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Review

Handling uncertainty when performing economic evaluation of healthcare interventions

AH Briggs
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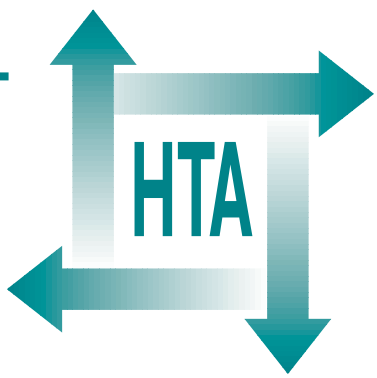
Health Technology Assessment
NHS R&D HTA Programme



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Handling uncertainty when performing economic evaluation of healthcare interventions

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NHS R&D HTA Programme

The overall aim of the NHS R&D Health Technology Assessment (HTA) programme is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS. Research is undertaken in those areas where the evidence will lead to the greatest benefits to patients, either through improved patient outcomes or the most efficient use of NHS resources.

The Standing Group on Health Technology advises on national priorities for health technology assessment. Six advisory panels assist the Standing Group in identifying and prioritising projects. These priorities are then considered by the HTA Commissioning Board supported by the National Coordinating Centre for HTA (NCCHTA).

This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care. It was identified as a priority by the Methodology Panel and funded as project number 93/48/07.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The editors have tried to ensure the accuracy of this report but cannot accept responsibility for any errors or omissions. They would like to thank the referees for their constructive comments on the draft document.

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Contents

List of abbreviations

CABG	coronary artery bypass graft*
CAPD	continuous ambulatory peritoneal dialysis
CRD	Centre for Reviews and Dissemination
CS	coefficient of sensitivity
CT	computerised tomography
DALY	disability-adjusted life-year
ERCP	endoscopic retrograde cholangiopancreatography
ESWL	extracorporeal shock wave lithotripsy
HEED	Health Economic Evaluations Database
HTLV	human T-lymphotrophic virus
HYE	healthy year equivalent
ICD	implantable cardioverter–defibrillator*
ICD-9	*International Classification of Diseases,* 9th edition
ICER	incremental cost-effectiveness ratio
IFPMA	International Federation of Pharmaceutical Manufacturers' Associations
MAUS	Multi Attribute Utility Scale
MeSH	medical subheading
NHP	Nottingham Health Profile
OHE	Office of Health Economics
PWFA	pain walking function activity
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RFA	radiofrequency ablation
SA	scenario analysis
SF36	Short Form (36-item) Questionnaire
SG	standard gamble
SSCI	Social Science Citation Index
TTO	time trade-off
VAS	visual analogue scale

* Used only in tables and figures

Executive summary

Aims

- To perform a structured review of the way in which uncertainty has been handled in economic evaluation.
- To assemble data on the actual distributional form and variance of healthcare costs, and to devise guidelines to improve current practice. In particular, the focus was on the handling of cost and cost-effectiveness data.

Methods

The structured review was conducted at a number of different levels, reflecting the detail of the review process. At a general level, a search of the literature was undertaken to identify published economic evaluation studies that reported results in terms of cost per life-year or cost per quality-adjusted life-year values. This form of study was chosen as it is the results of these studies that are commonly grouped together and reported in cost-effectiveness league tables. Articles meeting the search criteria were reviewed using a review proforma designed to collect summary information on each study. These results were then entered as key words into a database, to allow interrogation and cross-referencing of the database by category.

This overall data set was then employed to focus in on two specific areas of interest, using subsets of articles to perform more detailed reviews:

- All studies reporting UK results were identified from the wider group of articles. These studies were reviewed in detail, and information on the baseline cost-effectiveness results, the methods underlying those results, the range of results representing uncertainty and the number of previously published results quoted in comparison were entered into a relational database. By matching results by the methods employed using a retrospective application of a methodological 'reference case', a subset of results with improved comparability was identified, and a rank ordering of these results was then attempted. Where a range of values accompanied the baseline results, the implications of this uncertainty for the rank ordering was also examined.
- All studies which reported patient level cost data were identified from the overall database and reviewed in detail with respect to how they had reported the distribution and variance of healthcare costs. In addition, five available data sets of patient level cost data were examined in order to show how the healthcare costs in those data were distributed and to elucidate issues surrounding the analysis and presentation of healthcare cost differences.

Economic analyses are not simply concerned with costs but also with effects, with the cost-effectiveness ratio being the outcome of interest in most economic evaluations. Unfortunately, ratio statistics pose particular problems for standard statistical methods. In this report, a review of a number of proposed methods for estimating confidence limits for cost-effectiveness ratios when patient level data are available for both cost and effectiveness is presented.

Results

A total of 492 articles were found to match the search criteria, and were fully reviewed and entered into the database. Analysis of this database in terms of the method employed by analysts to handle uncertainty shows that the vast majority of studies use one-way sensitivity analysis methods only. Of some concern is that 17% of studies did not attempt any analysis to examine uncertainty, although there is weak evidence to show that this situation is improving.

Of these 492 studies, 60 reported results for the UK. From these UK studies, 548 baseline cost-effectiveness results were extracted relating to 106 methodological scenarios. Application of a retrospective 'reference case' gave a single methodological scenario for each article with 333 associated baseline results. These results were converted to a common cost base year, and rank ordered to give a comprehensive 'league table' of UK results. Of the 333 results, 61 had an associated full range of values to represent uncertainty. Alternative rankings based on the high or low values from this range showed that there could be considerable disruption

to the rank order based on the baseline point estimates only.

The review of patient level cost data showed that 53 of the 492 studies in the database had patient level cost data and that just 15 of these had reported some measure of cost variance. Only four studies had calculated 95% confidence intervals for cost. The review of five available cost data sets showed that the cost data were not normally distributed, and in two cases showed substantial skewness.

A number of methods for estimating confidence intervals for cost-effectiveness ratios have appeared in the recent literature. Examination of their statistical properties and evidence from recent Monte Carlo simulation studies suggests that many of these methods may not perform well in some circumstances. The parametric method based on Fieller's theorem and the non-parametric approach of bootstrapping produced consistently the best results, and are the preferred methods for estimating confidence intervals for cost-effectiveness ratios. However, the use of cost-effectiveness acceptability curves may provide more useful information to decision makers than standard confidence intervals.

Conclusions

General recommendations

Potential guidelines arising from this review are:

- analysts should aim to present results using a methodological reference case in order to increase the comparability of results between studies
- analysts should be aware of the potential for the incremental cost-effectiveness ratio to vary at the margin
- analysts should avoid selective comparison of their results with the results from other studies
- analysts should ensure that they consider the potential implications of uncertainty for the results of their analysis
- interval estimates should accompany each point estimate presented
- where sensitivity analysis is employed to estimate an interval, analysts should be comprehensive in their inclusion of all variables in the analysis
- when reporting sensitivity analysis, analysts should be aware of the probabilistic nature of the reported range
- when reporting patient level cost information, analysts should make more use of descriptive statistics
- even when data are skewed, economic analyses should be based on means of distributions
- when reporting statistical tests of cost differences, analysts should be aware that significance tests may be more powerful on a transformed scale but that confidence limits should be reported on the original scale
- where patient level data on both cost and effect are available, the parametric approach based on Fieller's theorem or the non-parametric approach of bootstrapping should be employed to estimate a confidence interval for the cost-effectiveness ratio
- sensitivity analysis has a continuing role in handling uncertainty not related to sampling variation
- consideration should be given to using cost-effectiveness acceptability curves to present uncertainty in stochastic cost-effectiveness studies.

Recommendations for future research

Three main areas for future research arise from this review:

- research into the appropriate reference case for the UK
- research into the application of probabilistic sensitivity analysis methods
- research into the willingness to pay for health gain and the likely value of a ceiling cost-effectiveness ratio appropriate for decision making, estimated from consumer surveys and implied through the application of cost-effectiveness databases.

Chapter 1

Project background

Health economics is a burgeoning discipline, particularly in the area of the economic evaluation of healthcare interventions. In the 1980s, much of the literature concerning economic analysis related to justifying the application of economic thinking to the health-care sector. In the 1990s, with a much wider acceptance of the need to economically evaluate new and existing healthcare interventions, the focus has become more methodological – with much more attention being placed on the appropriate methods to employ when evaluating healthcare interventions. The most popular evaluative technique for economic evaluation is cost-effectiveness analysis.[1] The additional costs of a particular intervention are compared with the additional benefits it achieves. In order to decide whether it is appropriate to provide a particular intervention in the context of a publicly funded NHS, it is necessary to weigh these additional costs and benefits against the costs and benefits of alternative uses of scarce healthcare resources. Many cost-effectiveness studies present only point estimates of the value for money of particular healthcare interventions. However, it is clear that there is often considerable uncertainty in the evaluative process, such that it is more appropriate to include an analysis of uncertainty as part of the study.

The aim of this report is to perform a structured review of the way in which uncertainty has been handled in economic evaluation, to assemble data on the actual distributional form and variance of healthcare costs, and to devise guidelines to improve current practice. Before introducing a summary of the chapters of the report, some background to the project is developed in order set the importance of the research agenda in context. First, we discuss the types of economic analysis commonly employed in the evaluation of healthcare interventions. This is followed by a discussion of the decision rules of the most popular form of evaluative technique: cost-effectiveness analysis. The importance of uncertainty in cost-effectiveness results is then highlighted and a taxonomy of the types of uncertainty encountered in economic evaluation is presented.

Types of economic evaluation

Economic evaluation of healthcare interventions is the systematic evaluation of alternative courses of action in terms of both **costs** and their health outcome **consequences**.[2] Types of economic evaluation can usefully be categorised into two broad groups, depending on how the health outcome benefits of healthcare interventions are measured and valued. In cost–benefit analysis, health outcomes are valued in monetary units, which allows direct comparison with the costs of the intervention. If the monetary value of the health outcome benefits exceed the costs of the intervention, that intervention represents good value for money and should be employed. If the benefits do not outweigh the costs, then that intervention should not be undertaken and instead the resources should be employed elsewhere. Despite the clear nature of the decision rules in cost–benefit analysis and its theoretical grounding in welfare economics, problems associated with measuring health outcomes in monetary terms have resulted in very few reported cost–benefit analysis studies in a healthcare setting.[1]

To date, the most popular form of economic analysis has been cost-effectiveness analysis, where the health outcome benefits of healthcare interventions are measured in natural units (such as adverse events avoided, symptom-free days or cases detected). Although this form of analysis can be extremely powerful when a healthcare intervention dominates an alternative intervention (in other words, when it can be shown to be both more effective and less costly), its results are more difficult to interpret when they show an intervention to be both more effective, but also more costly. In such situations a trade-off must be made between the increased effectiveness on one hand and the increased resource requirements on the other. In order to judge whether the health outcome benefits are worth the additional costs, economists employ the notion of opportunity cost, which is defined as the value of the resources in their next best alternative use. In the context of healthcare interventions, the opportunity costs of employing resources to fund one intervention are the health outcome benefits forgone had those resources been used to fund a different intervention.

Hence, with many possible healthcare interventions making claims on healthcare resources, it becomes necessary when deciding whether to employ resources in one area to be able to compare health gain in that area with health gain in all other potential areas where those resources could be employed. This requires a generic health outcome measure, which can be compared between disease areas. Perhaps the best known generic health outcome measure is the quality-adjusted life-year (QALY). Although other measures have been suggested (such as the healthy year equivalent (HYE)), all such measures essentially recognise that both mortality and morbidity are important features of health status. Hence, in this report we use the term 'QALY' in a general sense to mean any attempt to adjust mortality for underlying morbidity. Economic analyses employing such generic measures of health outcome are known as cost–utility analyses, so called because the unit of health outcome is assumed to have a 'utility' value that is equal for all patients. Cost–utility analyses are often considered as a special case of cost-effectiveness analysis,[2,3] and we follow that convention in this report.

In this report we focus on cost-effectiveness analyses that report their results in terms of cost per QALY (i.e. cost–utility analyses) or in terms of cost per life-year. Although no adjustment for morbidity takes place for straightforward life-year results, it is clearly possible to compare life-years across different life-saving interventions. Indeed, it is common to find direct comparisons of cost per life-year results and cost per QALY results in the literature. We now turn to a discussion of the decision rules for cost-effectiveness analysis, assuming that cost-effectiveness is expressed in terms of cost per life-year or cost per QALY such that the decision rules revolve around how best to distribute resources between different healthcare interventions.

Decision rules of cost-effectiveness analysis

O'Brien *et al.* suggest that the aim of cost-effectiveness analysis 'is to compare the costs and effects of one treatment compared to some **relevant alternative**' (emphasis added).[4] Suppose that we are comparing a new experimental therapy (or treatment group) with some currently provided standard (or control) therapy, which represents the most cost-effective treatment available at present (the importance of this assumption is addressed in detail below). Further suppose that we know both the true costs of the new therapy (C_T) versus the control therapy (C_C) and the true effectiveness (in terms of health outcome) of the new therapy (E_T) versus the control therapy (E_C). O'Brien *et al.* identify four situations that can arise in relation to the incremental cost and effectiveness of the therapies:[4]

(1) $C_T - C_C < 0$; $E_T - E_C > 0$;
dominance – accept experimental therapy as it is both cheaper and more effective than existing therapy
(2) $C_T - C_C > 0$; $E_T - E_C < 0$;
dominance – reject experimental therapy as it is both more expensive and less effective than existing therapy
(3) $C_T - C_C > 0$; $E_T - E_C > 0$;
trade-off – consider magnitude of the additional cost of the new therapy relative to its additional cost
(4) $C_T - C_C < 0$; $E_T - E_C < 0$;
trade-off – consider magnitude of the cost-saving of the new therapy relative to its reduced effectiveness.

