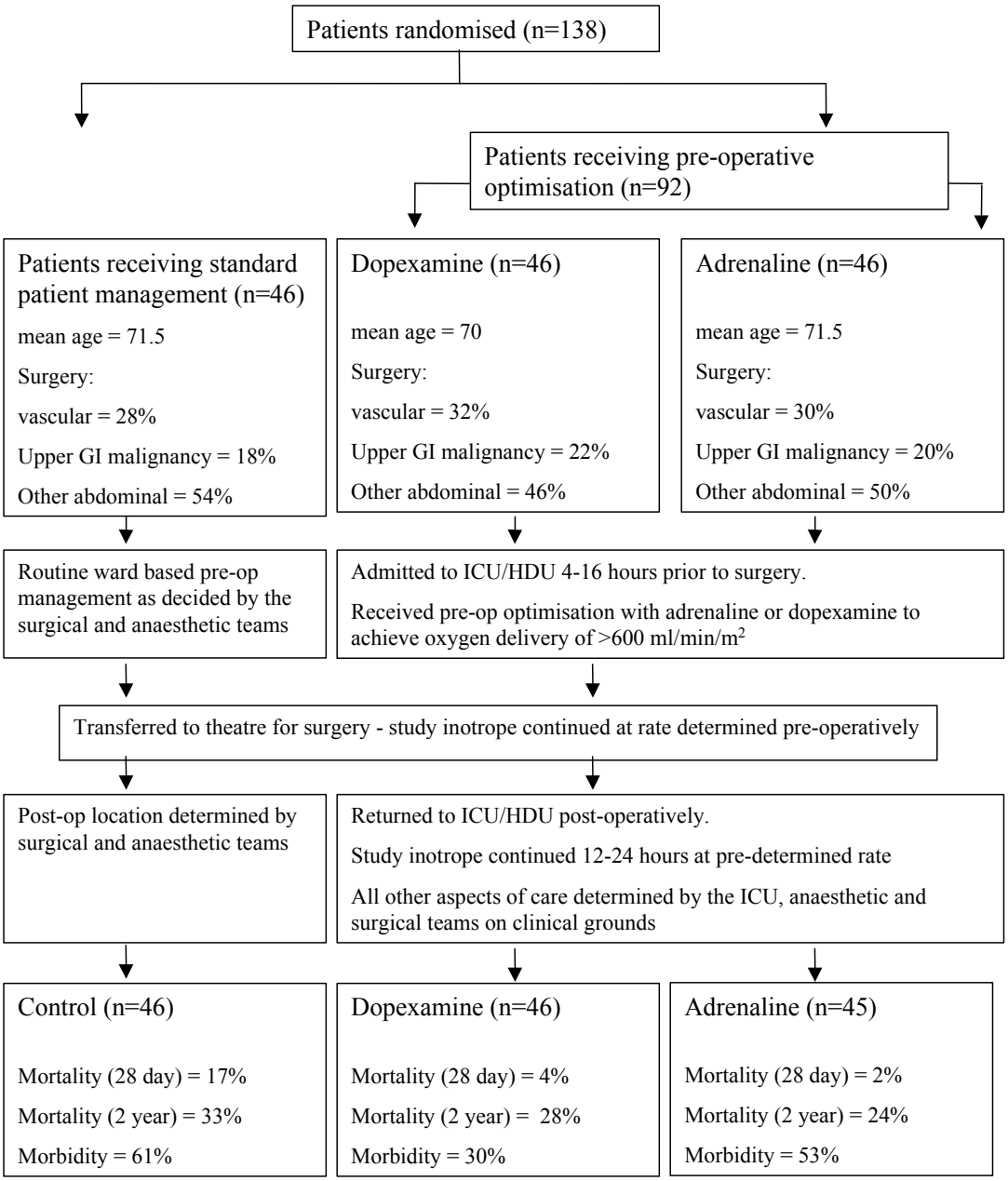


Figure 8 EVPI (per surgical procedure) vs CEAcc frontier



Morbidity is defined as the % of patients developing one or more of a predefined range of complications.

Figure 9 Patient flows through the study

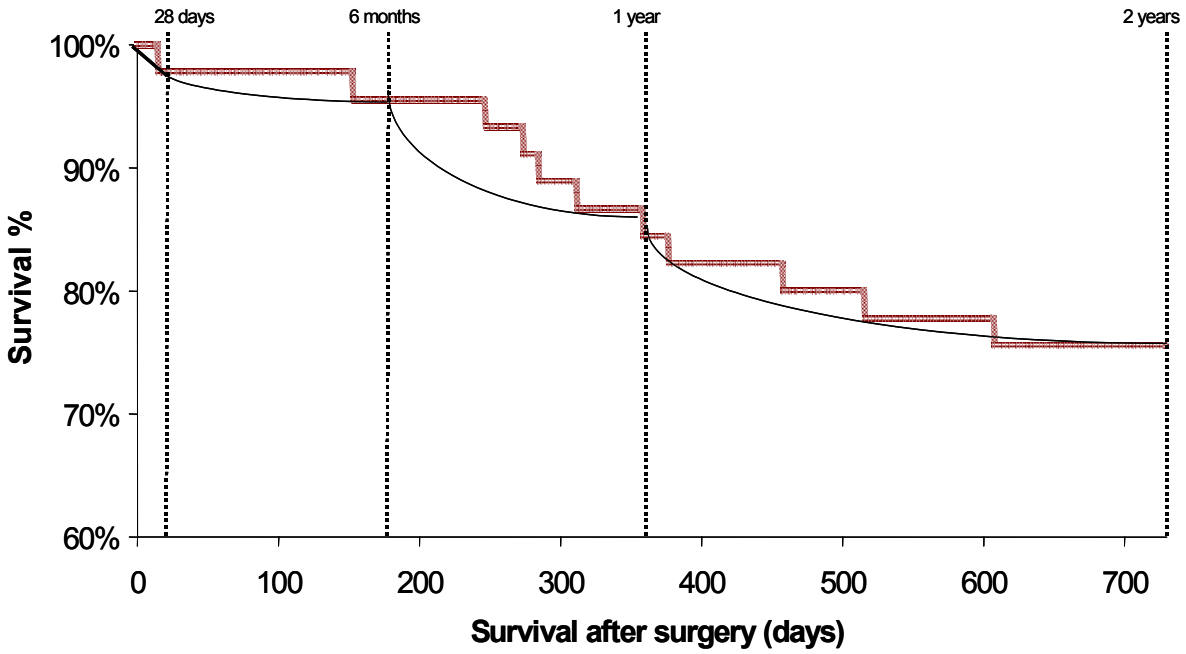


Figure 10 Estimation of Piecewise exponential

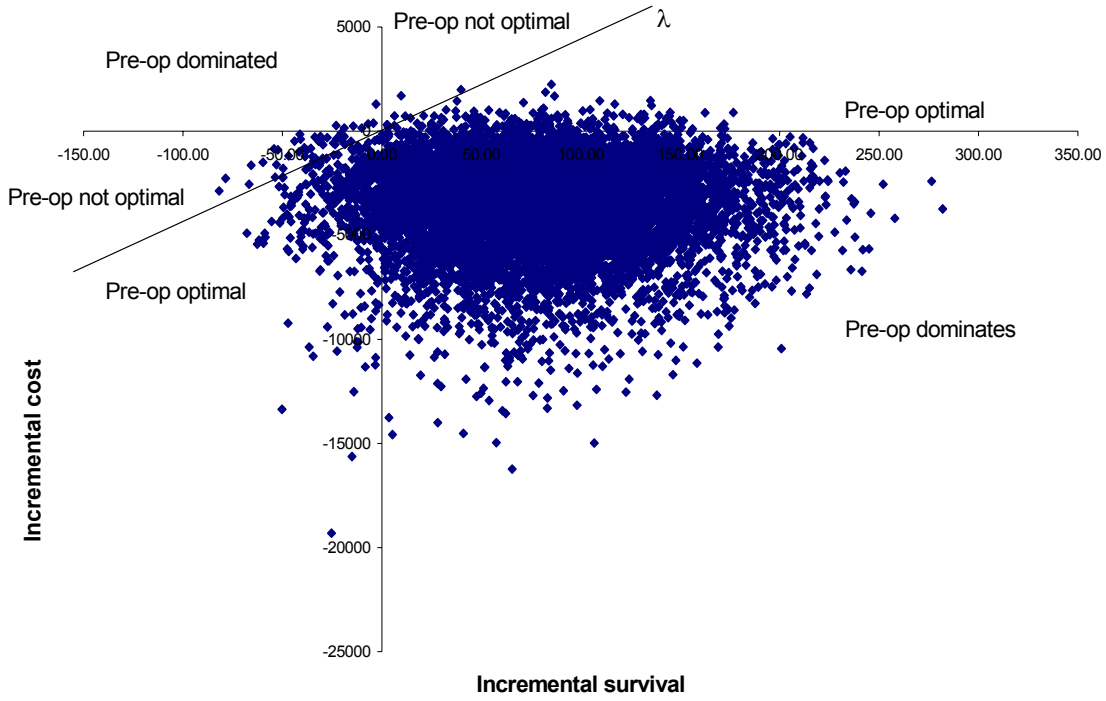


Figure 11a Cost-effectiveness plane for pre-operative optimisation vs Standard treatment