These four situations are equivalent to the four quadrants of the cost-effectiveness plane, which has commonly been advocated for the analysis of cost-effectiveness results.[5,6] The cost-effectiveness plane is presented in *Figure 1*. Note that the cost-effectiveness space illustrated in the figure is incremental such that the comparison therapy (control treatment in this case) is the origin in the figure and the horizontal and vertical axes therefore relate to the effect and cost **differences**, respectively. Where one intervention is simultaneously cheaper and more effective than the other (situations (1) and (2) above and quadrants II

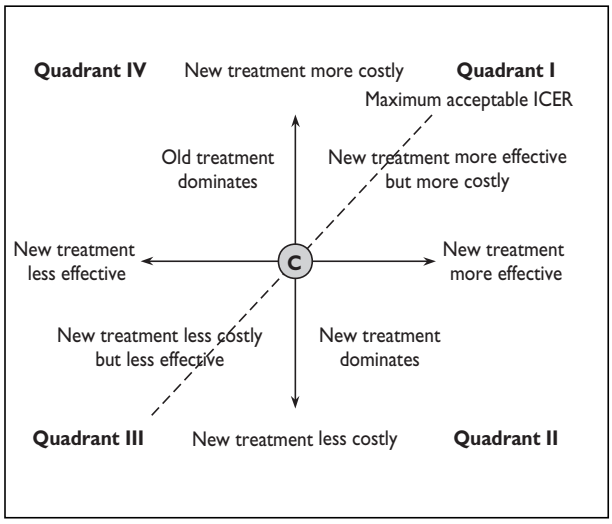


FIGURE 1 *The cost-effectiveness plane*

and IV on the cost-effectiveness plane), it is clearly the treatment of choice since it dominates the alternative intervention. However, where one intervention is both more effective and more costly (situations (3) and (4) above and quadrants I and III on the cost-effectiveness plane), then the decision is no longer clear. Rather, a judgement must be made concerning whether the additional costs of the more expensive therapy is justified by the additional effectiveness associated with that therapy. In order to aid such judgement, an incremental cost-effectiveness ratio (ICER) can be calculated which provides a summary of the cost-effectiveness of one intervention relative to the other. In terms of the notation introduced above, the ICER is given by

$$\text{ICER} = \frac{C_T - C_C}{E_T - E_C} \qquad (1)$$

League tables

Weinstein has argued that the most theoretically correct way of determining whether an intervention represents an appropriate use of resources should be based on the shadow price of an explicit budget constraint.[7] This involves rank ordering all possible uses of resources in terms of their ICER, and working down the list implementing the most cost-effective interventions first until the available budget for health care is exhausted. At this point, the cost-effectiveness ratio of the marginally funded programme gives maximum willingness to pay for an additional unit of health or ceiling cost-effectiveness ratio, implied by the setting of the budget.* Perhaps the most straightforward illustrative example of how this approach should be undertaken is given by Karlsson and Johannesson.[8]

The rank-ordering nature of this exercise has led to the coining of the term 'cost-effectiveness league tables' to describe the process.[9–13] and it is common for analysts to present the results of their own evaluation in the context of *ad hoc* league tables in order to compare the cost-effectiveness of the intervention under consideration to other cost-effectiveness estimates in the literature. Consider, for example, *Table 1,* which is based on the presentation by Pickard *et al.* of their estimate of the cost-effectiveness of neurosurgical care for different diagnostic categories and groups of patients.[14] Interventions are rank ordered by the estimated cost per QALY ratio from the highest (least cost-effective) at the top to the lowest (most cost-effective) at the bottom. On the right they give their own estimated cost-effectiveness figures for neurosurgery (by diagnosis/group) and on the left are general interventions chosen for comparison. The clear implication to be drawn from such a presentation is that, with the exception of treating malignant brain tumours and metastatic tumours of the central nervous system, neurosurgery represents good value for money in comparison to the other interventions listed in the table.†

In practice, there has been much criticism of league tables, and caution suggested for their use in decision making,[10,13,15,16] much of it related to the practical problems of making disparate comparisons in simplified form. However, even those commentators who favour cost–benefit analysis as the theoretically correct method of evaluation recognise that this approach to decision making will maximise health outcome effects from a given healthcare budget, albeit under a restrictive set of assumptions.[17,18] It has been pointed out that one of those assumptions must be that costs falling outside the specific budget of the health service should be excluded since costs falling on other parties are not pertinent to the problem of maximising outcomes from a specific budget.[13]

A shadow price rule?

It is perhaps the practical problems associated with league tables that have resulted in other forms of decision rules for cost-effectiveness analysis being discussed. Perhaps the most intuitive and straightforward decision rule is simply to define a cut-off value of the maximum acceptable cost-effectiveness ratio appropriate for decision-making purposes explicitly. This can be represented by the (slope of the) dashed line in *Figure 1,* which divides the cost-effectiveness plane in two such that points to the right of the line suggest that the intervention in question is cost-effective, while points to the left of the line are associated with cost-ineffective interventions. Funding interventions up to the point that their marginal (incremental) cost-effectiveness approaches this maximum or ceiling value would

* Clearly, if it was felt that worthwhile health care interventions are not covered under such an approach, the implication would be that the budget for health care should be increased.

† Note that the purpose of this example is simply to illustrate how such league tables are commonly presented in the literature. Whether in fact neurosurgery is a cost-effective intervention or not is beside the point. It will be argued in chapter 3 that comparisons of this nature should be far more comprehensive than can be made in a simple league table of this sort.

TABLE 1 *Example of a cost per QALY league table (1983–1984 prices)*

Intervention (general)	Cost per QALY (£)	Neurosurgery
	69,000	Malignant brain tumours
Haemodialysis in hospital	14,000	
CABG (moderate angina and one vessel disease)	12,000	
	11,000	Metastatic tumours in central nervous system
Heart transplantation	5000	
Cervical cancer screening	2500–15,000	
Breast cancer screening	3000	
Renal transplantation	3000	
CABG (main vessel disease)	1040	
Thrombolytic treatment for acute myocardial infarction	600–3000	
Hip replacement	750	
Pacemaker for atrioventricular heart block	700	
	350	All neurosurgery
	310	Subarachnoid haemorrhage
	300	Miscellaneous
	260	Spinal disorders
	240	Benign intracranial tumours
	150	Head injury

Adapted from Table IV of Pickard et al.[14]
CABG, coronary artery bypass graft

therefore set the marginal product of further investment in healthcare interventions to be equal. The problem is in setting the relevant ceiling value.

Perhaps the most widely cited likely magnitude of the ceiling ICER was given by Laupacis *et al.* with reference to the Canadian healthcare system.[19] They suggested that interventions associated with cost per QALY values less than Canadian $20,000 per QALY probably represent good value for money, while interventions costing over Canadian $100,000 per QALY probably represent poor value for money. Interestingly, Weinstein has pointed out that exactly the same limits had been suggested 10 years previously, but in US dollars,[7,20] and he goes on to suggest that 'round numbers' may have some intrinsic appeal. In the USA, a figure of US $50,000 per QALY has been mentioned, although again it has been suggested that this may owe more to being a convenient 'round number' than to any formal attempt to measure the maximum acceptable ICER.[21] More recently, attempts have been made to estimate the maximum willingness to pay for a QALY by comparing responses to willingness to pay questions with QALY estimations made side by side in the same study.[22] This process generated a maximum willingness to pay of approximately US $20,000 per QALY.

Despite the intrinsic appeal of an explicit shadow price decision rule for cost-effectiveness analysis, several commentators have warned that such an approach is not consistent with maximising health outcomes from a fixed budget for health care.[17,23] Although such a decision rule allows for additional resources to generate additional health outcome effects (up to the ceiling value of the cost-effectiveness ratio) it does not address the issue of where such additional resources will come from. Hence, the use of such a shadow price decision rule has been described as a prescription for growth in healthcare resource use as more expensive (and more effective) interventions replace those currently provided.*

* In theory, the use of an explicit price rule should apply to all interventions, irrespective of whether or not they are currently provided. Therefore, the optimal shadow price rule could be set at the point that would just equate with the budget constraint. In practice, it is unlikely that the shadow price rule can be set at exactly the correct level.

Other commentators, however, have argued in favour of an explicit shadow price decision rule on the basis that maximisation of health outcomes from a fixed budget requires the exclusion of healthcare-related costs that fall outside of the healthcare budget. Since an approach based on an explicit shadow price decision rule can include all costs no matter to whom they accrue, this approach is argued to be consistent with the overall societal perspective, strongly favoured by many economists.[24]

The economic evaluation literature makes wide use of the shadow price decision rule when placing the results of individual studies in context. Sometimes this may involve direct comparison with the shadow price rules quoted in the literature, such as in an evaluation of maintenance treatment of recurrent depression which concluded that the £557 to £5260 cost per QALY figures associated with the use of sertraline were 'well within the range of incremental cost-effectiveness ratios that support the adoption and appropriate utilisation (i.e. less than $Can20 000 per QALY) ... of a medical intervention.' [25†]Alternatively, many authors take a revealed-preference-type approach, where the intervention that they have evaluated is considered cost-effective on the basis that an intervention that is less cost-effective is already widely accepted as an appropriate use of resources. For example, in looking at the cost-effectiveness of radiofrequency ablation (RFA) for the treatment of the Wolf–Parkinson–White syndrome, Hogenhuis *et al.* estimated cost-effectiveness for four patient risk groups.[26] These authors chose a 'threshold cost-effectiveness ratio of $40,000 per QALY gained ... to correspond loosely to commonly used but "expensive" therapies, such as percutaneous transluminal coronary angioplasty for stable angina pectoris'. On the basis of this value of a QALY, the authors concluded that RFA therapy was appropriate for symptomatic patients, but that the unfavourable cost-effectiveness ratio for asymptomatic patients confirms the appropriateness of the current policy of observation in these patients.

In the UK, the NHS provides health care for the population within a fixed budget. If the aim of economic evaluation of healthcare interventions is to inform resource allocation decisions within the NHS, a league table approach to decision making is the most consistent with the aim of maximising health outcomes within the NHS budget.

Uncertainty in economic evaluation

One problem with the league table approach is that the rank ordering which takes place in such league tables is usually made on the basis of point estimates of cost-effectiveness alone. Consider *Figure 2,* where the point estimates for seven different healthcare interventions are plotted in increasing order of magnitude. The 'I' bars in this figure represent the estimated range of uncertainty around the point estimates. It is immediately apparent that the range of uncertainty is so wide that it would be possible to rank these interventions in a completely different order than that obtained from the point estimates. If policy makers are to be fully informed when making decisions based on the results of economic evaluations, it is imperative that analysts attempt to estimate the level of uncertainty inherent in their results rather than simply presenting point estimates. These interval estimates should also accompany point estimates when reproduced in league tables.

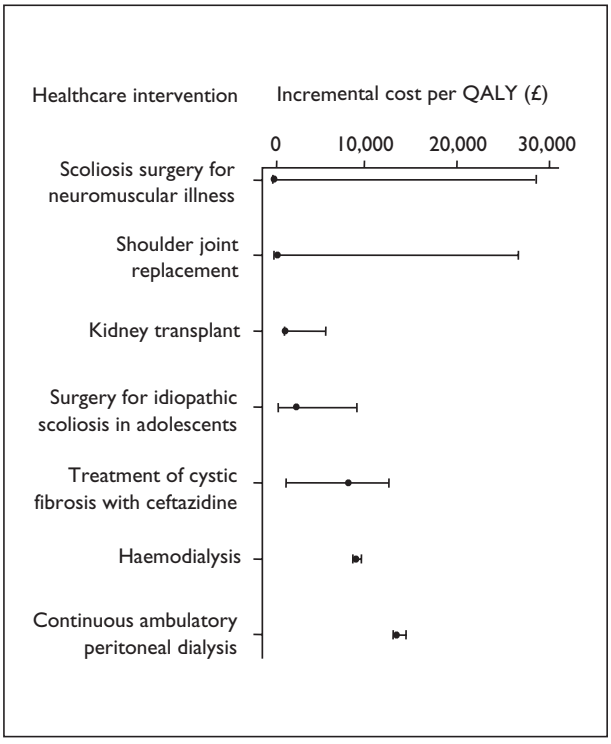


FIGURE 2 *Point estimates of cost-effectiveness together with estimates of the associated uncertainty (●, point estimate of cost-effectiveness; ├─┤, estimated range of uncertainty). (Adapted from Table II of Petrou* et al.[27]*)*

† Note that in addition to accepting the appropriateness of the Canadian $20,000 shadow price rule, these authors are also implicitly assuming that (after conversion) this is the appropriate shadow price rule for the UK.

Uncertainty in economic evaluation is pervasive, entering the evaluative process at every stage. It is useful to identify four broad areas of uncertainty encountered in economic evaluation. These relate to uncertainty in: (1) the appropriate analytic methods employed in conducting the evaluation; (2) the data requirements of a study; (3) the extrapolation of study results; and (4) the generalisability of those results.

Methodological uncertainty

The analytic methods underpinning an economic evaluation include the perspective adopted, which defines the choice of costs and benefits to include in an evaluation, and the methods of measurement and valuation to be applied to those costs and benefits. There exists, in a number of these areas, disagreement amongst practitioners about the most appropriate analytical method.[28] An example of one such disagreement is the debate in the literature about the preferred way to incorporate time preference into economic evaluation, and in particular the role of differential discounting of costs and benefits.[29–32] Uncertainty also exists concerning the methods selected to value the resource and health outcome consequences in an evaluation. The problems involved in estimating unit costs that accurately represent the opportunity cost of resources are well known. There has also been extensive debate over the choice of instruments to value health outcome.[33–36] It should be noted, however, that uncertainty relating to the validity and reliability of measurement instruments exists in the clinical, as well as the economic, domain.[37] Perhaps a less obvious lack of consensus exists regarding such issues as whether or not to include in economic assessments the cost of healthcare resources consumed, due to unrelated illness, during extra years of life generated by the intervention under evaluation.[3] Similarly, there is some debate concerning whether (and how) to include the cost of production losses from time away from work and/or time losses* from general activities which may not receive a wage, but which may be valued by society or the individual nonetheless.[3,38–43]

As noted by Drummond *et al.*,[28] Russell has argued for a set of core methods to be employed to facilitate comparisons between evaluations.[44] This idea has been adopted by the recent US panel on cost-effectiveness,[3] which recommended the use of a 'reference case' of core methods to be used by analysts when conducting economic evaluations, which could then be supplemented by additional analyses employing other methods thought appropriate by the authors.

Uncertainty in data requirements

The data required for any full economic evaluation are the resource use consequences and health outcome consequences of the programmes under evaluation, and the data necessary to value those consequences (unit cost/price information for resource use and quality of life weights for cost–utility analyses). Variability within different populations with respect to these sorts of data is a key source of uncertainty in economic evaluations. The increasing use of the clinical trial as a vehicle to collect economic data prospectively encourages the analyst to describe distributions of stochastic data in the different arms of the study and to represent uncertainty in the difference between the study arms as a point estimate accompanied by a confidence interval through the use of standard statistical techniques. For example, in an economic evaluation of synthetic surfactant use for the treatment of respiratory distress in premature infants, Mauskopf *et al.*[45] collected resource use data on total length of stay, days in intensive care, days on a mechanical ventilator and days on oxygen for infants randomised to either synthetic surfactant or placebo–air therapy. The total cost difference between the two arms of the trial was found to be insignificant using standard statistical techniques.

Even when an economic evaluation is not being run alongside a clinical trial, the process of sampling from a specific population encourages the use of conventional statistical methods to handle data variability. For example, if the hospital notes of patients admitted to hospital with acute myocardial infarction are studied to ascertain what resources were consumed during their stay, the variability in those sample data can be expressed as confidence intervals around a mean value.

If the values to be attached to the health outcome consequences of trials are obtained by sampling patients and/or other groups (such as care givers, healthcare professionals or the general public), the variability in those data can also be handled

* These costs are often referred to as indirect costs; however, this term is avoided in this report since Drummond *et al.*[28] have argued that this terminology can cause confusion through the use of the same term in accountancy to mean overhead costs.

statistically. For example, utility and willingness to pay data were collected as part of a multicentre placebo-controlled trial of auranofin for rheumatoid arthritis, and *p* values for treatment effect reported.[46] If the resources consumed by patients in a trial are valued according to where treatment was undertaken, there will be limited variability in the required unit cost data – at any given location at a given point in time the unit cost of, for example, an hour of a particular clinician's time, or the unit cost of a day's dosage of a specific drug, will effectively be fixed. In the analysis of a recent evaluation of endometrial resection versus abdominal hysterectomy,[47] the resources that patients were observed to have consumed during the trial were valued using a fixed vector of unit costs from the hospital in which they were treated, and a mean difference in total cost between treatments reported together with a confidence interval.*

A clear limitation to the use of statistical methods in economic evaluation occurs, however, when sample data are not available for a particular parameter. In an economic evaluation of two drug therapies for cryptococcal meningitis in AIDS patients, effectiveness data were available from a clinical trial, but a panel of clinicians from various European countries was used to provide information on resource use associated with the therapies.[48] In the absence of sample data, uncertainty in data requirements can only be handled using sensitivity analysis.

Generalisability

Generalisability relates to the extent to which the results of a study, as they apply to a particular patient population and/or a specific context, hold true for another population and/or in a different context. Whether or not the results of a study are generalisable – and attempts to strengthen a study in this regard – is another source of uncertainty in economic evaluation. One of the key forms of uncertainty regarding generalisability concerns whether the results of a study conducted on one group of patients are also valid for another. For example, would the most cost-effective form of screening for retinopathy in non-insulin-dependent diabetes also be the preferred option for insulin-dependent diabetes? Is a cholesterol-lowering drug, which is cost-effective when prescribed to men, also cost-effective for women? Is breast screening as cost-effective in women aged 40–50 years as it is for women aged 50–64 years?

Another level of generalisability is concerned with whether the relative cost-effectiveness observed within a trial would hold true in routine clinical practice.[49] It is a well-known limitation of the experimental evaluative design that it can impose atypical patterns of care on patients that may affect the consequences of that care.[50,51] That is, the clinical trial may lack external validity, which can generate uncertainty in an economic evaluation as it may not be clear whether an intervention judged cost-effective on the basis of efficacy data is also attractive when the evaluation is based on effectiveness data.

A further level of generalisability relates to the setting of the study: for a given population of patients, would the resource use and health outcome consequences observed in one hospital, region or country be replicated in other locations? This area of uncertainty is linked to known variations in clinical practice within and between countries.[52–54] It is generally accepted, for example, that hospitals in the USA tend to be more resource-intensive in their treatment of a given condition than those in the UK. If these variations are particularly pronounced, the results of a particular study may only have relevance in the setting in which it was undertaken.

Even if variations in clinical practice are not significant, the particular contexts of hospitals may result in new technologies having different impacts. The fact that certain types of capital tend to be used for a variety of purposes and that their cost functions with regard to their utilisation may be 'stepped' is important in this regard: the use of a new technology which reduces the demands on a particular capital asset may result in different policy actions in different hospitals. In an economic evaluation of day case surgery for hernias and haemorrhoids[55] the cost savings resulting from the use of day-case surgery were estimated using two assumptions about the use of surgical wards: firstly, the introduction of day case surgery would facilitate the closure of a five-bed ward resulting in a net cost saving to the NHS of £20 per case; secondly, without this new approach to surgery, a new five-bed ward would have had to be constructed

* It is common in so-called stochastic cost-effectiveness analysis for costs to be presented as a random variable with an associated confidence interval. It is important to note, however, that it is usually only resource use that is truly stochastic and that costs have been obtained by weighting stochastic resource use variables by deterministic unit costs.

just to maintain existing levels of service resulting in a cost saving of £29 per case.*

In addition to uncertainties about the generalisability of resource and health outcome consequences of technologies between settings, the valuation of those consequences may also differ. The relative prices of resources can vary quite considerably between countries and even between different regions within countries. It is less clear if there will be important variations in the values attached to health status. The EuroQol instrument[56] (recently relaunched as the EQ-5D) has been used in many different countries, although no direct international comparisons of the tariff values have yet been published. It may be that cultural differences will generate important differences in values at a worldwide level, particularly perhaps between developed and developing economies.

Conventional statistical methods are likely to have mixed success in handling uncertainty relating to generalisability. Some of the types of generalisability discussed above are tied to uncertainty in stochastic data which, in principle, can be expressed in the usual statistical ways. For example, the results of an economic evaluation using data from a clinical trial undertaken in the USA are unlikely to be directly generalisable to the UK to the extent that an intervention judged cost-effective in the USA might not necessarily be considered cost-effective in the UK. Differences in the intensity of resource use between the USA and the UK are well known, but also differences in clinical practice and valuations data may mean that important context specific differences in cost-effectiveness exist. It may be feasible to acquire UK sample data relating to clinical and resource use variables and substitute those for the USA-specific ones. However, exploring whether incorporating a limited amount of UK-specific data into the analysis changes the results would most effectively be undertaken using a sensitivity analysis.

In practice, the data necessary to generalise the results of studies in this way are frequently unavailable; for example, the resource and health outcome consequences of using a technology in a non-trial situation may simply be unknown. In these circumstances, modelling using best available data could be undertaken,[57] but sensitivity analysis would have to be used to explore the inherent uncertainty relating to this process.

Extrapolation

Many economic evaluations seek to extrapolate from their primary data source, and this introduces another form of uncertainty. One form of extrapolation is where the primary data source relates to an intermediate health outcome from which a final health outcome for cost-effectiveness analysis is modelled. For example, in an analysis of the cost-effectiveness of the treatment of chronic hepatitis B, Wong *et al.*[58] conducted a meta-analysis of nine randomised-controlled trials (RCTs) to estimate the effectiveness of interferon-α2b. The long-term consequences of hepatitis B infection are liver cirrhosis and hepatocellular carcinoma. However, patients may live many years with asymptomatic infection before such complications become manifest. No long-term randomised trial of interferon therapy for hepatitis B exists in relation to final health outcomes such as survival, cirrhosis or hepatocellular carcinoma,[58] due to the cost and other practical limitations of conducting such a long study. Instead the clinical trials in this area use viral markers of hepatitis B infection as intermediate health outcome end-points. The cost-effectiveness presented by Wong *et al.* was based on extrapolation of the effectiveness of interferon based on loss of viral markers of infection to model the long-term clinical and resource implications of treatment. Hence, this process of extrapolating from intermediate to final health outcomes introduces additional uncertainty into the analysis.

Even where the primary data source is related to final health outcomes, economic evaluation ideally requires a much longer time horizon than is feasible for the clinical trials that provide the primary data source. This is because economic analysis is concerned with the lifetime costs and benefits of therapy. In an economic evaluation of zidovudine therapy versus no therapy for asymptomatic HIV-infected patients, the authors considered the cost-effectiveness of the drug on the basis of the clinical trial results at 1 year and then sought to extrapolate those results to patients' entire lifetimes by modelling the profiles of the

* Although a policy of increasing day case surgery seems to be cost-saving, the authors of this study stress that this will be dependent on the use to which resources released by the programme are put. A not unlikely scenario could be that beds freed up by increasing day case surgery for hernia treatment are used by another speciality. Although the average cost per case for hernia treatment may decrease, failure to close a ward would mean that no cost savings would be realised by the health service.

survival curves in each arm of the trial.[59] The uncertainty inherent in this process was largely responsible for the wide range of cost-effectiveness ratios generated by the study – these varied from approximately US $7000 to US $70,000 per year of life gained. The most favourable cost-effectiveness ratio corresponded to an assumption that the observed survival benefit in the first year continued in future years, while the least favourable ratio corresponded to the assumption that the survival benefit in the first year was an isolated benefit that did not continue in the future. In retrospect, it appears that even this assumption was optimistic – the Concorde trial contradicted these results by failing to show any significant survival differences associated with therapy in the longer term.[60,61] In turn, these results have themselves been rendered obsolete with the introduction of combination therapy rather than zidovudine alone, which does appear to be associated with significant survival gains for HIV-infected patients.[62]

The process of extrapolating the results of economic evaluations is invariably undertaken using modelling exercises.[57,63] The handling of uncertainty that is inherent in this process is likely to rest heavily with sensitivity analysis, as modelling involves synthesising data from various sources or using assumptions rather than data from the primary source.

The traditional method for handling uncertainty due to sampling variation in many forms of evaluation, most notably clinical evaluation, has been statistical analysis. Where patient-specific resource use and health outcome data have been collected (for example, as part of a prospective clinical trial) in a so-called stochastic analysis,[4] then statistical techniques have been developed to calculate confidence intervals around point estimates of cost-effectiveness, although the methods required to estimate confidence limits around a ratio statistic are less straightforward than for many other statistics.

In practice, however, a relatively small proportion of all economic evaluations are conducted alongside clinical trials. Instead, data are synthesised from a number of different sources – including reviews of the literature, hospital records and even clinical judgement – in a deterministic analysis. Hence, standard statistical methods cannot be employed. Moreover, even where a stochastic analysis is possible, the remaining levels of uncertainty that are not related to sampling variation need exploration and quantification. To do this, a technique known as sensitivity analysis is used, which involves systematically examining the influence of the variables and assumptions employed in an evaluation for the estimated cost-effectiveness results.

Although the general methods literature and recently published guidelines often give a contrary impression, sensitivity analysis is not a single approach. It is useful to distinguish four main types of sensitivity analysis and relate these to the sorts of uncertainty that are encountered in economic evaluation.

Simple sensitivity analysis

The most common form of sensitivity analysis is where one or more components of an evaluation are varied across a plausible range of values in order to examine the effect on the results. A distinction can be made between one-way and multiway analysis. With one-way analysis, each uncertainty component of the evaluation is varied individually, while the others are held at their baseline values, in order to establish the separate effect of each component on the results of the evaluation. For example, in a cost-effectiveness analysis of a screening programme for hepatitis B surface antigen in India,[64] the authors carried out a one-way sensitivity analysis on all variables, which they illustrated graphically by plotting the effectiveness and cost results against a range of each of the uncertain variables. It has been argued that a set of one-way analyses such as these may be sufficient if each of the uncertain variables is independent of the others.[65] However, this argument can be questioned since, even if variables are independent, they do not vary one at a time. The effect of joint uncertainty in many variables will often be wider than suggested by one-way sensitivity analysis.[66]

A multiway simple sensitivity analysis involves varying two or more inputs at the same time, and studying the combined effect on the results of the evaluation. An example of this sort of analysis is found in a cost-effectiveness analysis of antihyperlipaemic therapy in the prevention of coronary artery disease.[67] This study considered the impact on the cost per year of life gained from therapy according to the variation in age at the initiation of therapy, the level of additional coronary risk factors and age at termination of therapy. Inevitably, it becomes progressively more difficult to present the results of multiway analyses the greater the number of inputs that are varied, and evaluations frequently exhibit uncertainty on more inputs than can be feasibly handled with simple sensitivity analysis.

One solution is to present multiway analyses in the form of what has been termed 'scenario analysis'. This can be used to explore the implications of different 'states of the world', each of which affects a number of different parameters in the evaluation. For example, in an analysis of the costs of a midwife-managed labour unit compared with a consultant-led labour ward, Hundley *et al.* explored uncertainty using nine different scenarios relating to assumptions concerning staffing levels, consumables and capital arrangements underlying their analysis.[68]

Simple sensitivity analysis is a valuable means of addressing uncertainty when high-quality sample data are not available. For example, it is rarely possible to acquire good sample data on the utilisation of capital equipment prior to its widespread use. In a study of the relative cost-effectiveness of alternative forms of screening diabetics for retinopathy,[69] a one-way simple sensitivity analysis graphically plotted the annual utilisation of a retinal camera against its cost-effectiveness ratio and found that there was a very limited reduction in the cost of detecting a true positive case once about 1400 patients per year were screened with the equipment.

Studies which provide a source or explanation for the ranges used in simple sensitivity analysis are likely to be of more use to decision makers than those that employ an arbitrary range. Furthermore, it may be useful to provide a summary measure of the sensitivity of results to changes in each variable. In the analysis of a screening programme for hepatitis B surface antigen referred to above,[64] the authors reported, for each variable in their model, a partial derivative which, when multiplied by a change in a given parameter, generated the impact on costs and effectiveness results. They also suggested an alternative measure based on elasticities that can be applied when it is not possible to calculate partial derivatives. The elasticity is given by the percentage change in the results divided by the percentage change in the input variable. Such an approach has been employed in a preliminary economic evaluation of new prostheses for total hip replacement in preference to specifying arbitrary ranges of values to represent uncertainty in the variables used in the study.[70]

The use of simple sensitivity analysis can improve the generalisability of a study. For example, uncertainty about capital costs is a frequent problem with regard to generalisability: the purchase price to a specialist research centre of a major new item of capital equipment at an early stage in its product life-cycle may change when other hospitals are considering the investment. It may be the case that utilisation levels achieved in large specialist centres are not typical of those in smaller hospitals. In an economic evaluation of extracorporeal shockwave lithotripsy versus percutaneous nephrolithotomy for the treatment of renal and uretic stones,[71] simple sensitivity analysis was used to handle differences between hospitals in the capital cost of the lithotripter. Cost-effectiveness results were recalculated assuming that the installation cost and annual utilisation of the equipment were lower in routine clinical practice than in the teaching hospital in which the clinical study was undertaken.

Simple sensitivity analysis can also play an important role in coping with uncertainty in some forms of analytic method. If the data are available, results can be recalculated using alternative approaches. For example, in a cost–utility analysis of in-centre haemodialysis, the cost per QALY gained was recalculated using alternative methods of eliciting health state values from patients with chronic renal failure,[72] As another example, in a cost-effectiveness analysis of end-stage renal disease treatment, cost-effectiveness ratios were calculated with and without estimates of the cost associated with production losses from lost work days.[73]

Threshold analysis

Threshold analysis is concerned with identifying the critical value of parameter(s) above or below which the conclusions of a study will change.[74] Threshold analysis is particularly useful when a parameter is indeterminate, such as the price of a drug in a study undertaken prior to the drug being marketed. For example, in the economic evaluation of a new antiemetic, the authors undertook two alternative threshold analyses with respect to the price of the new drug: the price which would equate the expected total cost of treatment for the new versus the old drug therapies; and the price that would equate the cost-effectiveness ratios.[75]

A limitation of threshold analysis is that it can only be used to deal with uncertainty in continuous variables, which would normally mean that it is only useful for handling uncertainty in the data requirements of a study. Furthermore, even when uncertainty in continuous data is being assessed, the lack of clear decision rules for cost-effectiveness analysis complicates the situation. In the special case of cost-minimisation analysis, a meaningful threshold can be defined in terms of the point at which the costs of the two interventions are equal. A similar position exists concerning cost–benefit analysis, where the threshold could be defined in

terms of zero net-benefit. In cost-effectiveness or cost–utility analysis, as discussed above, there is no universally accepted cost-effectiveness ceiling ratio appropriate for decision-making purposes. However, in the preliminary economic evaluation of total hip replacement introduced above, a threshold was identified for the two most critical variables relating to three possible values of the ceiling ratio.[70]

Extreme scenario analysis

Another form of sensitivity analysis, closely related to the multiway/scenario sensitivity analysis described above, is extreme scenario analysis. In this form of analysis the aim is to generate a best- and a worst-case scenario by systematically combining all the most optimistic and pessimistic values for the inputs to the study, from the point of view of the intervention under evaluation. If an intervention is preferred using baseline estimates of the evaluation variables and under the best- and worst-case scenarios, then a high degree of confidence can be attached to the conclusions of the study. In the economic evaluation of alternative drug therapies for cryptococcal meningitis in AIDS patients referred to above, cost estimates were presented according to three different intensities of resource use, based on data provided by the expert panel, which were then valued using 'low' and 'high' unit cost vectors.[48]

The use of extreme scenario analysis can be an efficient way of dealing with uncertainty in the data requirements of a study when, for example, experts have been asked to provide a baseline value for a given variable and a plausible range but the distribution across this range is unknown. It has less value in addressing uncertainty related to analytic methods, however, since it is usually the case that different methods cannot reliably be termed 'optimistic' or 'pessimistic' prior to the evaluation being undertaken. It is possible to think of exceptions, however, such as the choice concerning whether to discount health outcome benefits in a screening programme: to discount future benefits would certainly reduce the potential for the programme to prove a cost-effective use of resources.*

Probabilistic sensitivity analysis

O'Brien *et al.*[4] have argued that the limitations of traditional sensitivity analysis methods in the clinical literature have led to the development of probabilistic sensitivity analysis methods based on Monte Carlo simulation methods. It is clear that one of the problems with extreme scenario analysis is that in most analyses it is unlikely that all the most pessimistic/optimistic factors will occur simultaneously, and therefore the impact of uncertainty may be overestimated. By contrast, by failing to allow for interactions and by keeping other variables constant, one-way sensitivity analysis may underestimate the impact of uncertainty. Probabilistic sensitivity analysis permits the analyst to examine the effect of joint uncertainty in the variables of an analysis without resorting to the wide range of results generated by extreme scenario analysis. A distribution is attached to the range associated with each of the variables in the analysis, and Monte Carlo simulation simultaneously selects values from the specified ranges and distributions of all the variables.[76] The simulations are run a large number of times in order to generate a distribution of the result of interest, which can then be used to estimate the variance of the result.