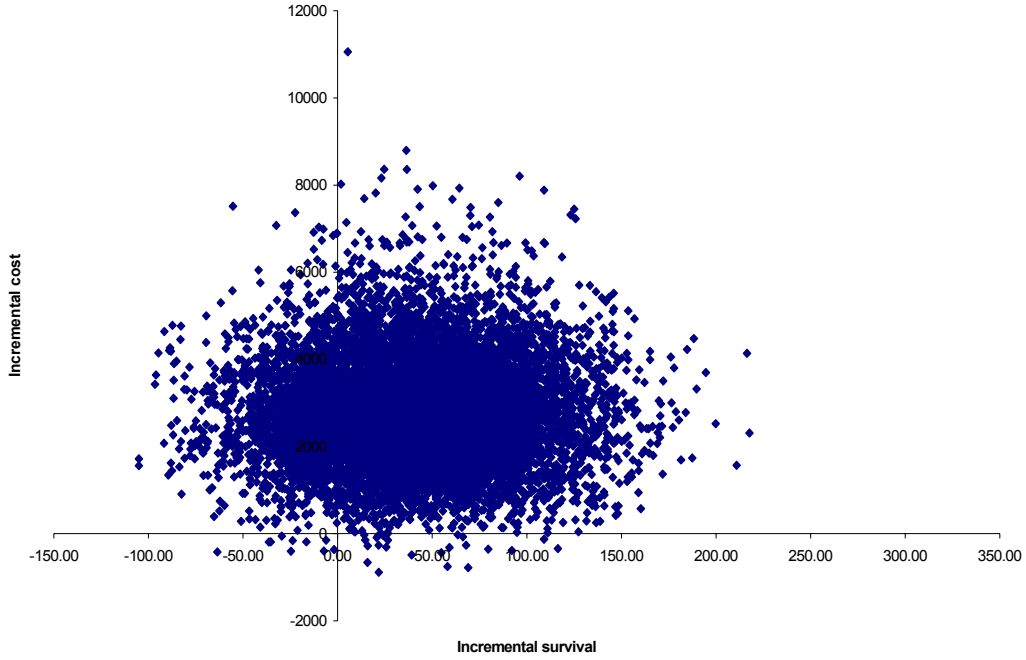


Figure 11b Cost-effectiveness plane for pre-operative optimisation with adrenaline vs pre-operative optimisation with dopexamine

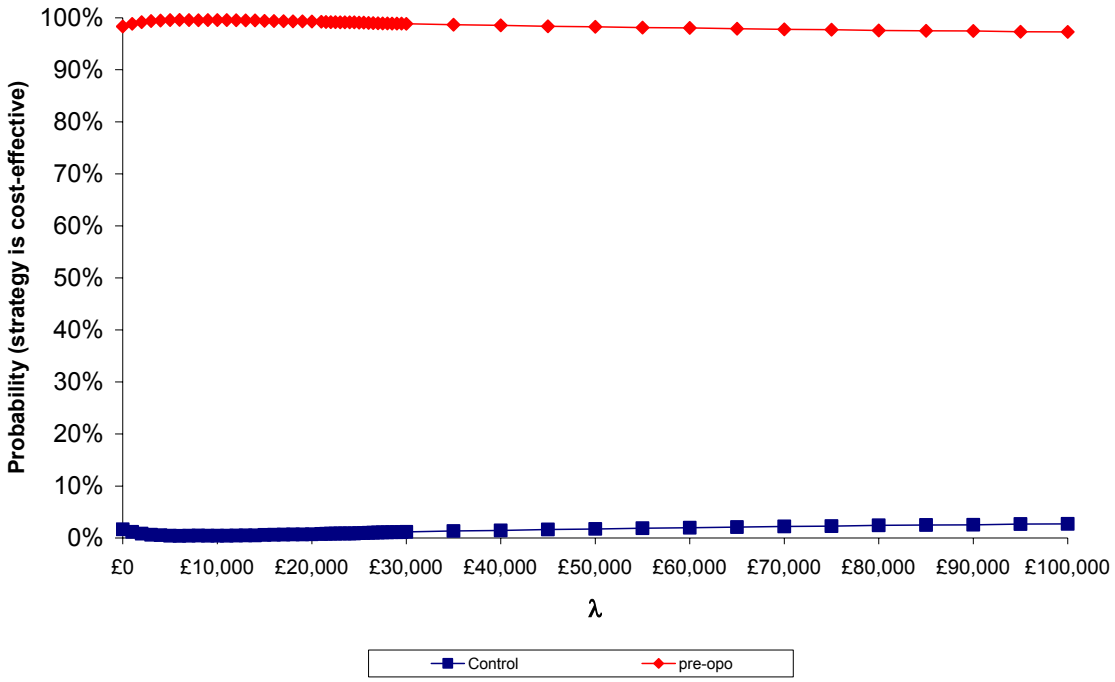


Figure 12a **Cost-effectiveness acceptability curves for the decision between pre-operative optimisation (either inotrope) compared with standard patient management**

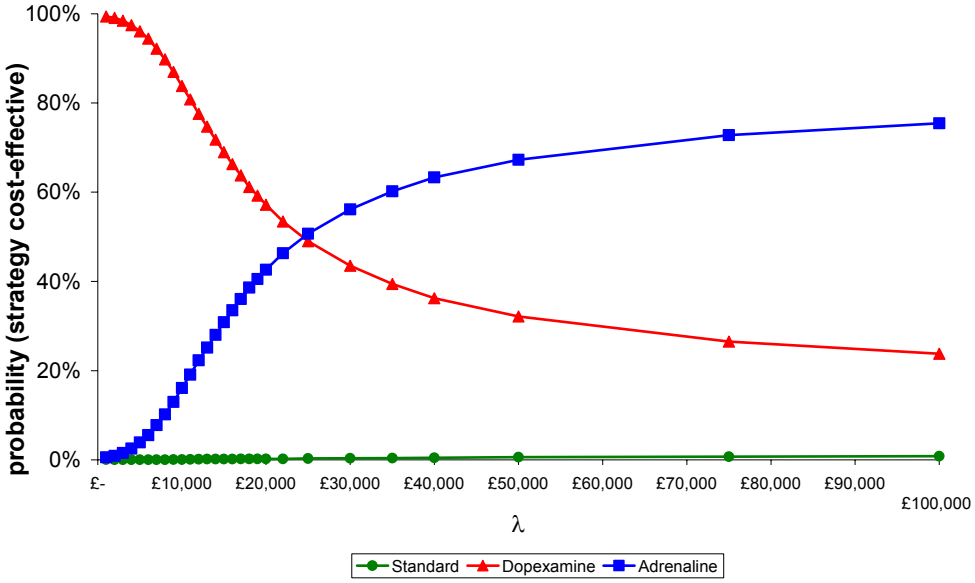


Figure 12b **Cost-effectiveness acceptability curves for the choice between the three methods of patient management strategies.**