A limitation of this form of analysis is that it can only handle uncertainty in the data requirements of the study. If, for example, the effects of including time costs were required, two probabilistic sensitivity analyses would have to be run, one with time costs and one without. To date, most examples of probabilistic sensitivity analysis are confined to the medical decision-making literature[77] where the particular problems associated with the simultaneous consideration of two outcomes (cost and effects) do not apply. Few examples applied to economic analysis have appeared in the literature, although recently some analysts have begun to report probabilistic results.[78–83]

If economic evaluations are to be useful for decision-making purposes then their results must include some estimate of uncertainty as well as a point estimate of cost-effectiveness. It is unlikely that statistical methods will be sufficient for estimating intervals due to other important forms of uncertainty besides sampling variation. Where sensitivity analysis is employed, it is important for analysts and decision makers to be aware that different methods will produce different widths of interval around the point estimate of cost-effectiveness.

* In fact, even if it were possible to identify optimistic and pessimistic methodological assumptions, it is not appropriate to include them in an analysis since this can make comparison with other studies less straightforward. The use of sensitivity analysis to provide an interval estimate for a given reference case of methods is therefore preferred.

Outline of chapters in this report

In the following chapters, we report the results of a major review of the economic evaluation literature. The review is conducted at a number of levels of detail. In chapter 2, the overall review process is described, including the search and identification methods used and the criteria for inclusion in the final sample. Descriptive statistics for the overall review are then presented, including the methods which were employed by analysts to quantify uncertainty in their study. This overall data set is employed to focus in on two specific areas of interest, which are then reported in the next two chapters. In chapter 3, the results of a detailed review of all studies reporting results for UK healthcare interventions are reported. This includes the development of a relational cost-effectiveness database with the ability to match study results by the underlying methods employed by analysts. Chapter 4 looks in detail at a subset of studies for which patient level cost information is available in order to develop a picture of how the distributional form of cost data are reported by authors. To aid the discussion of the distribution of healthcare cost data, actual cost information from a number of available data sets is reported. In chapter 5, the literature pertaining to confidence interval calculation for cost-effectiveness ratios is reviewed. Few studies have used such methods as yet, since patient level data on both costs and outcomes are required. However, with increasing numbers of economic analyses being performed alongside clinical trials, many future studies will have the potential for the use of confidence intervals to represent uncertainty due to sampling variation. In the final chapter, the findings of the report are summarised and some guidelines are proposed based on the findings of this study.

Chapter 2

Structured review of cost-effectiveness studies

Introduction

In this chapter, the selection and review of studies is described in detail. The aim was to identify and review as many published studies reporting results in terms of cost per (QA)LY gained as possible. This form of study was chosen as it is the results of these studies that are commonly grouped together and reported in cost-effectiveness league tables.

Selection process

Given recent interest in systematic reviews of the medical literature, in particular the methods proposed by the Cochrane Collaboration,[84] it is important that any review of the literature is conducted rigorously. In the past, many reviews of the literature have been criticised for being conducted in a rather unstructured and selective manner resulting in a review which is inherently subjective.[85] The main aim of systematising the process of reviewing the literature is to reduce potential biases and to improve the potential for other researchers to reproduce the results of the review.

In clinical evaluation, studies which fail to demonstrate a significant effect difference between two alternative treatments may not be submitted for publication or may not be considered of sufficient interest by journal editors/reviewers to merit publication. This results in a demonstrable publication bias whereby studies that show no difference in effect between two treatments may never enter the public domain. This potential for bias in reviews limited to the published literature has led to increasing numbers of searches of the 'grey literature' in an attempt to include all studies which have addressed the topic of interest. Whether the results of identified studies are included in any meta-analysis associated with the systematic review is determined by a set of predefined methodological criteria setting out the minimum required standard for inclusion, since it is obvious that incorporating results from a poor study is undesirable.

It is not clear how important publication bias is for economic evaluation studies. On the one hand, the problem of 'positive' and 'negative' results is not so acute in economic evaluation. Since the cost-effectiveness of an intervention is compared with an existing treatment, it is less likely that results will not be submitted or published on the grounds of lack of interest. On the other hand, it is possible that research sponsors may exert pressure to prevent the submission for publication of cost-effectiveness analyses that are unfavourable from the sponsor's perspective. Given the considerable effort required to search the grey literature (both in terms of the time and expense of communicating with known authors and analysts in the field) and given that published studies represent those results that are publicly available to policy and decision makers in the health service and to other analysts, for the purposes of this review the search strategy was designed to identify only published economic evaluations. We have recorded details of research sponsorship and may be able to examine some aspects of potential publication bias by assessing whether sponsorship is systematically related to methods or reported results. Due to the close association between systematicity and the 'Cochrane' style review process outlined above, we prefer to use the term 'structured review' to describe our review process.

The main focus of the search strategy was the electronic searching of available computerised databases. Three SilverPlatter™ databases – MEDLINE, CINAHL and EconLit – and two BIDS databases – EMBASE and the Social Science Citation Index (SSCI) – were searched. It was anticipated that MEDLINE would be the most important database to search, hence the search strategy was initially devised around MEDLINE and then used on the other databases. Although MEDLINE has a categorisation system which allows the selection of medical subheading (MeSH) terms to identify articles, the use of 'economics' produced in excess of 6000 hits, the majority of which are not economic evaluations. This experience of the rather general nature of MEDLINE indexing terms has also been found in the area of RCTs.[86] Instead, a search strategy was devised to identify key words and phrases from the title and abstract of records which were likely to indicate appropriate studies. Starting with a number of known economic evaluation studies appropriate for the review and which were listed on MEDLINE, various search strategies were tested to establish how many of the known articles were identified.

It became clear during this process that there was a distinct trade off between the sensitivity and specificity of the search strategy used. Ideally, of course, a strategy should be both sensitive (identifying a large proportion of appropriate articles) and specific (rejecting a large proportion of inappropriate articles). The problem in this particular case was that although the majority of studies that report cost per life-year results make reference to 'life-years' (or a similar term) in the title or abstract, a number of studies do not. Of those studies that do not, most do refer to cost-effectiveness (or a similar term); however, cost-effectiveness is a very non-specific term, and including it in the search strategy identifies a very large number of inappropriate articles. The final search strategy is detailed in *Table 2*, and shows that the term 'cost-effectiveness' was omitted on pragmatic grounds, despite the fact that the search was less sensitive as a result.

Having identified studies from the above electronic databases and downloaded bibliographic information, all studies underwent an initial screen to ensure that they met the following criteria:

- **Primary studies**. Only studies reporting first-hand results were included. Any studies that summarised or discussed the results of studies reported elsewhere were excluded, including letters and editorial articles.
- **Healthcare interventions**. Studies were included only if the intervention under evaluation fell within the normal bounds of a healthcare system (broadly defined to include health promotion strategies).
- **Life-year results**. Only studies explicitly comparing both cost and effectiveness, usually in terms of a cost per life-year ratio* (with or without quality adjustment), were included.

Where it was clear from the title or abstract details downloaded from the electronic database that the article failed on one of these criteria it was excluded; otherwise, and where any doubt remained, the full printed article was obtained.

In addition to the widely available commercial databases detailed above, two other electronic databases were searched. Firstly, the database compiled by the Centre for Reviews and Dissemination (CRD)

TABLE 2 *Searching electronic online databases*[a]

Search terms[b]	MEDLINE[c]	CINAHL[d]	EconLit[e]	EMBASE[f]	SSCI[g]
(YEAR* OF LIFE) and COST	519	28	7	173	16
LIFE-YEAR* and COST	308	9	5	142	51
WELL YEAR* and COST	9	0	1	2	0
HEALTHY YEAR and COST	12	3	0	8	6
COST UTILITY	132	11	30	26	28
Total	607	46	38	326	85
Total (after limits applied)[h]	491	37	36[i]	[z]326[j]	85[j]
Total including 1996 publication year	570	52	43	449	109

[a] *Results by search term apply up to and including the 1995 publication year. The final row gives updated figures for the 1996 publication year*
[b] *An asterisk indicates a wildcard character (i.e. will pick up the plural 'years')*
[c] *MEDLINE records begin in 1966*
[d] *CINAHL records begin in 1982*
[e] *EconLit records begin in 1969*
[f] *EMBASE records begin in 1980*
[g] *SSCI records begin in 1981*
[h] *Limits applied were: published in English, in or before 1995, and not document types 'letter' or 'editorial'*
[i] *Document type not recorded for EconLit so this limit does not apply*
[j] *BIDS requires limits to be applied before searching, hence totals are the same*

* In the case of dominance for one of the interventions under consideration, it is not appropriate to present the results as a ratio. For the purposes of the review, however, it was the comparison of intervention cost with health outcomes in terms of life-years which was important.

at York University and available via the Internet from the web site http://york.ac.uk/inst/crd/info.htm/, and, secondly, the Office of Health Economics (OHE) and International Federation of Pharmaceutical Manufacturers' Associations (IFPMA) Health Economic Evaluations Database (HEED), available on CD-ROM. The CRD database includes the Department of Health's Cost-effectiveness Register,[87] and the OHE database includes the Wellcome economic evaluation bibliography[1] and the Medical Care bibliography of economic evaluations.[88] Since both of these databases seek to provide information on economic evaluation studies, they should have already identified all appropriate economic evaluations from the general medical literature. Hence the search terms employed focused only on the health outcome aspects of the full set of terms employed in the main search strategy outlined in *Table 2*.

To supplement the electronic searching, where reviewed studies made comparisons with cost per life-year figures obtained from other referenced published studies, these studies were obtained and, providing they met the criteria laid out above, then became part of the review sample. Additional articles, not already identified were obtained from a review of cost–utility studies by Gerard.[89] Finally, an *ad hoc* group of studies of which we were aware and that met the criteria but which had not been identified by the search strategy detailed above were included in the review sample. The overall identification process is illustrated in *Figure 3*. Where it was decided that the identified studies did not meet the criteria for the review, details were recorded of the reason for failure.

Review process

All identified studies were reviewed using a checklist of questions concerning the study. This review proforma is reproduced in appendix 1, and contains a number of categories or 'fields'. The funding source of the study was recorded as either 'industry' (i.e. funded by a private company involved in the manufacture of healthcare technologies), 'non-industry' (including research bodies, charitable institutions and educational establishments) or 'not clearly stated'. The country the results were relevant to and the currency in which the results were reported were recorded as a free text field. A description of the disease groups relevant to the study as given by the authors was recorded together with our classification of that disease into the relevant *International Classification of Diseases,* 9th edition (ICD-9) code chapter heading. A description of the intervention (as presented by the authors) was recorded, and a classification by type of intervention was added. The presentation of health outcomes in the study was recorded as life-years or QALYs (or both). Where QALYs were presented, the source of the quality adjustment weights were also recorded.

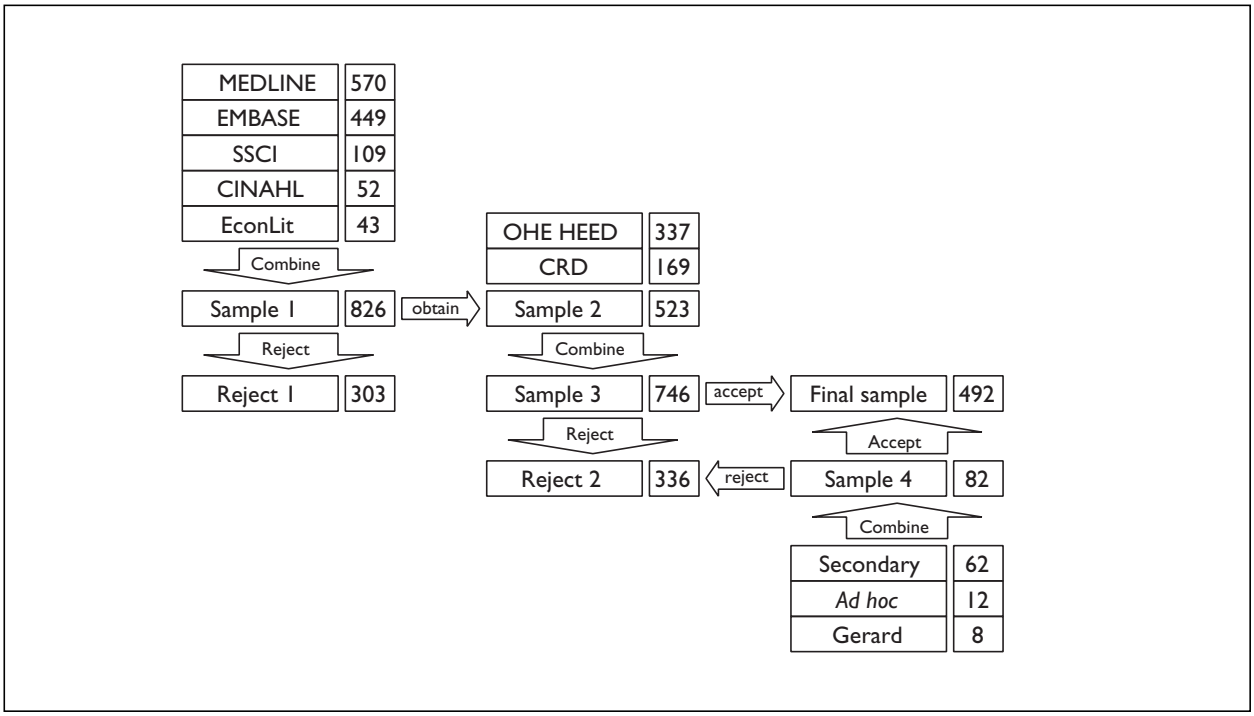


FIGURE 3 *Schematic diagram of the overall identification and review process*

The study design categories used to classify the articles included 'alongside trial', to classify studies where costs and outcomes were compared between two different arms of a trial, and 'other prospective evaluation', for studies that prospectively collected cost and outcome information outside of a trial design. 'Secondary analysis of trial results' was used to classify studies which had added an economic analysis to the results of a trial, although the trial had not been designed to collect economic data, and 'retrospective evaluation' was used to classify studies based on returning to existing records to collect data for the evaluation. A general category of modelling was used to describe studies which had synthesised data from a number of sources.* Where the authors had explicitly used decision analytic techniques, this was recorded (and further categorised as 'decision tree' or 'Markov' based).