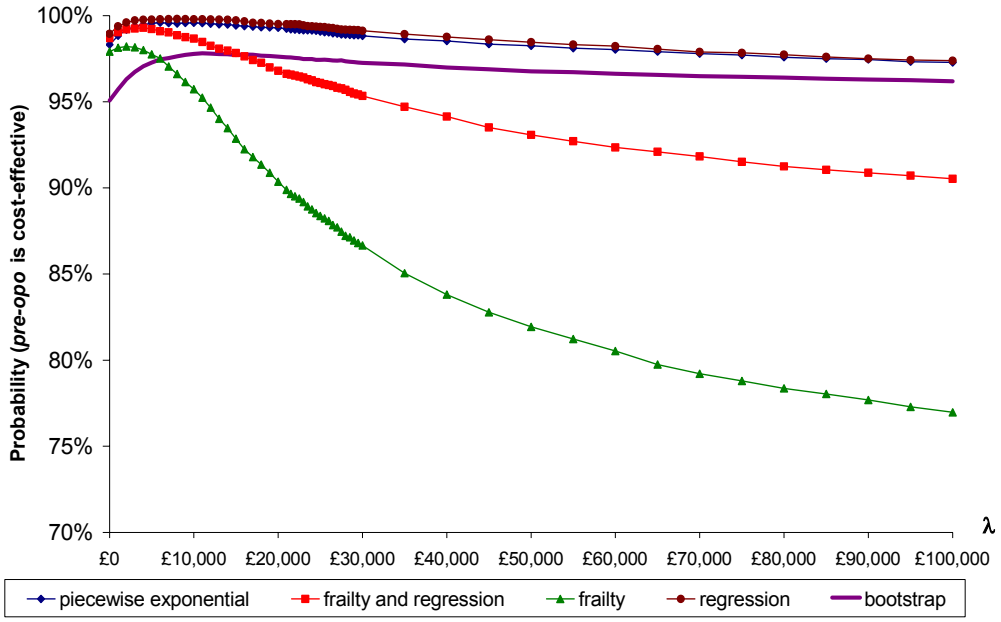


Figure 13 **Cost-effectiveness acceptability curves for *pre-opo* for the different models and the Frequentist analysis**

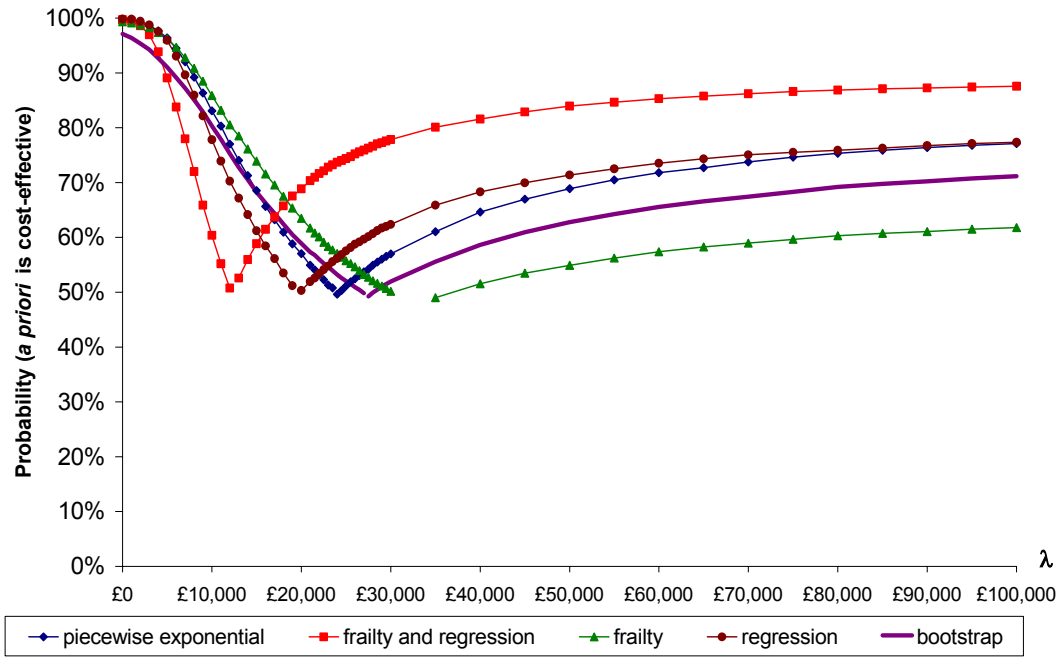


Figure 14 **Cost-effectiveness acceptability frontiers for the choice between the three methods of patient management for the different models and the Frequentist analysis**

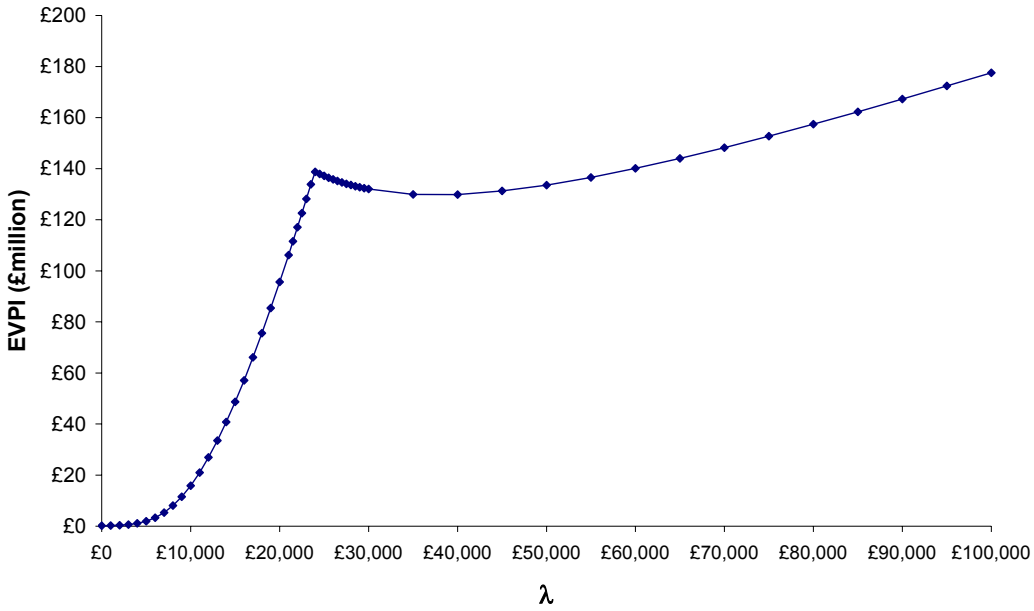


Figure 15 Expected value of perfect information for the decision between three patient management strategies – £ population

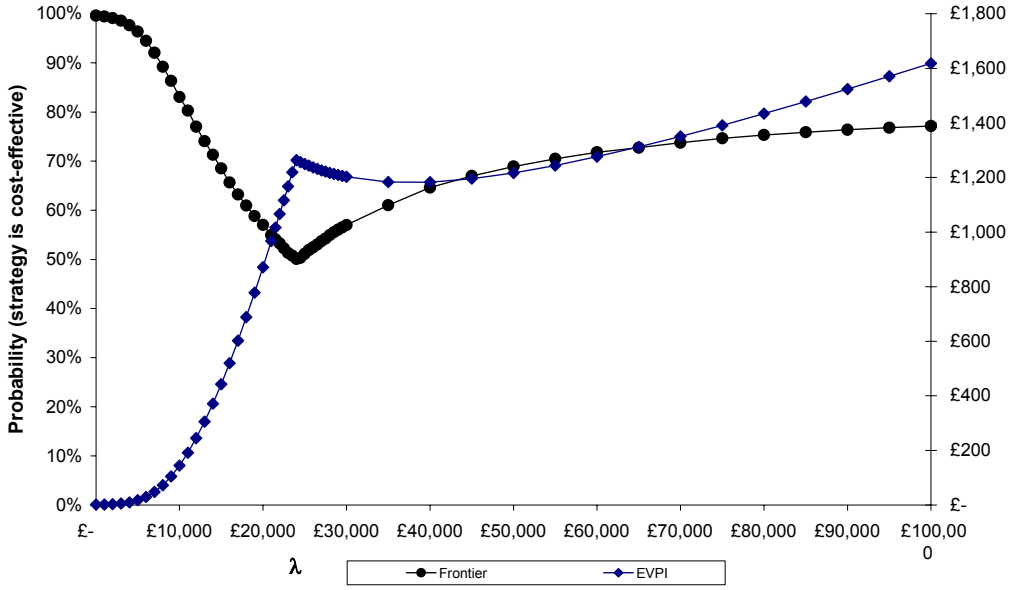


Figure 16 EVPI (per surgical procedure) vs CEAcc frontier

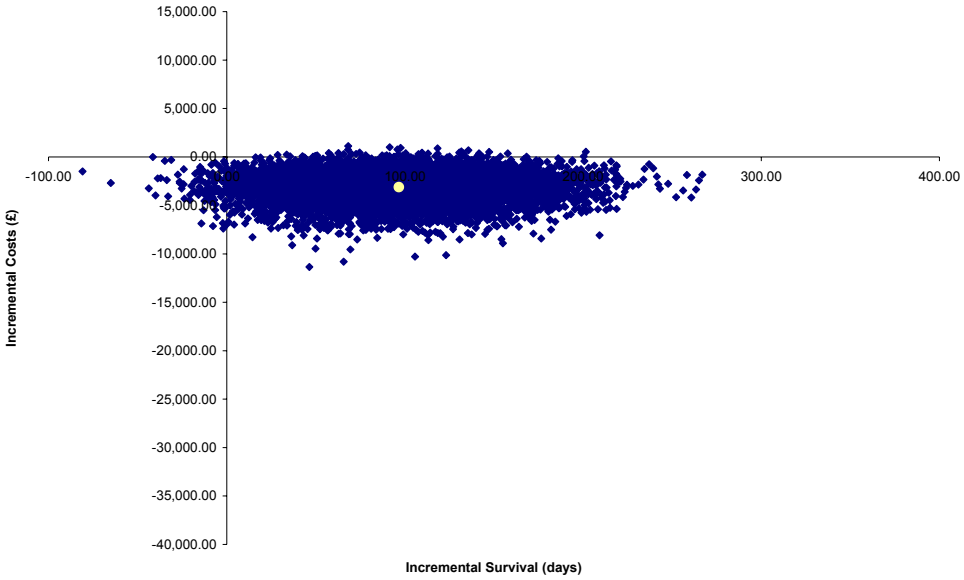


Figure 17a: Cost-effectiveness plane for pre-operative optimisation vs Standard treatment

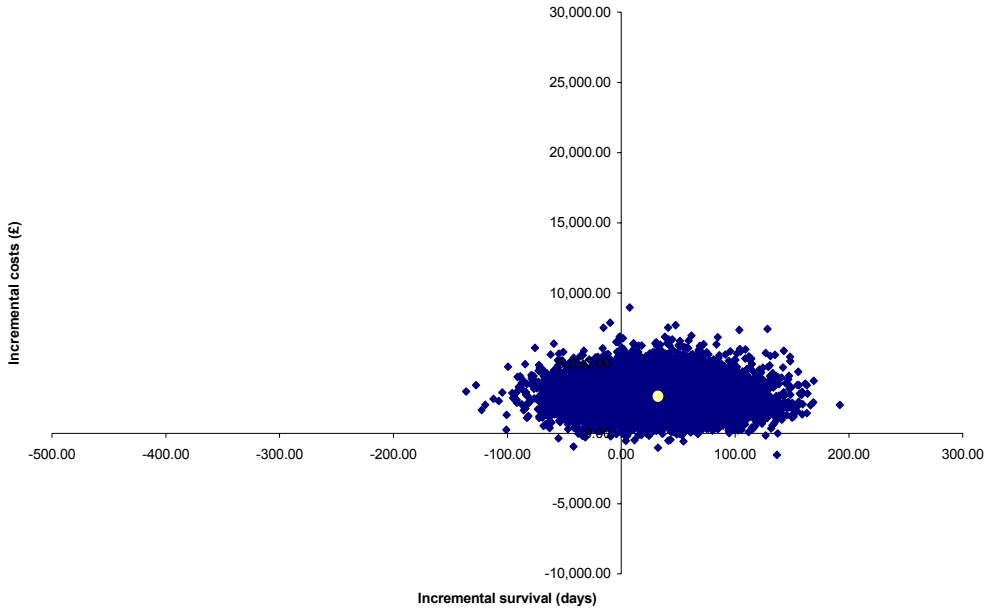


Figure 17b: Cost-effectiveness plane for pre-operative optimisation with adrenaline vs pre-operative optimisation with dopexamine

Figure 18a: Cost-effectiveness acceptability curve showing the probability that pre-operative optimisation (either inotrope) is optimal, compared with standard patient management, for a given willingness to pay for an additional life-year (λ).

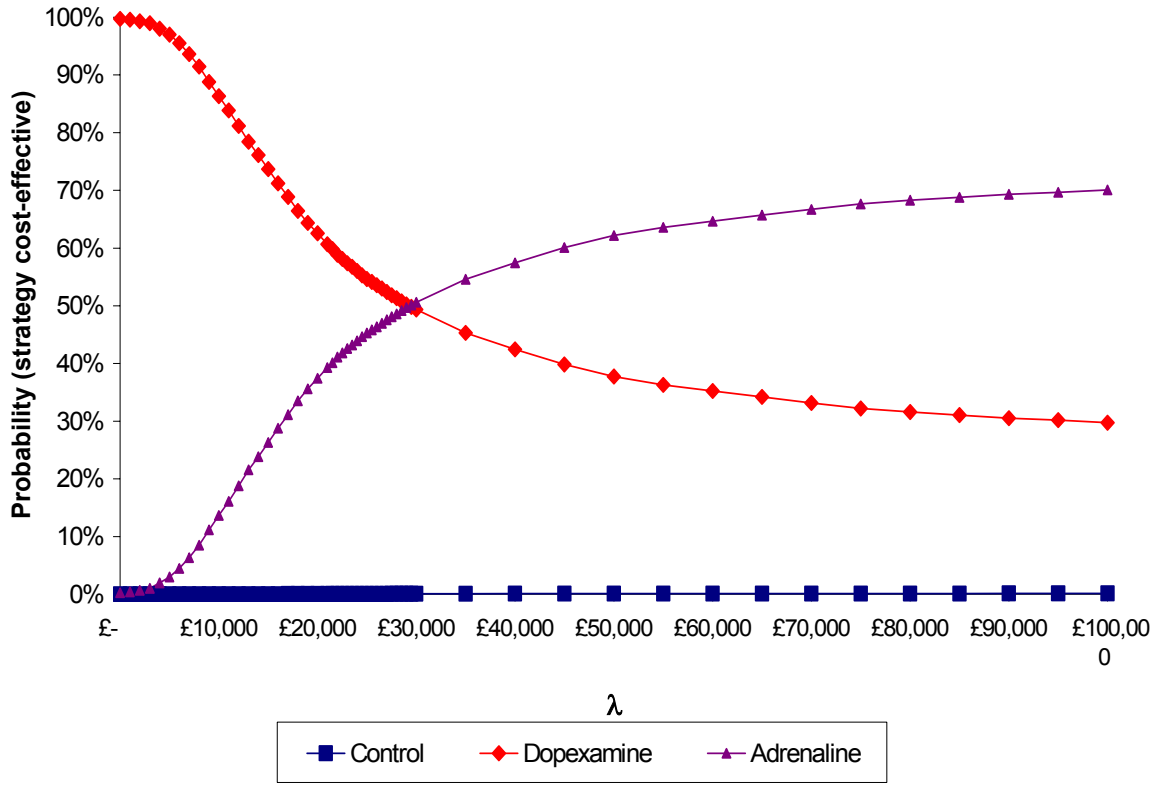


Figure 18b: Cost-effectiveness acceptability curves showing the probability that each management option is optimal for a given willingness to pay for an additional life-year (λ).

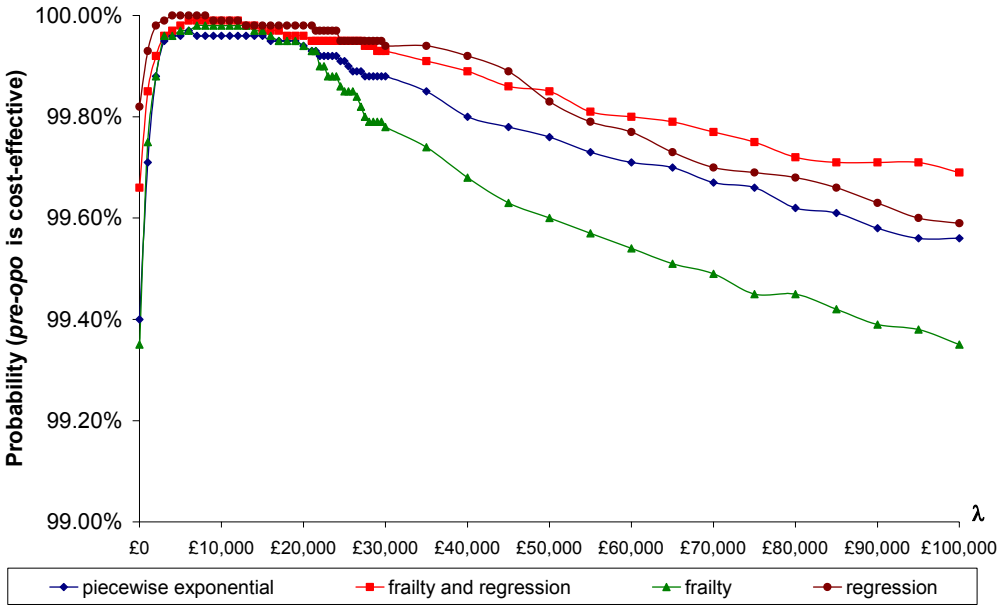


Figure 19 **Cost-effectiveness acceptability curves for *pre-opo* for the different WinBUGS models**