Where patient level data on resource use or health outcomes had been collected, this information was recorded, as was information on extrapolation of resources, health outcomes, or extrapolation from an intermediate clinical end-point (such as cholesterol reduction) to a final health outcome (such as (QA)LYs). Finally, the methods used by analysts to quantify uncertainty was recorded as 'no analysis', 'sensitivity analysis' or 'statistical analysis'. On occasion, the authors reported that sensitivity analysis had been conducted although they chose not to report the results quantitatively and this was also recorded. In addition, the type of sensitivity analysis was recorded using the defined taxonomy outlined in chapter 1.[90]

Having reviewed the studies using the proforma from appendix 1 as described above, the results were entered into Reference Manager®[91] in the form of key words. This effectively creates a database of cost–utility analyses which allows the interrogation of the database by any of the categories described above and cross-referencing between categories. Examples of the use of the database in this way are given in the following two chapters in relation to the specific concern of this report. However, the potential for this database goes beyond the scope of this report. For example, it would be possible to use the database to identify previously published cost–utility analyses in a particular disease area, for a particular type of intervention, or by country and time period.

Results of the review

The results of searching the online databases up to the end of the 1995 publication year are presented in *Table 2,* which also shows how many studies were identified by each of the search terms. This update of the review to cover the 1996 publication year involved repeating the exact same process; however, it was not possible to include the results of this update broken down by subterms of the search strategy.† However, *Table 2* does show the overall totals, by database, following the update of the review to cover the 1996 publication year. *Figure 3* illustrates the overall process of review and shows that combining the searches of the five databases reported in *Table 2* yielded a total of 826 unique articles (sample 1). Reviewing the title and abstracts of these potential studies led to the rejection of 303 of the articles as clearly not cost-effectiveness studies, leaving 523 potential articles (sample 2).

A total of 337 potential studies in the OHE–IFPMA HEED database and 169 potential studies in the CRD database were identified. These studies were subjected to an initial screen to see if they were appropriate since all studies were known to be economic evaluation related. Combining the sample 2 results with those articles identified from the OHE and CRD databases gave a total of 746 unique articles for the review (sample 3). These articles were obtained and due to a cautious approach to rejecting articles on the basis of titles or abstracts alone, some studies were found to be inappropriate on examination of the full article.

During the process of reviewing the full articles it was clear that a number of the identified studies

* All economic evaluation could be described as including some form of modelling, indeed modelling has been described as 'an unavoidable fact of life'.[63] However, the category of modelling implied here is those studies that are predominantly modelling based as opposed to those based on designs indicated by the alternative categories.

† The reason for this is that the search for articles published up to and including the 1995 publication year was conducted in 1996 and included all available CD-ROMs (for the SilverPlatter™ databases). Notice that the limits (including publication date) are applied after the databases are interrogated by the search terms. The results in *Table 2* therefore included some of the publication year 1996. When the search was subsequently updated to add articles published in 1996, only the most recent CD-ROMs were searched. Although we have results for this search by index term, there is overlap with the results reported in *Table 2*. Since, it is impossible to tell which and how many items in the results overlap, it is not possible to update the table to include results from 1996.

made reference to other studies that had not been identified. Hence, as illustrated in *Figure 3*, secondary identification feeds in to the overall identification process. The results shown apply to all articles that have been obtained and reviewed. However, since this process is dynamic, there are (to date) an additional 16 studies identified from other articles that have not been obtained and reviewed, and these will be added to the results in due course. In addition to all the methods of identification described above, *Figure 3* shows that consideration was given to a further 20 articles identified as potentially relevant either from Gerard's review of cost–utility studies,[89] or through serendipity. Together with those identified through reviewing other articles, this generated a total of 82 additional candidates for the review (sample 4).

To date, a total of 492 studies have been judged appropriate and have been fully reviewed and entered into the database, while 336 of the studies obtained were found to be inappropriate and were rejected (reject 2). The reason for rejection was recorded, and the results are shown in *Table 3*. As the table shows, although a number of studies were rejected for being the wrong type of document or the wrong type of article, the majority of rejected studies were related to economic evaluation. However, 28% of rejected articles related to a review or discussion of economic analysis rather than an applied study, 4% reported results as cost per life saved, but did not take the next step to presenting cost per life-year results, 29% presented a cost-effectiveness ratio other than a cost per life-year saved and 6% of rejected articles presented results which had been presented primarily elsewhere. These rejected articles were used to identify further articles for the review, as described above.

Having identified studies as appropriate for the review, it is interesting to compare the sources from where those studies were originally identified. *Figure 4* shows the 492 studies in the database categorised by source in the form of a Venn diagram. The 'other' category in *Figure 4* relates to the electronic online databases, and *Figure 5* gives

TABLE 3 *Reasons for rejecting articles once obtained*

Reason for rejection	Number	Percentage
Wrong type of document[a]	24	7
Wrong type of study[b]	76	23
Economic evaluation related, but:		
• no applied results reported – review or discussion	3	28
• cost per life saved not cost per life-year	13	4
• other cost-effectiveness ratio not cost per life-year	96	29
• discusses results reported primarily elsewhere	21	6
• cost–benefit analysis	2	1
Other	11	3
Total	336	100

[a] *Including abstracts, reports conference proceedings, book chapters, and discussion papers*
[b] *Including non-healthcare interventions, outcome-only analyses, cost-only analyses, burden of disease studies and other non-economic evaluation studies*

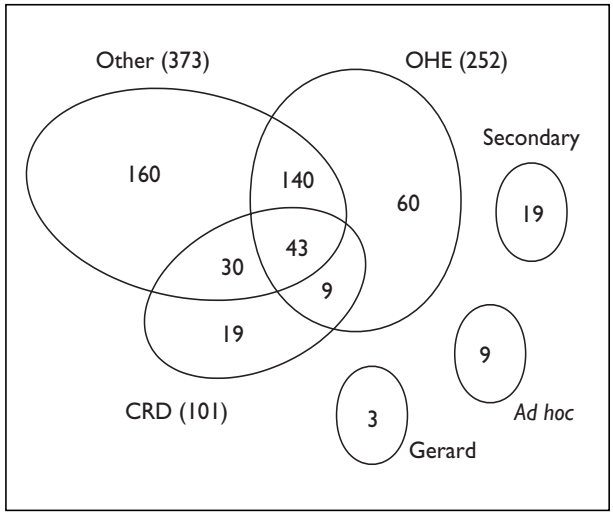


FIGURE 4 *Original identification source of the 492 articles comprising the final sample for the database (see* Figure 3*)*

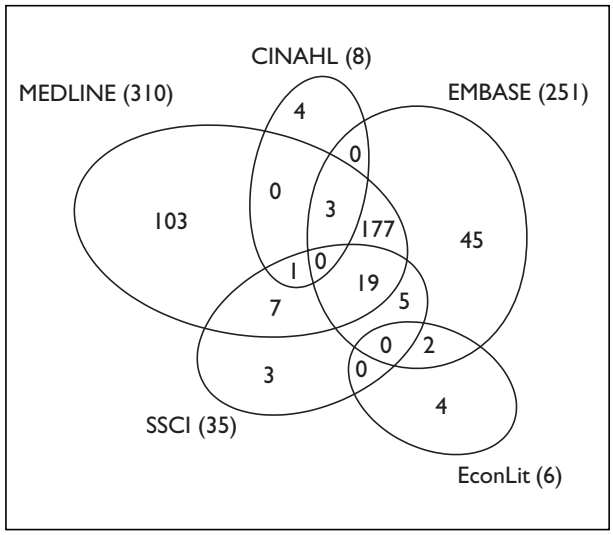


FIGURE 5 *Original identification source for the 373 articles in the final sample identified from one of the general online databases (see* Figure 4 *and* Table 2*)*

the detail of the source of these 373 studies in a further Venn diagram. These results show that none of the methods used for identifying studies in this review were redundant since unique articles were obtained by every method – although it might be argued that the searching of the EconLit, SSCI and CINAHL databases is only of marginal benefit as they identify just 11 studies (2%) of the total.

It is clear that the compiled database represents a substantial body of literature on the cost-effectiveness of healthcare interventions. Since these studies represent outcomes in terms of a common unit, (QA)LYs, the **potential** exists for all the results of these studies to be directly compared.* Before examining the results that relate directly to the subject of this review, it is interesting to look at some of the summary information concerning the studies in the database. One of the most interesting observations is the growth of published studies in recent years. *Figure 6* shows a bar chart illustrating the number of published studies by year, indicating an exponential pattern of growth in the publication of these studies. In addition, *Figure 6* shows the relative share in these studies of cost per life-year versus cost per QALY results. We are currently planning to extend the database to cover the 1997 publication year. On the basis of the pattern shown, we expect to add in the region of 150 articles to the database in the process.

Figure 7 shows the relative shares of the published studies by area of the world. Of course, since only publications reported in the English language were reviewed, the relative shares of studies from Europe and the rest of the world are underrepresented. However, it is clear that North American studies still dominate the literature, as was observed over 10 years ago.[92] Analysis of the database by ICD-9 chapter heading (*Figure 8*) shows that interventions for circulatory diseases, neoplasms and infections dominate the literature – which roughly accords with the burden of these diseases in terms of death rates.[93] Analysis by type of intervention in *Figure 9* shows that the evaluation of medical interventions is much more common than other types of intervention, with twice as many studies as surgery, which is the next highest category. Screening and preventive interventions are the next most popular subjects for evaluation.

The design of a particular study will have an influence over the methods employed by analysts to quantify uncertainty. *Figure 10* summarises the study design results from the database. Of the

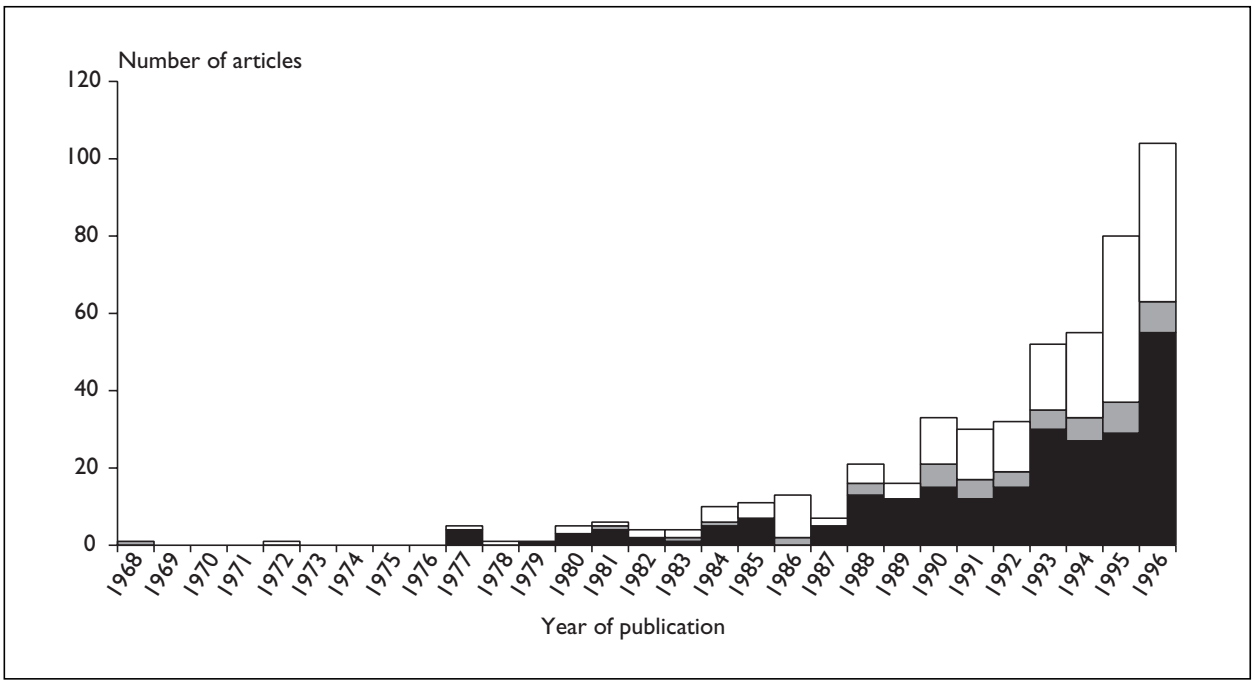


FIGURE 6 *Growth in the cost–utility analysis literature up to and including 1995 (□, QALY results only; ▩, both life-year and QALY results; ■, life-year results only)*

* Care should be taken when comparing results of different studies for a number of reasons, and we discuss these issues in the next chapter.

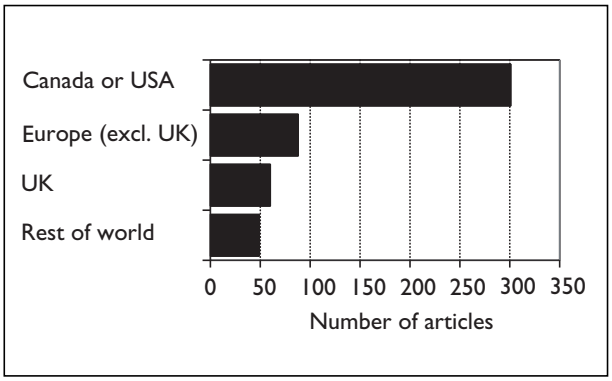


FIGURE 7 *Studies in the database by country to which the results are applicable*

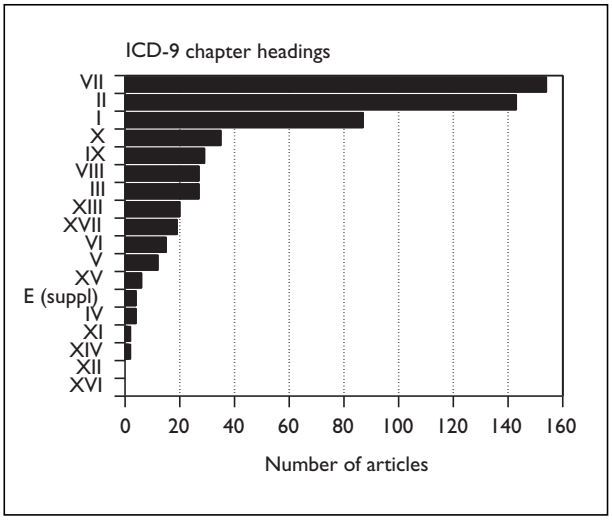


FIGURE 8 *Articles in the database by the ICD-9 chapter heading of the disease/condition to which the results pertain*

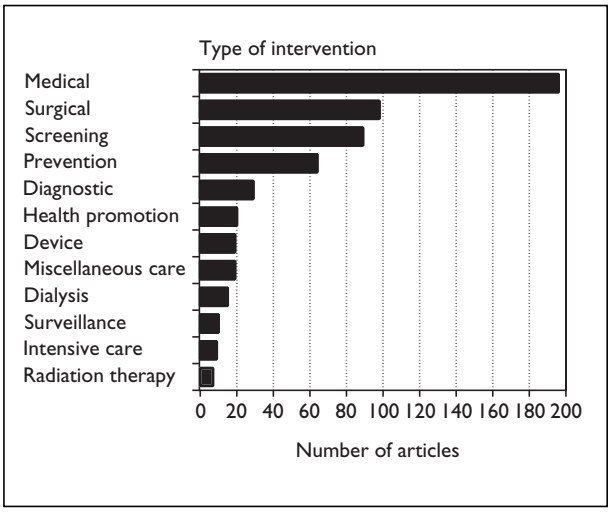


FIGURE 9 *Articles in the database by the type of intervention under evaluation*

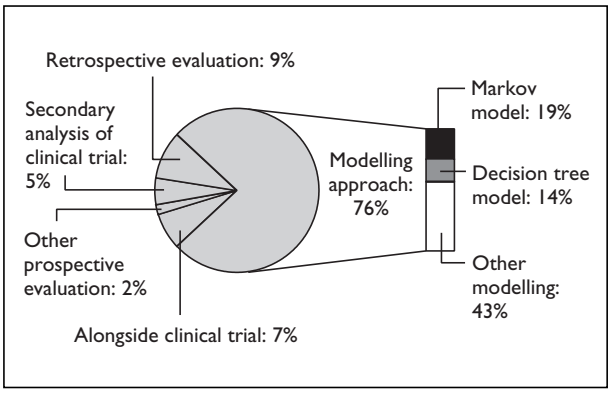


FIGURE 10 *Proportions of articles in the database by type of study*

492 studies, 37 (7%) had conducted an economic analysis alongside a clinical trial, and ten (2%) had been conducted prospectively, but not in a trial situation. A secondary analysis of trial data had been conducted in 27 (5%) of studies, and a retrospective evaluation had taken place in 47 (9%). By far the majority of articles had presented a predominantly modelling-based approach to their study, with data synthesised from a number of different sources. In 33% of articles, the authors had chosen to present their model in formal decision analytic-type terms, with just over half employing a Markov model-type approach, and the rest employing a standard decision tree approach.