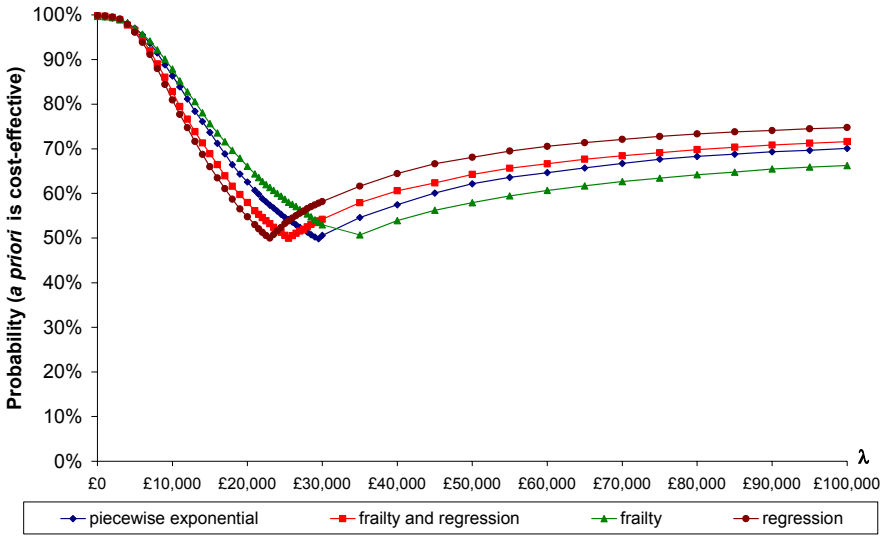


Figure 20 **Cost-effectiveness acceptability frontiers for the choice between the three methods of patient management for the different WinBUGS models**

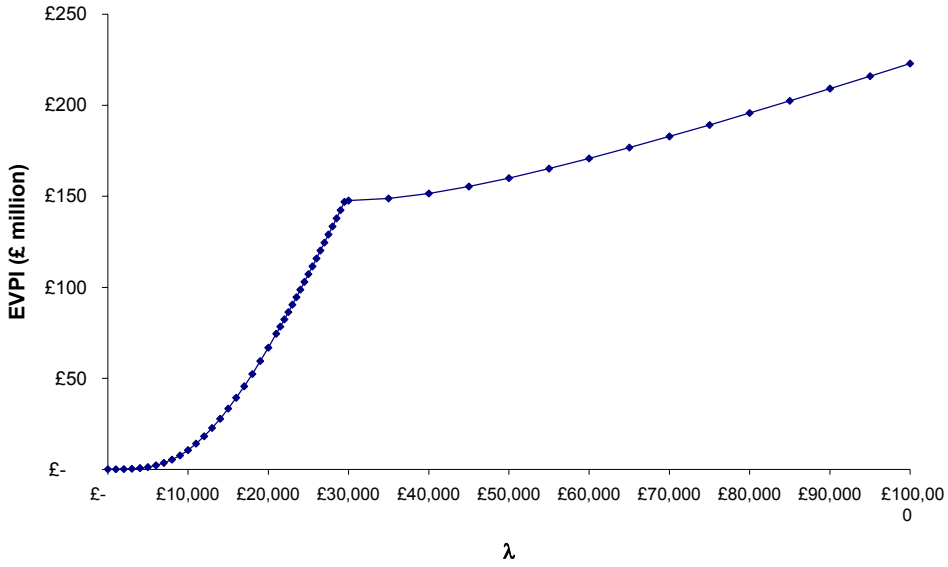


Figure 21: Expected value of perfect information for the decision between three patient management strategies – £ population

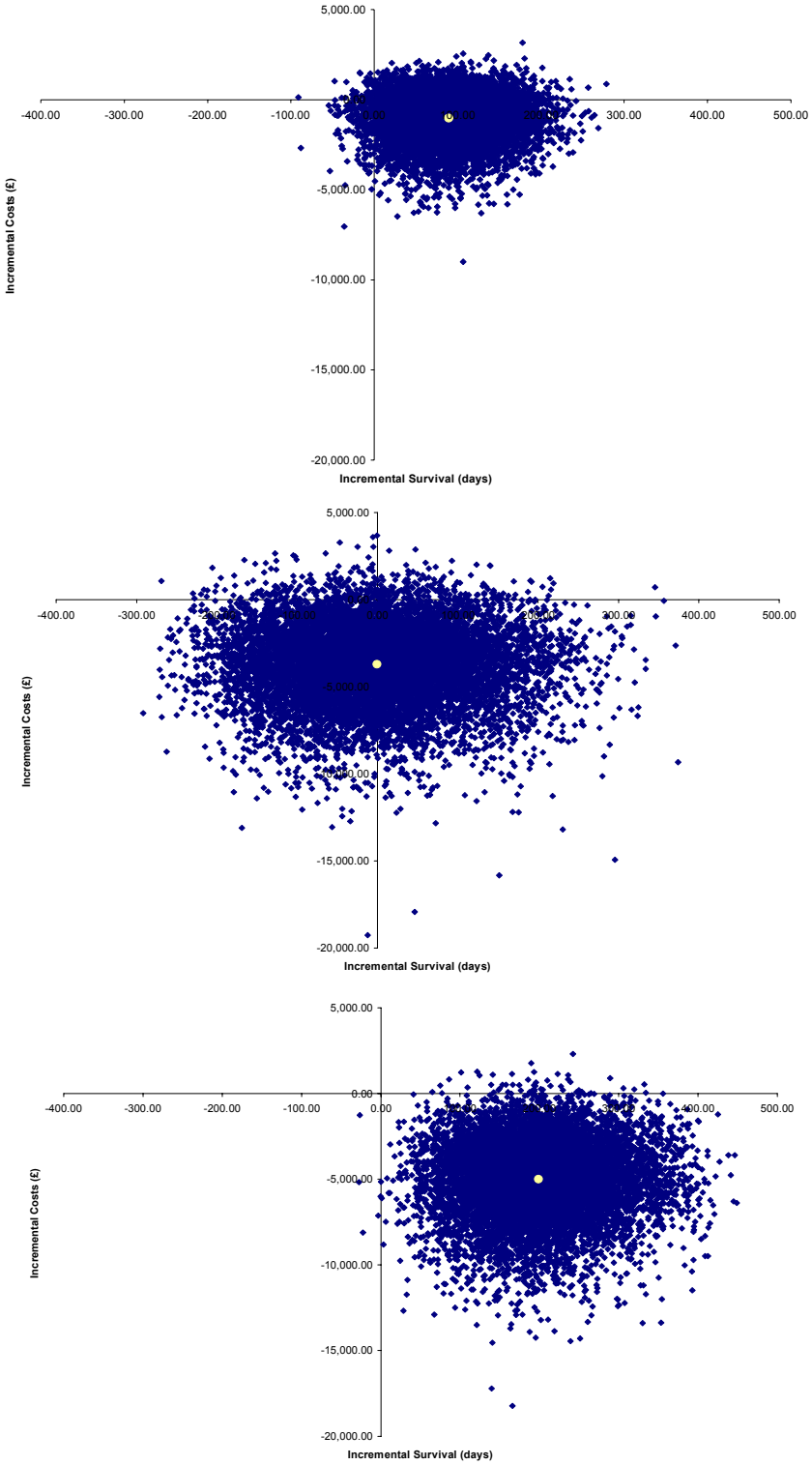


Figure 22: Cost-effectiveness planes for pre-operative optimisation vs standard treatment – a) Other abdominal b) Upper GI malignancy c) Vascular