The breakdown of the methods employed by analysts to represent uncertainty in their results is presented in *Figure 11*. As the majority of study designs were based on modelling-type approaches, it is not surprising that the majority of analyses used some form of sensitivity analysis to represent the uncertainty in their results. Of these approaches, a simple one-way sensitivity analysis was the most commonly employed method. Some form of statistical analysis was attempted in just 5% of studies, although this was rarely related to the cost-effectiveness ratio itself. Of some concern was that 17% of analysts failed to provide any attempt to quantify the inherent uncertainty in their results. *Figure 12* plots the number of studies failing to report any analysis of uncertainty by publication year for the last 10 years in order to examine whether there has been any improvement over time.

Discussion

The original purpose of the review described in this chapter was to examine in detail all economic evaluations to ascertain the methods which had been employed to handle uncertainty in economic

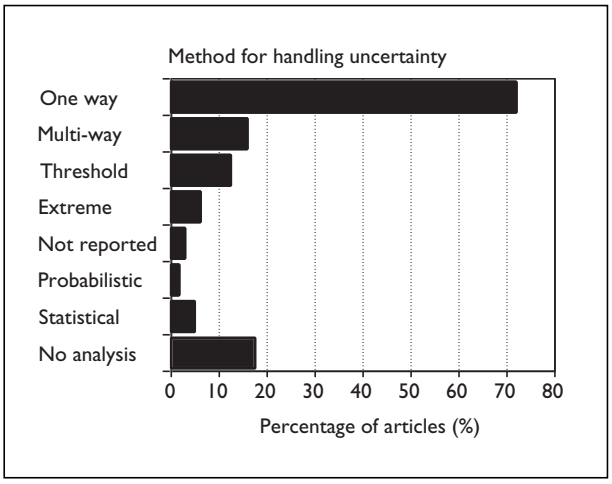


FIGURE 11 *How articles handled uncertainty in their results*

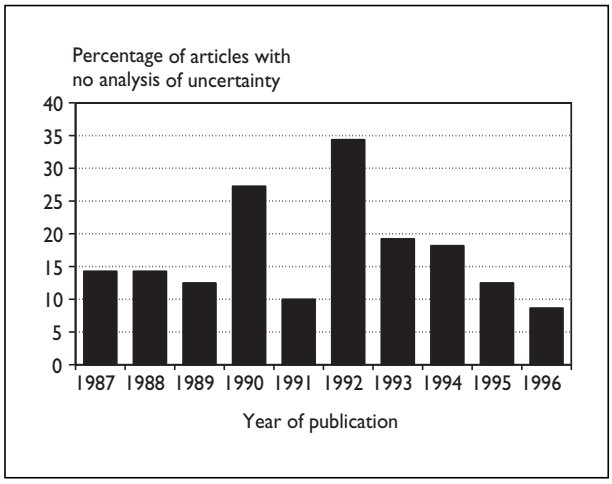


FIGURE 12 *Percentage of analysts failing to undertake any analysis of uncertainty by year of publication*

evaluations reporting results in cost per (QA)LY terms. However, the process of identification and review described in this chapter produced many more studies than was originally anticipated. This made a detailed review of all identified studies beyond the scope of this particular project. Instead, a practical approach was taken, whereby all identified articles were obtained and reviewed by means of a review proforma designed to extract summary information on a number of aspects of the study in question. This overall database of cost-effectiveness studies was then employed to focus in on subgroups of studies for detailed analysis, as described in the following two chapters.

A number of interesting patterns emerge from the data from the overall review described above. The first, and most obvious characteristic, is the exponential pattern of published cost-effectiveness studies. One consequence of this is that if the data collection process for this database is continued, we might expect as many new studies to be added to the database in the next few years as are included in the database now. It is also interesting to note the disease/condition groups and the intervention types of the evaluations in the database in relation to the proportions these diseases/conditions and interventions currently occupy in healthcare provision. Are some more strongly represented in terms of economic evaluation? In particular, to what extent is the evaluative process aimed specifically at medical interventions?

In terms of the handling of uncertainty, it is interesting to note that very few studies are based on primary data collection and instead the majority of studies make use of modelling techniques to synthesise data from a number of different sources. This pattern may change over the coming years, with the increasing tendency to incorporate an economic component in the design of clinical trials. This is likely to produce a greater number of studies that report standard statistical confidence intervals around cost-effectiveness ratios. Of the 15 studies in the database that incorporated some form of statistical analysis of uncertainty, only three attempted any kind of statistical analysis of the cost-effectiveness ratio itself. This may be due to the intractable nature of ratio statistics, which means that the calculation of the confidence interval for a ratio is not straightforward. However, this problem has been the focus of recent research, a review of which is given in chapter 5.

Of some concern is the observation that, at nearly 17%, a considerable minority of studies do not attempt to quantify in any way the uncertainty in their analysis. This figure is less than the 70% of studies identified by Udvarhelyi *et al.*[94] as failing to employ sensitivity analysis in a study of methods employed in cost-effectiveness and cost–benefit analyses. This may suggest that analysts conducting cost–utility type analyses are more careful to include an analysis of uncertainty – particularly since Gerard[89] found that 79% of studies had employed sensitivity analysis in her review of cost–utility analyses. These two reviews are some years old and it is true to say that there has been a proliferation of published reviews and guidelines for analysts, reviewers and editors in recent years which emphasise the importance of sound evaluative methods, including the use of sensitivity analysis. An interesting question is therefore whether there is any evidence that the situation regarding quantifying uncertainty has improved over time. Although no clear trend is discernible

over the last 10 years shown in *Figure 12*, there would appear to be a downward trend from 1992 onwards. Bearing in mind the increasing number of articles over this period (cf. *Figure 6*) there are grounds for optimism that methodological standards are improving.

Although these results seem encouraging, the reliance on simple one-way sensitivity analysis is less so. It is almost certain that the range of results obtained by independently varying a single parameter at a time will underestimate the level of uncertainty compared with a statistical 95% confidence interval.[95] By contrast, extreme scenario analysis might be expected to overestimate such an interval, and could therefore be seen as a more conservative approach; however, only 6% of analysts utilised this approach. The methods of probabilistic sensitivity analysis may offer a compromise between these two methods,[66] but have so far been underutilised in the economic evaluation literature. A further concern is that the use of one-way sensitivity analysis often seemed less than comprehensive, with only select variables subjected to the analysis. This was quantified in Gerard's review by her judgement that over half the sensitivity analyses conducted were limited in scope.[89] No such judgement or analysis was attempted at this level of the review; however, we deal directly with this problem in the next chapter, as we consider the detailed review of all studies reporting cost-effectiveness results for the UK.

Chapter 3

Detailed review of UK studies

Introduction

Performing a reliable economic evaluation is not a simple task. First, several aspects of the underlying methodological framework are still being debated among health economists. Second, there is often considerable uncertainty surrounding the data and assumptions that may have been used, and a lack of consensus over how to handle and express this uncertainty. And finally, there is a substantial amount of subjectivity in presenting and interpreting the results of economic evaluations. What to one analyst is clearly 'a highly cost-effective use of resources' may to another analyst seem poor value for money compared with alternative uses of these scarce resources.

More standardised methodologies and better techniques for handling uncertainties in data and assumptions should be engendered by the recent trend towards the development of agreed guidelines for analysts, reviewers, editors and decision makers.[2,3,96] Here we concentrate on the presentation and interpretation of results, and suggest an approach derived from a structured review of published UK cost-effectiveness studies identified from the overall database reported in chapter 2. A total of 60 studies* were identified that had presented cost per life-year or cost per QALY results in a UK context – the bibliographic references for these studies are listed in full in appendix 3.

Database structure

Each article was reviewed with respect to (1) the methods employed in the study, (2) the baseline results reported and (3) the range of values reported to represent uncertainty. The data from each of these categories were entered into a relational database, a schematic diagram of which is given in *Figure 13*. A relational database structure was chosen since each article could employ a number of different methods, for each method a number of different baselines

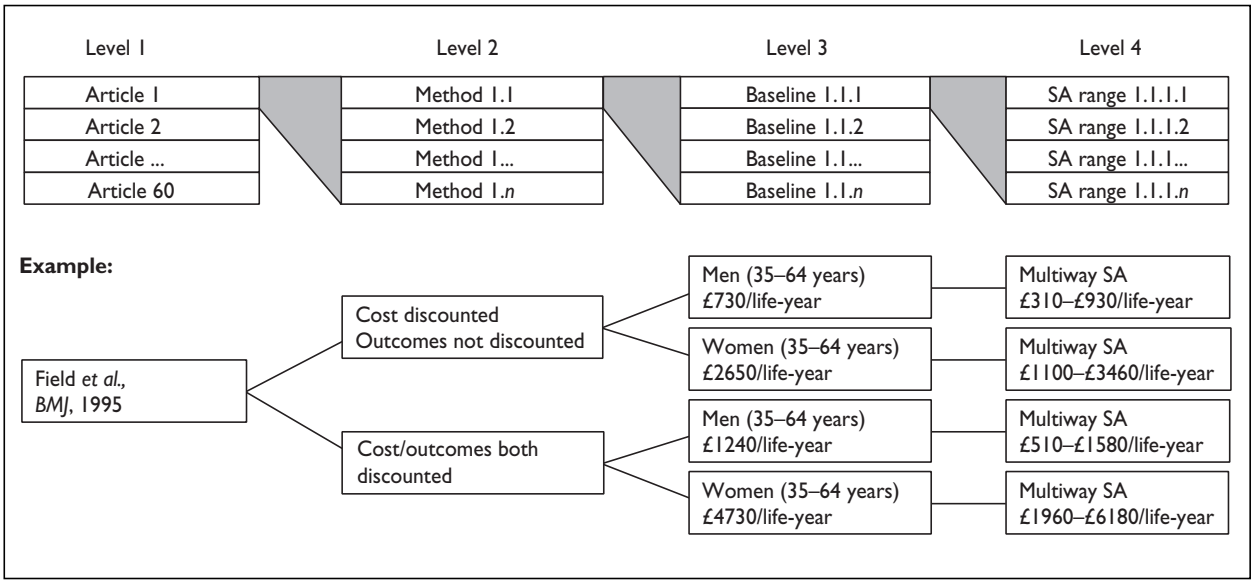


FIGURE 13 *Schematic diagram of the relational database structure (SA, sensitivity analysis)*

* In chapter 2, one of the specified criteria for inclusion in the overall database was that studies were published journal articles. We made two exceptions to this rule by including the Forrest report[97] on breast cancer screening and the Standing Medical Advisory Committee report[98] on cholesterol testing. Both were felt to be high-quality reports that had been influential from a policy perspective without being published in a journal.

could be reported, and for each of those baselines a number of ranges to represent uncertainty could be reported. For each article the number of external cost-effectiveness results quoted by the authors to set their results in context was also collected. Details relating to each level of the review process are given below.

Methodological scenario

Although many methods for economic analysis are uncontroversial, there is still ongoing debate concerning the appropriate methods for some aspects of an economic analysis. The two main areas of controversy are the appropriate discount rate (and whether to employ differential discounting between costs and health outcomes) and the appropriate cost categories (or perspective) for an analysis (for example, should patient costs/loss of earnings be included?) Many analysts recognise that decision makers may well be interested in the effect of a different set of methodological assumptions on the results of their study. Hence it is common to find variations in the discount rate and/or inclusion of various cost categories presented as part of a sensitivity analysis. However, uncertainty related to the appropriate methods for an analysis is fundamentally different from other forms of uncertainty in economic evaluation. Therefore, the first stage of the review process was to identify each 'methodological scenario' (the underlying set of methodological assumptions employed by the analysts) to which the results presented pertain. For example, Field *et al.*,[99] in their evaluation of health promotion strategies in primary care, presented results for two scenarios: firstly, where health outcomes generated by the programmes were discounted at the same rate as costs and, secondly, where those health outcomes were not discounted (this study is used as an example in *Figure 13*).

Baseline analysis

Having specified the underlying methodological scenarios employed in the study, the baseline cost-effectiveness results given by the analysts were reviewed and attached to the appropriate scenario. It is clear that many such baseline results can be presented for each scenario, relating to the disease in question, the type of intervention, and the clinical characteristics and age/sex distribution of the patient population. For example: Dusheiko and Roberts[100] evaluated interferon treatment for both hepatitis B and C; Daly *et al.*[101] presented baseline results for three different combinations of hormone replacement therapy for menopausal women; and Fenn *et al.*[102] presented baseline results for thrombolytic therapy by age and by sex subgroups of patients attending with symptoms of acute myocardial infarction. However, it was not always the case that baseline results were clearly presented as such. Sometimes, subgroup analyses were presented by authors as sensitivity analyses, and in such cases these results were reclassified in terms of this database.

Sensitivity analysis

For each baseline result presented in an article, consideration was given to whether the analysts had recorded a range of values around the baseline estimate in order to represent uncertainty in that estimate. Since sensitivity analysis is not a single method, it is possible for a number of different ranges to be attached to a single baseline result. For example, Freemantle *et al.*[103] calculated results for their analysis of the use of selective serotonin reuptake inhibitors for the prevention of suicide using different combinations of values for the underlying parameters of their model. Consideration of each parameter varied across its plausible range independently (a so-called one-way sensitivity analysis) implies a range of values of £31,000 to £155,000 per life-year saved, whereas consideration of simultaneous variation in each of the parameters varied (a so-called multiway analysis) implies a range of £19,000 to £173,000 per life-year saved.