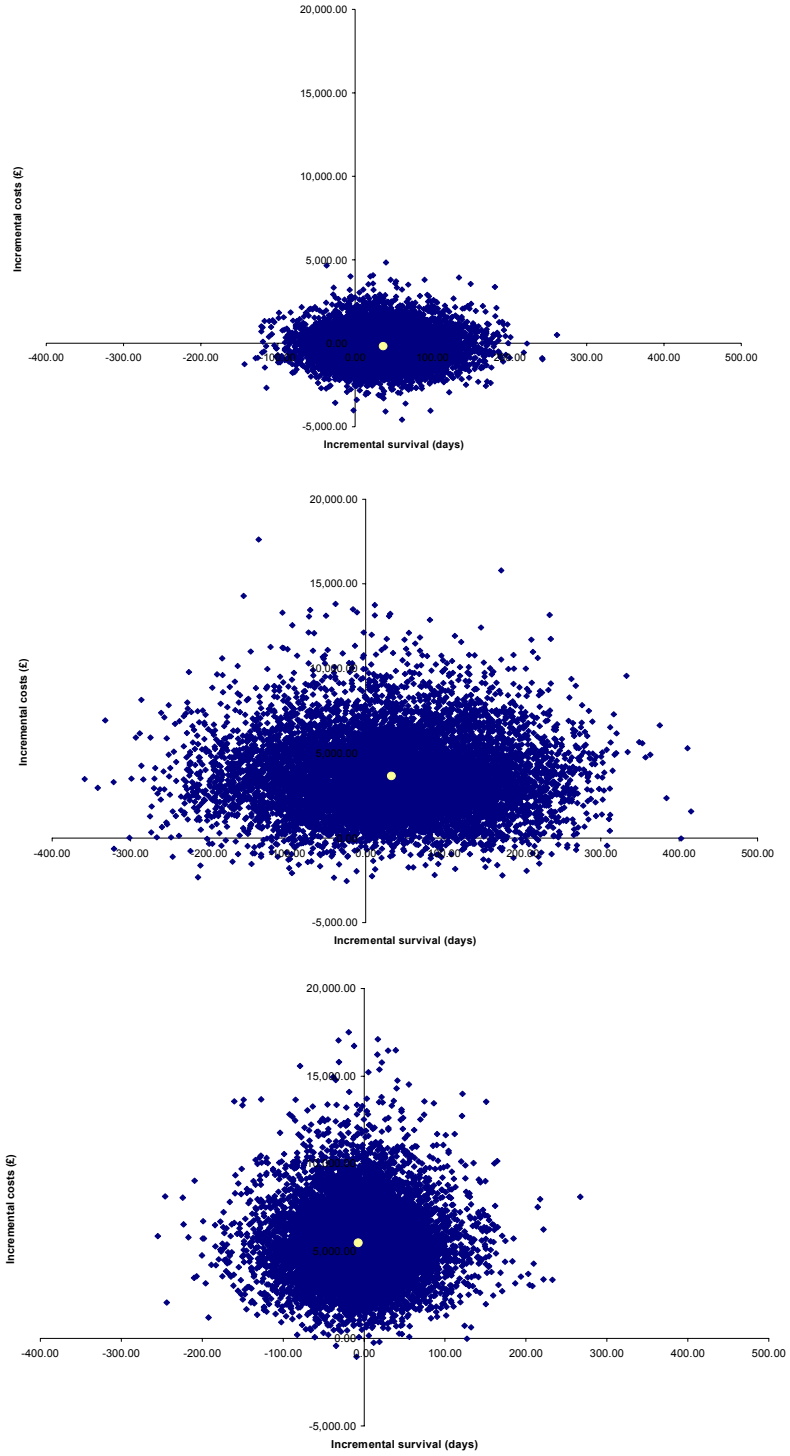


Figure 23: Cost-effectiveness planes for pre-operative optimisation with adrenaline vs pre-operative optimisation with dopexamine – a) Other abdominal b) Upper GI malignancy c) Vascular

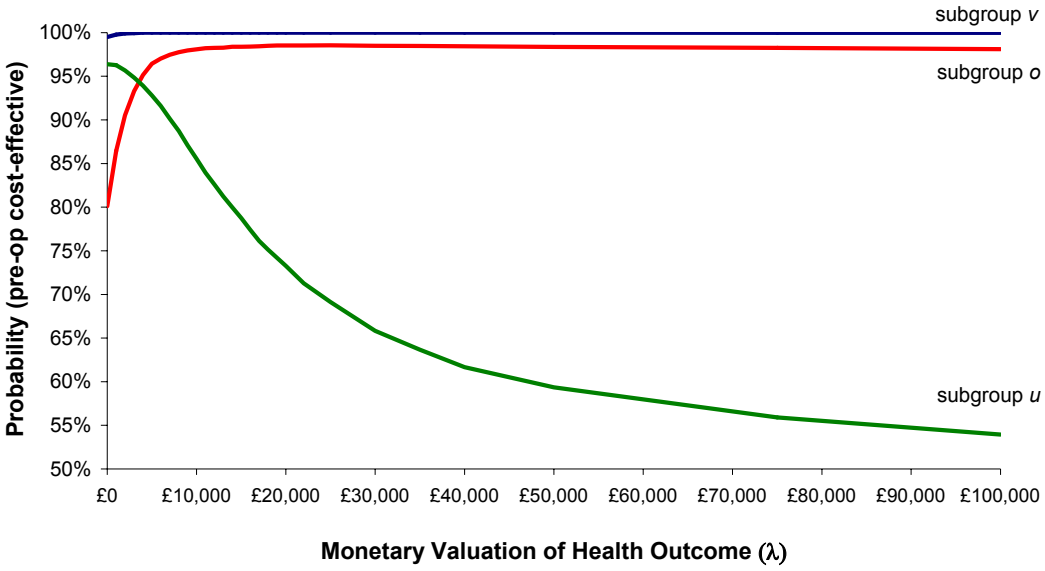


Figure 24: Cost-effectiveness acceptability curves for pre-opo vs standard patient management for each sub-group

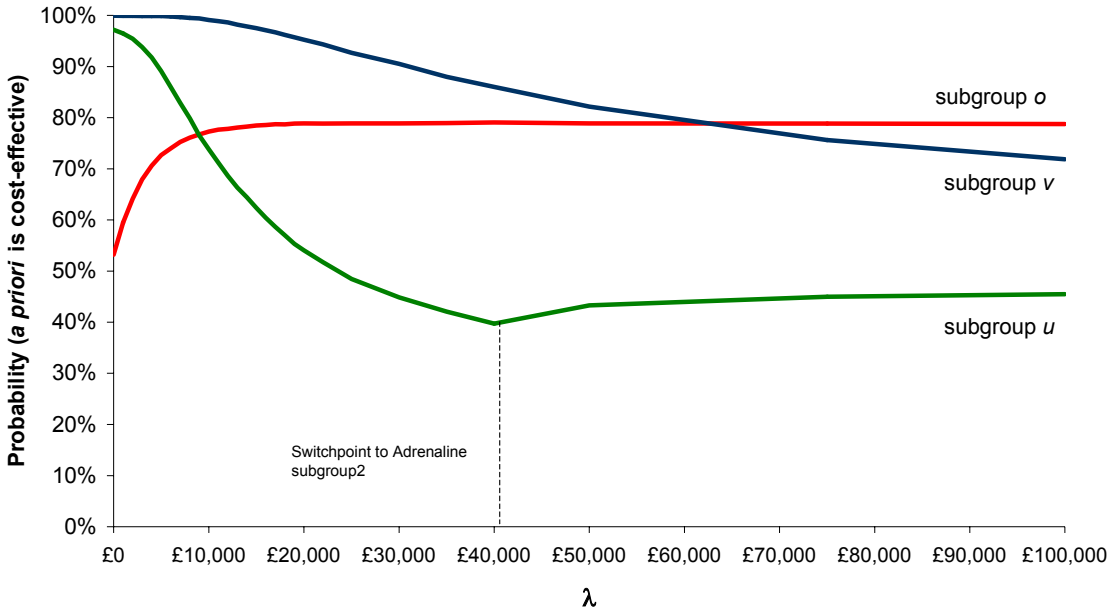


Figure 25: Cost-effectiveness acceptability frontiers for the choice between the three management strategies for each sub-group