External results

It was argued in chapter 1 that where interventions are shown to be both more costly and more effective than a comparison treatment, consideration should be given to the opportunity cost of using resources for that intervention compared with other alternative uses for those resources. Hence, it is common for analysts to attempt to put their results in context by comparing their results with the results reported in other studies. The final stage of the review was to record all references to cost-effectiveness results made by analysts. The purpose of this was twofold. Firstly, the process provided a useful check on the identification process of the review – references not already in the database were obtained and reviewed. Secondly, recording details of external cost-effectiveness results quoted permitted an analysis of whether the external results chosen for comparison were related to the magnitude of the results obtained by the analysts: that is, whether there was systematic bias in the chosen values.

Results from the database

A summary of the entries on each level of the database is given in *Table 4*. A total of 60 studies which reported cost per (QA)LY results were

TABLE 4 *Summary of the relational elements of the database*

	Articles	Methodological scenarios	Baseline results	Range of values	External ICERs
Total	60	106	548	209	268
Mean per article	NA	1.77	9.13	3.48	4.47
Minimum	NA	1	1	0	0
Maximum	NA	6	82	42	21
Proportion (%)[a]	NA	100	100	66	61

NA, not applicable
[a] *Proportion of articles which report at least one of each element*

identified and reviewed. For these 60 studies, a total of 106 methodological scenarios, 548 baseline results, 209 range of values and 268 externally quoted ICERs were recorded. The mean, minimum and maximum values for each level in relation to the next level in the database hierarchy are also given. A range of values to represent uncertainty for at least one of the baseline results was recorded for 66% of studies, and 61% of studies quoted an external ICER for comparison with their own results.

A major criticism of cost-effectiveness league tables is that they often contain results derived from studies using different methods.[13,16,104] A recent panel on cost-effectiveness analysis in the USA[3] has recommended that all analysts consider reporting results for a 'reference case' of methods, in order to increase the comparability of studies. In presenting results from our database we adopt a similar approach (although the nature of the reference case varies from that suggested by the US panel). We define a methodological 'reference case' with respect to the perspective of the analysis and the rate of discount. Although traditional welfare economic theory suggests that all costs and benefits are important, no matter to whom they accrue, it has been argued that in attempting to maximise health gain from a limited budget allocated to health care in the UK, only costs to the health service should be included in cost–utility analyses.[13] In practice, this is the approach adopted by many analysts, and we therefore employ a health service perspective as the basis for our reference case. We also adopt the UK Treasury recommended 6% rate of discount[105] for both costs and health outcomes.* Finally, despite clear guidance concerning the appropriate use of incremental analysis, it is common to find average cost-effectiveness ratios (or incremental ratios relative to a common comparator) presented in the literature. Where both average and incremental ratios were presented, these were recorded as different methodological scenarios, and the appropriate incremental ratios were used in our reference case.

Taking each of the articles in turn, we considered each of the methodological scenarios recorded for that article, and chose the scenario that most closely reflected our 'reference case.'† Deviations from the reference case were recorded and then the scenario, together with all the baseline results and ranges attached to that scenario, was employed in the analysis. Where more than one range was associated with a single baseline result, the wider of the ranges was chosen. The 60 methodological scenarios chosen (one for each article) represent 57% of the scenarios in the database. Similarly, the 333 baseline results related to these scenarios represent 61% of the baseline results in the database. Of these, 41% had a range of values associated with the baseline result. Almost half of the baseline results included a cost per QALY figure, and 55% included a cost per life-year result. Hence, just 6% of baseline results were presented both with and without quality of life adjustment.

The 333 baseline ICER results were inflated to represent a common base year (1996) using the

* The Treasury has recently revised its recommendation concerning the rate of discount for health outcomes to 1.5–2%, while the recommended rate for costs stays at 6%. We adopt the previous recommendation here, since this was the recommendation applicable when the review was started and that applicable for when most analysts were conducting their studies.

† Due to the relatively low numbers of methodological scenarios per article, it was clear which scenario conformed to our reference case most closely. Criteria used to choose between scenarios were that appropriate incremental analysis was most important, followed by appropriate discounting, followed by appropriate perspective.

combined *Hospital and Community Health Services Pay and Price Inflation Index*.[106] Where no cost base year was reported, we assumed this to be article publication year minus 2 years. Once all results were on a common price base, we rank ordered the results, employing the QALY result in preference to the life-year result when both were available.

Figure 14 presents the minimum, maximum, mean and decile points from this rank-ordering exercise, and *Figure 15a* shows a histogram of the distribution.* It is clear from these figures that the range of reported ICERs is huge (from £9 to £900,000 per (QA)LY), and that there is a pronounced skew to the results such that the median of £4961 is very much lower than the mean of £30,376. Note that the distribution of the ICER results and reporting of statistics excluded ten of the 333 baselines which reported that the intervention in question was dominated by the comparator.

Extracts from the rank ordering of interventions are shown in *Table 5* (the full version of the table, showing all 333 results is reproduced in appendix 4). Results shown are the (closest) corresponding baseline to the results shown in *Figure 14* (excluding the ten dominated results). The rank ordering of the baseline results is shown adjacent to the article identifier. Deviations from the reference case of appropriate methods is listed in order to elucidate issues of comparability. Although not shown in *Table 5*, some baseline results concurred with the reference case exactly such that no deviations were recorded (see appendix 4). The intervention description includes a description of the patient subgroup to which the result pertains (where appropriate) and the comparator against which incremental costs and health outcomes were judged.

Since 61% of articles quoted external ICERs from other studies for comparison with their own results, it was possible to compare the distribution of these external ICERs (similarly inflated to 1996 values) as shown in *Figure 15b* with the baseline results from the rank-ordering exercise shown in *Figure 15a*.

Of the 333 baseline results, 133 (40%) had some form of sensitivity analysis recorded for that result. To illustrate the importance of uncertainty for the rank ordering of cost-effectiveness results, we identified 61 of these results (i.e. 18% of the overall baseline results) that had reported a 'two-sided'

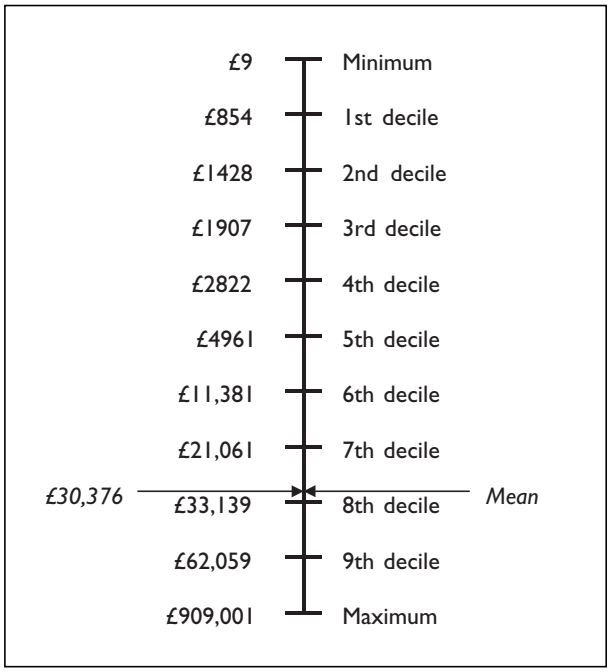


FIGURE 14 *Summary of the distribution of the rank-ordered ICERs*

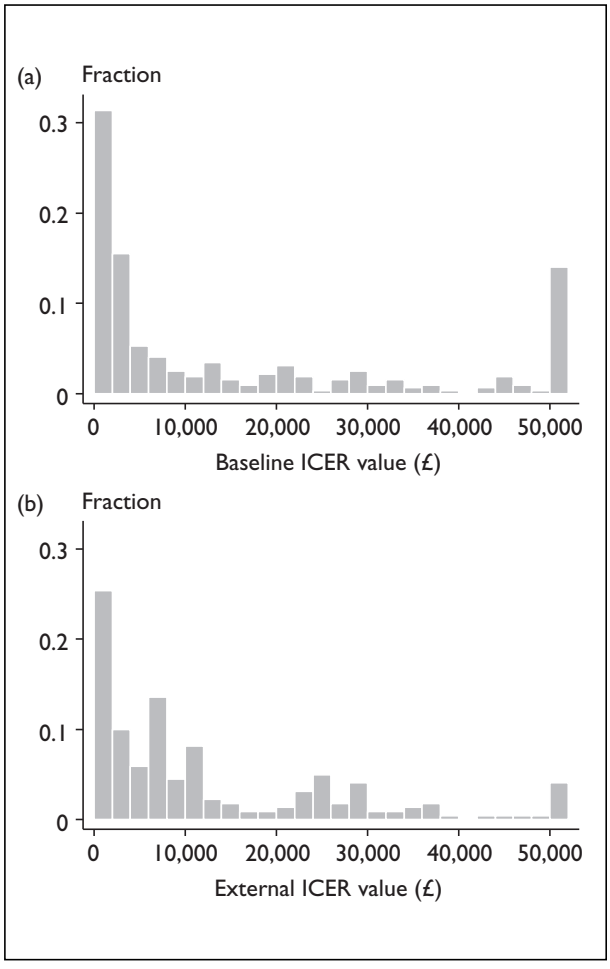


FIGURE 15 *Histograms of the distribution of (a) baseline ICERs from the database analysis and (b) external ICERs quoted in studies for comparison*

* In order to better see the distribution, ICER values greater than £50,000 are represented by a single bar in the histogram.

TABLE 5 *Extract from the league table of analysed ICERs*

Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Phillips 1993	1	No mention of discounting for health outcomes	Introduction of the 'Heartbeat Wales' no-smoking programme compared with no programme	0	£9	1	2	2		£97
Russell 1990	33	No averted costs included. Health outcomes discounted at 5%	Screening for abdominal aortic aneurysm and early repair compared with no screening for men aged 65 years	1	£849	0				
Parkin 1986	65	No averted costs. Health outcomes discounted at 5%. Inappropriate ICER	5-yearly screening programme for women aged 25–65 years compared with an opportunistic screening programme	0	£1428	1	1	1	£886	
Haigh 1991	97	Costs and health outcomes discounted at 5%	Thrombolytic therapy administered between 7 and 24 hours of onset of symptoms suggesting acute myocardial infarction for patients aged between 55 and 64 years compared with no therapy	1	£1906	0				
Hatziandreu 1994	129	Costs and health outcomes discounted at 5%	Selective serotonin reuptake inhibitors compared with tricyclics for preventing suicide in depressed female patients aged 35 years with two previous depressive episodes	1	£2820	1	2	8	£1073	£6830
Akehurst 1994A	162	No averted costs included	Nicorette® patch in addition to general practitioner counselling to help smokers to quit	0	£4994	0				
Pharoah 1996	194	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for males aged 55–64 years with existing heart disease (myocardial infarction) and cholesterol concentrations of 6.6–7.2 mmol/l	0	£11,440	0				
Drummond 1992	226	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Angiotensin-converting enzyme inhibitor therapy for male hypertensive patients (100 mmHg) aged 40 years compared with no therapy	1	£21,173	1	1	2		£39,523
Anderson 1993	253	No averted costs included. Health outcomes not discounted	Implantable cardioverter defibrillator (ICD) compared with no ICD for patients with cardiac fibrillation and with non-sustained ventricular tachycardia and inducible arrhythmia not suppressed by drugs	0	£30,516	0				
Field 1995	258	No averted costs included	Screening strategy for heart disease risk factors with appro priate treatment and cholesterol-lowering drugs for total cholesterol > 7.5 mmol compared with screening with cholesterol-lowering drugs for total cholesterol > 8.5 mmol for reducing risk factors for heart disease in women	0	£33,210	0				

[a] See appendix 3; [b] 0, no; 1, yes; [c] 1, on-way; 2, multiway

continued

TABLE 5 *Extract from the league table of analysed ICERs*

Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Richards 1996	290		Home parenteral nutrition compared with no feeding in patients with intestinal failure aged under 44 years	1	£62,137	0				
Anderson 1993	322	No averted costs included. Health outcomes not discounted	ICD compared with no ICD for patients with cardiac fibrillation and inducible arrhythmia suppressed by drugs plus high-ejection fraction	0	£909,001	0				

[a] *See appendix 3;* [b] *0, no; 1, yes;* [c] *1, on-way; 2, multiway*

range of results in the sensitivity analysis.* These 61 results were then rank ordered on the basis of their baseline values, but included information on the range of possible values as reported in the sensitivity analysis was included. *Figure 16* illustrates the results – with point estimates represented by circles and ranges around those point estimates represented by 'I' bars (arrowheads for the upper range indicate that the 'I' bar has been truncated for purposes of presentation). Many of the results have only a small range of possible values, but a significant minority have substantial variation shown in their range. This means that the rank ordering of results could be significantly affected by the possible values within the range. For example, *Figure 17* shows the same group of results ordered on the basis of the lowest value in the range, and *Figure 18* shows the same results ordered by the highest value in the range. An overall summary of how the rank ordering is changed from that implied by the baseline rank order is given in *Figure 19*, where movements between rank orders

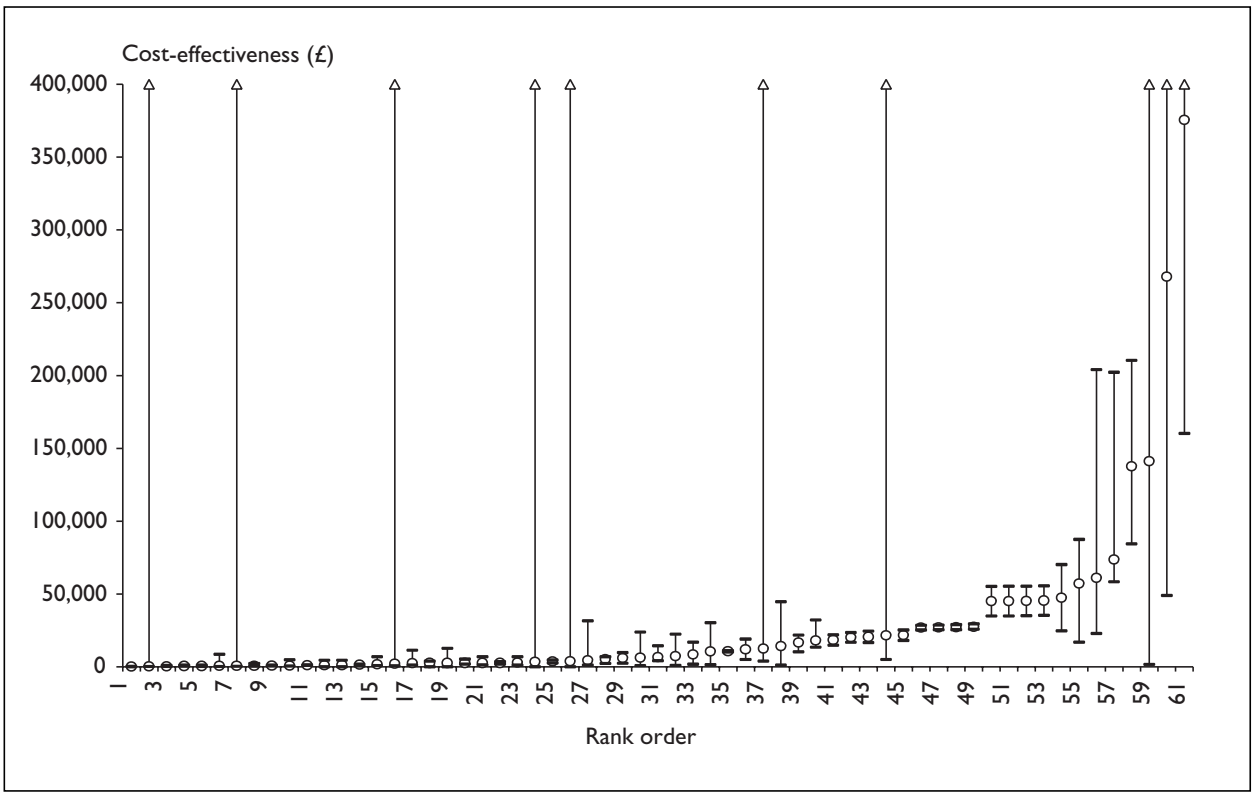


FIGURE 16 *Sixty-one cost-effectiveness results with ranges, rank ordered by baseline value*

* That is, we excluded those results for which the sensitivity analysis range was 'one-sided' in either direction such that the baseline result was also a high or low value for the range.