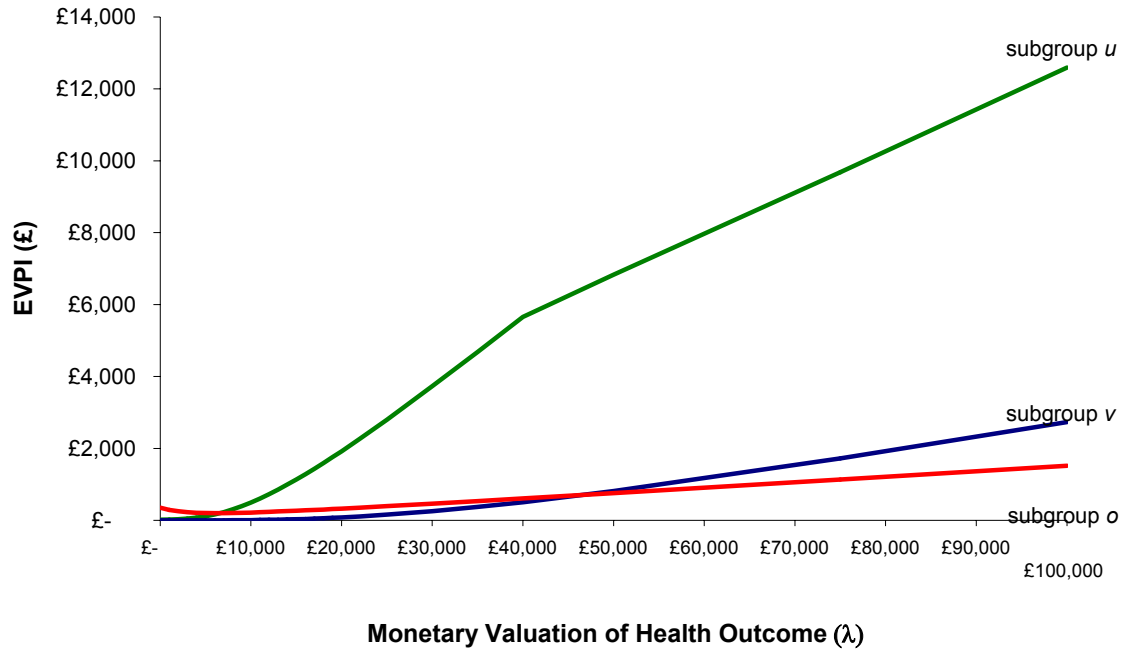


Figure 26: Expected value of perfect information for the decision between the three management strategies – per surgical procedure

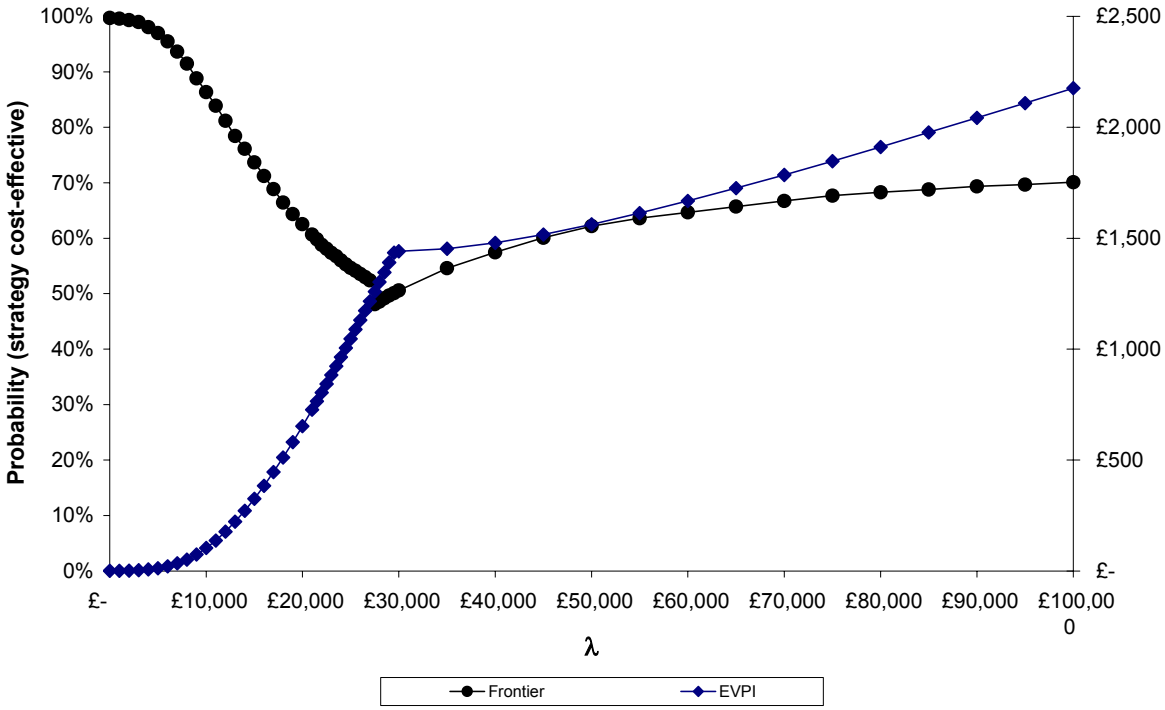


Figure 27 EVPI (per surgical procedure) vs CEAcc frontier

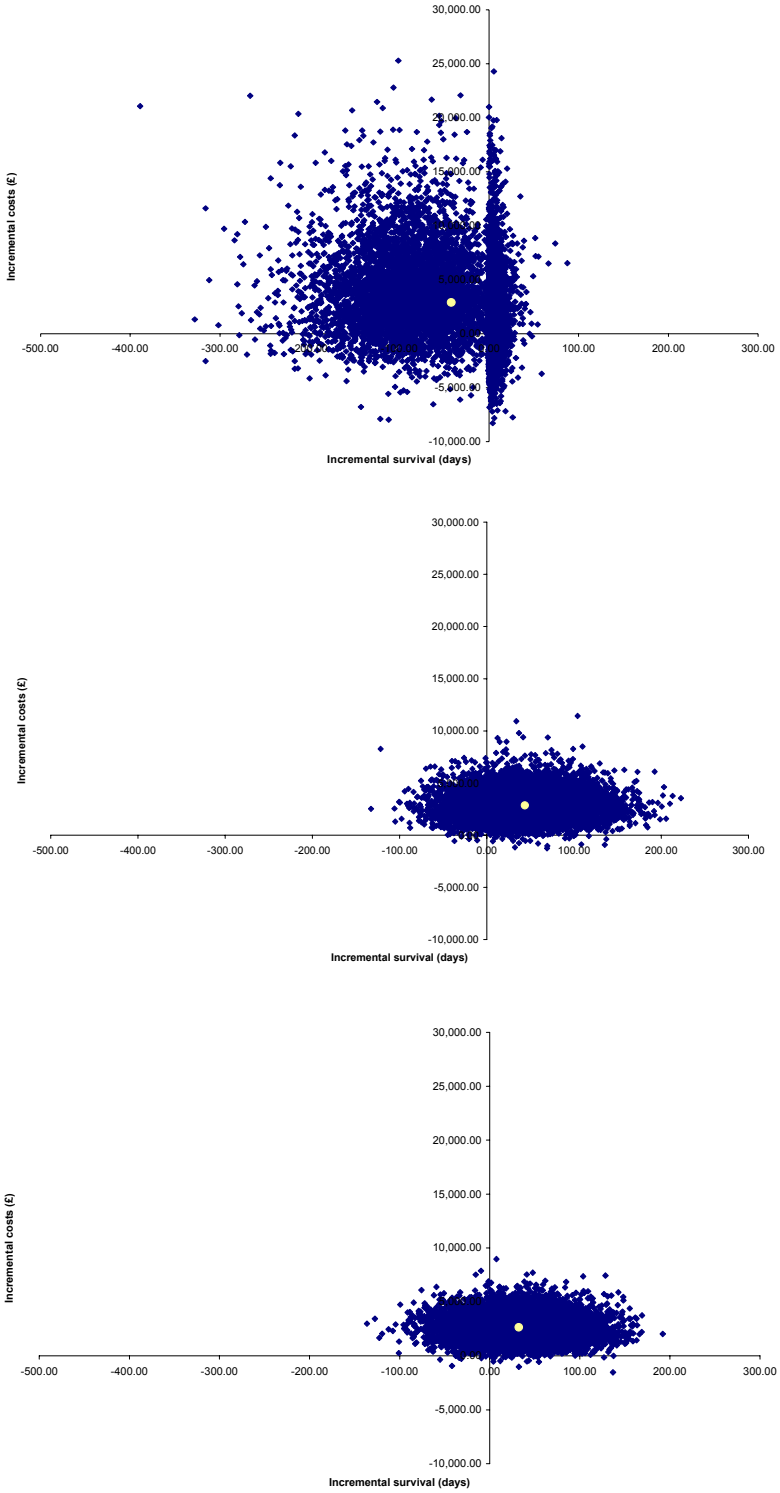


Figure 28: Cost-effectiveness planes for pre-operative optimisation with adrenaline vs pre-operative optimisation with dopexamine for each stage of the iterative framework

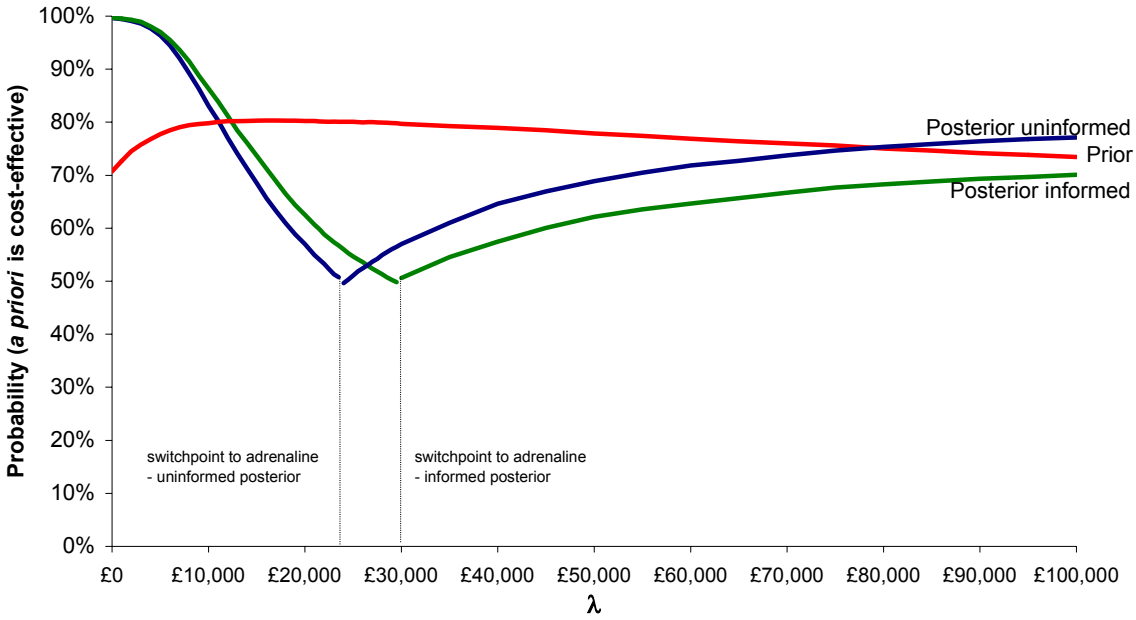


Figure 29: Cost-effectiveness acceptability frontiers for the choice between the three management strategies for each stage of the iterative framework

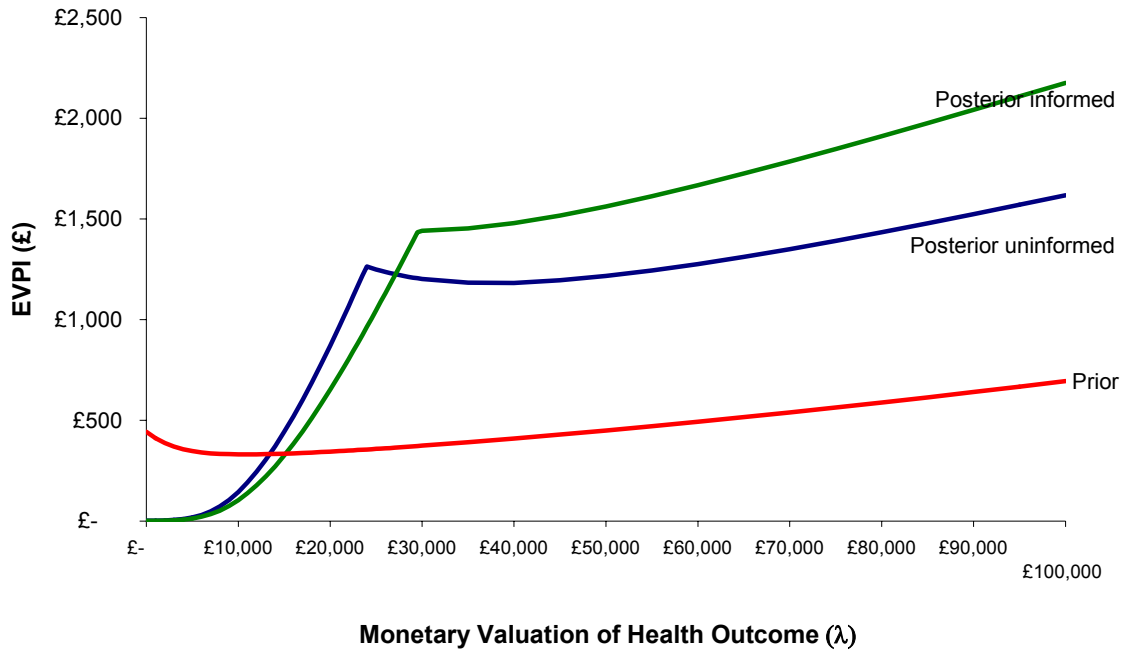


Figure 30: Expected value of perfect information for the decision between the three management strategies for each stage of the iterative framework - per surgical procedure

References

Berry, D. A. and Stangl, D. K. Bayesian methods in health related research. Berry, D. A. and Stangl, D. K. Bayesian Biostatistics. 96. Marcel Dekker Inc.

Bland, R.D., Shoemaker, W.C. and Shabbot, M.M. (1978) Physiologic monitoring goals for the critically ill patient. *Surg Gynecol Obstet* **147**, 833-841.

Boyd, A.D., Tremblay, R.E., Spencer, F.C. and Bahnson, H.T. (1959) Estimation of cardiac output soon after intracardiac surgery with cardiopulmonary bypass. *American Surgery* **150**, 613-626.

Boyd, O., Grounds, R.M. and Bennett, E.D. (1993) A randomised clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *JAMA* **270**, 2699-2707.

Briggs, A.H. and Gray, A. (1998) The distribution of health care costs and their statistical analysis for economic evaluation. *Journal of Health Services Research and Policy* **3** , 233-245.

British National Formulary (2000) London : British Medical Association Pharmaceutical Press [of the Pharmaceutical Society of Great Britain].

Claxton, K. (1999) The irrelevance of inference: a decision making approach to the stochastic evaluation of health care technologies. *Journal of Health Economics* **18**, 341-364.

Claxton, K. and Posnett, J. (1996) An economic approach to clinical trial design and research priority setting. *Health Economics* **5**, 513-524.

Drummond, M. F., O'Brien, B. J., Stoddart, G. L., and Torrance, G. W. Methods for the Economic Evaluation of Health Care Programmes. 1997. New York, Oxford University Press.

Fenwick, E., Claxton, K. and Sculpher, M. (2001) Representing uncertainty: The role of cost-effectiveness acceptability curves. *Health Economics Letters* **10**, 779-787.

Fryback, D.G., Chinnis, J.O. and Ulviva, J.W. (2001) Bayesian cost-effectiveness analysis. An example using the GUSTO trial. *International Journal of Technology Assessment in Health Care* **17**, 83-97.

Gelman, Carlin, Stern and Rubin (1995) Bayesian Data Analysis. Great Britain: Chapman & Hall.

Guest, J.F., Boyd, O., Hart, W.M., Grounds, R.M. and Bennett, E.D. (1997) A cost analysis of a treatment policy of a deliberate perioperative increase in oxygen delivery in high risk surgical patients. *Intensive Care Med* **23**, 85-90.

Karlsson, G. and Johannesson, M. (1996) The decision rules of cost-effectiveness analysis. *PharmacoEconomics* **9**, 113-120.

Office for National Statistics (1998) Monitor: Population and Health. MB1. London: HMSO.

Phelps, C.E. and Mushlin, A.I. (1988) Focusing technology assessment using medical decision theory. *Medical Decision Making* **8**, 279-289.

Rubin, D.B. (1981) The Bayesian Bootstrap. *The annals of statistics* **9**, 130-134.

Shoemaker, W.C., Appel, P.L., Kram, H.B., Waxman, K. and Lee, T. (1988) Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest* **94**, 1176-1186.

Spiegelhalter, D.J., Myles, J.P., Jones, D.R. and Abrams, K.R. (2000) Bayesian mehods in health technology assessment: a review. *Health Technology Assessment* **4**,

Stinnett, A.A. and Mullahy, J. (1998) Net Health Benefits: A new framework for the analysis of uncertainty in cost-effectiveness analysis. *Medical Decision Making* **18 Supplement**, S68-S80

Tambour, M., Zethraeus, N. and Johannesson, M. (1998) A note of confidence intervals in cost-effectiveness analysis. *International Journal of Technology Assessment in Health Care*

14, 467-471.
Wilson, J., Woods, I., Fawcett, J., Whall, R., Morris, C. and McManus, E. (1999) Reducing the risk of major elective surgery: randomised controlled trial of preoperative optimisation of oxygen delivery. *BMJ* **318**, 1099-1103.