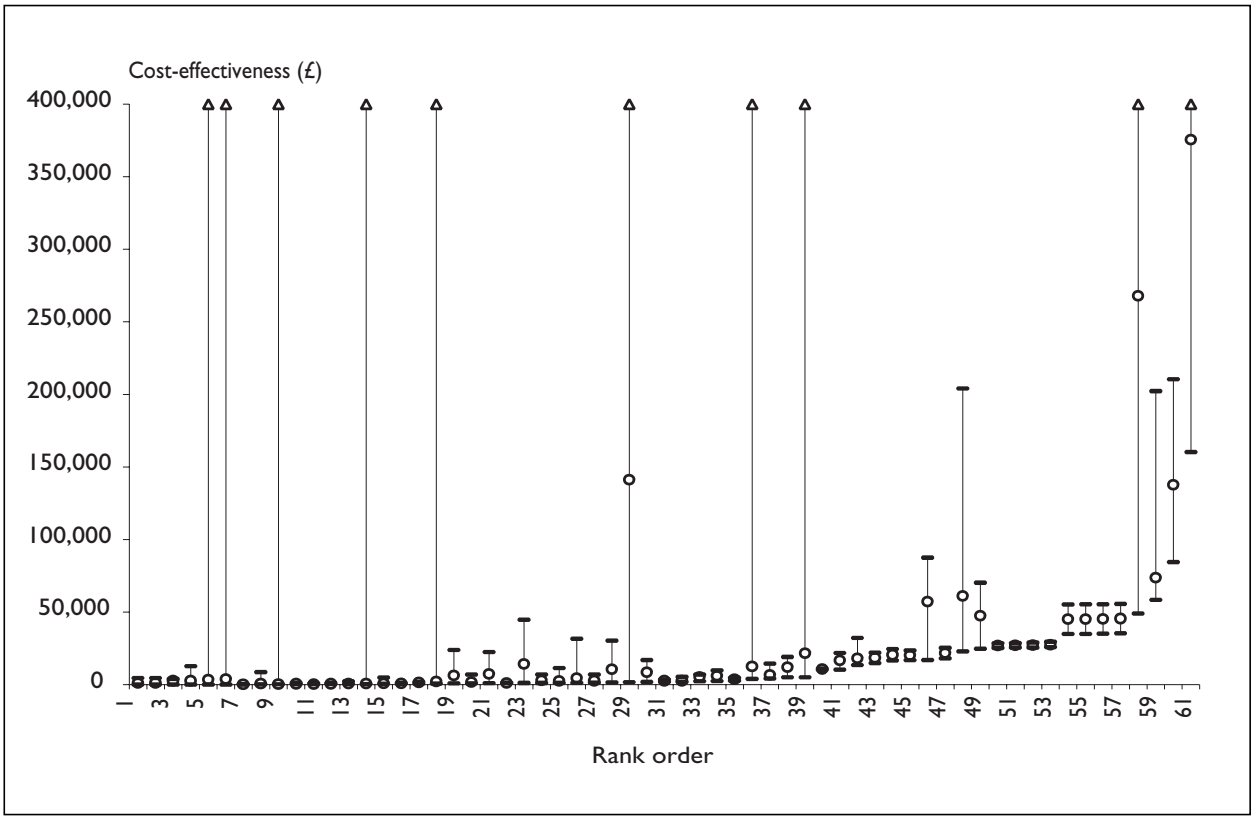


FIGURE 17 *Sixty-one cost-effectiveness results with ranges, rank ordered by lowest value from range*

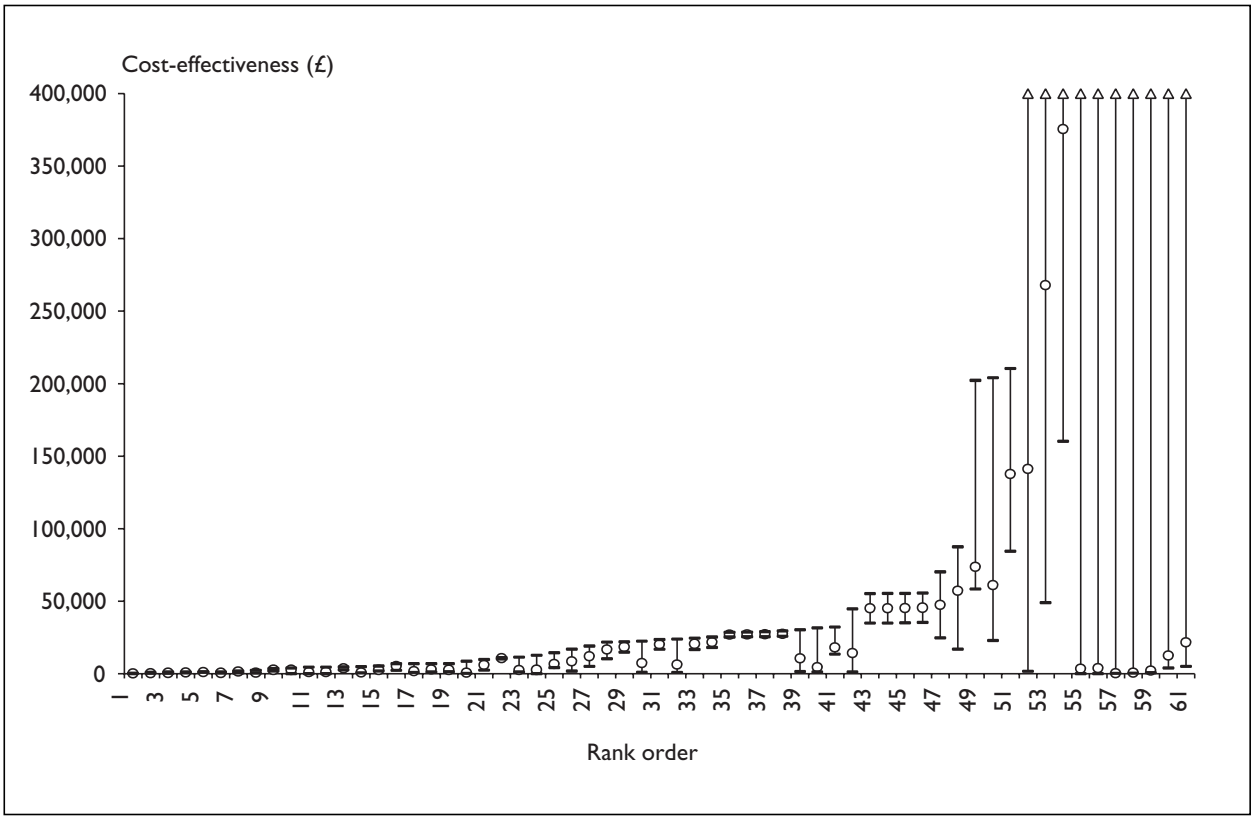


FIGURE 18 *Sixty-one cost-effectiveness results with ranges, rank ordered by highest value from range*

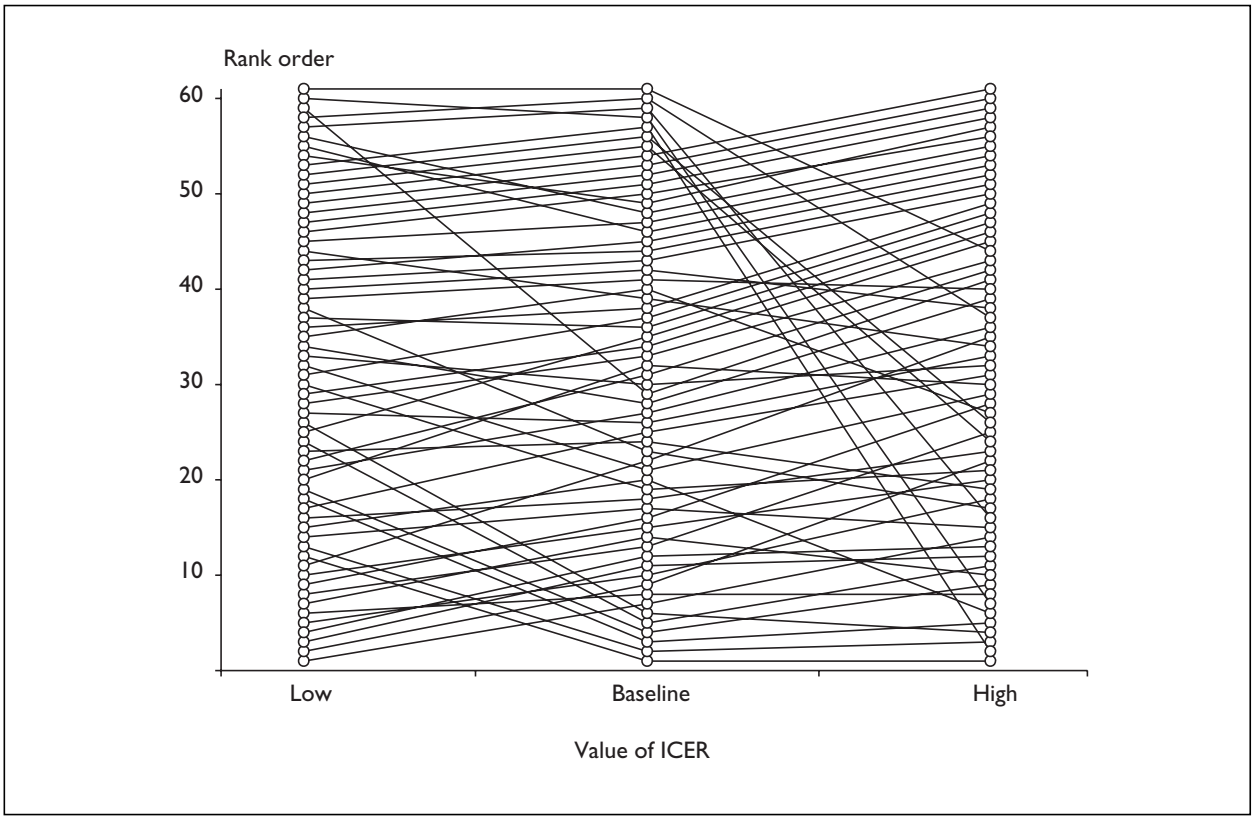


FIGURE 19 *Movements between the rank ordering by baseline, low and high values*

based on baseline, low and high values is illustrated. The correlation between the rank orderings was calculated as 0.89 between the rank order based on baselines and the rank order based on the lowest value from the range, 0.65 between the rank orders from the baseline and highest values, and 0.55 between the lowest and highest value-based rank orders.

Discussion

It might be argued that the results of our analysis are difficult to interpret due to the inclusion of cost per life-year and cost per QALY results in the same league table. While it is true that these figures are based on different assumptions so might be argued to be not strictly comparable, we believe that as a comparative methodology, cost-effectiveness analysis requires strict comparability between alternative uses of resources. It would make less sense to present two league tables of values, one for cost per life-year and one for cost per QALY. So few studies report both cost per life-year and cost per QALY figures that we do not attempt any comparison in the context of this review. However, we believe that authors tend to present cost per life-year values where mortality is the predominant effect, while it is clear that it would be inadvisable to report an analysis of cost per life-year when the predominant effect of treatment is on quality of life.

A case in point is the cost–utility analysis of laser-assisted angioplasty for the treatment of peripheral arterial occlusions by Sculpher *et al.*[107] Since one of the main consequences of failed treatment is amputation, the predominant effect of treatment is on quality of life, hence the authors present their results in cost per QALY terms, reporting a £3040 cost per QALY ratio for the use of laser-assisted angioplasty in claudicant patients. From the data reported in the article, it is possible to calculate a cost per life-year ratio of £18,270 for the same treatment. However, to suggest that this demonstrates that cost per QALY and cost per life-year results are not comparable would be to miss the point. The authors chose not to report a cost per life-year ratio because the important effect of treatment was on quality not quantity of life. We might expect therefore that cost per life-year results are only reported when the predominant effect of treatment is on mortality.

We also demonstrate the importance of considering uncertainty when rank-ordering cost-effectiveness results. In terms of our database, only 40% of baseline results were accompanied by some form

of sensitivity analysis to quantify uncertainty, with over half of these representing a one-sided or partial interval. Focusing in on those results for which a full interval as well as point estimates were available (18% of baseline cost-effectiveness results) showed important differences in rankings based on the baseline, low or high values of cost-effectiveness. A rank ordering on the basis of the highest value quoted for a particular result (see *Figure 18*) may give important information to risk-averse decision makers since those studies with greatest uncertainty are relegated to the bottom of the rank order.

However, it is important to emphasise the limitations of our analysis of rank-ordering changes at this point. Firstly, the point estimates and ranges were highly selected since the majority of baseline cost-effectiveness results are presented as point estimates with no accompanying interval estimate. Secondly, interval estimates are most commonly based on one-way sensitivity analysis, which may underestimate uncertainty. Furthermore, the average number of variables included in the sensitivity analysis for the results presented in this chapter was just 3 (range 1–13, median 2), which also suggests that analysts employ sensitivity analysis in a less than comprehensive way. This again could lead to underestimation of uncertainty. Thirdly, there seems to be a difference between the studies reporting the highest and lowest variance in their intervals in terms of the numbers of variables included in their sensitivity analyses. Using a definition of a coefficient of sensitivity (CS) equal to the difference between the highest and lowest values of the interval divided by the baseline value,[108] those results with a CS < 1 included, on average, only two variables in their sensitivity analysis. By contrast, results with a CS > 1 included a mean of four variables in their sensitivity analysis. All else being equal, it is expected that the greater the number of variables included in a sensitivity analysis, the greater the width of the resulting interval.

Notwithstanding these limitations, our analysis is illustrative of the importance of estimating an interval for **each** baseline result reported in a cost-effectiveness analysis. These intervals could then be used to explore the importance of uncertainty for the rank ordering of cost-effectiveness results. It is likely that risk-averse decision makers will want to attach less weight to results with a high degree of uncertainty.

The comparison of the distribution of baseline results with the external results quoted by analysts shows important differences. The external ICER values chosen misrepresent the actual distribution of published ICER figures. In particular, low-valued ICERs are substantially underrepresented and middle-range parameters are substantially over-represented. In addition, the top-end values of ICERs are also underrepresented in the external ICERs quoted.

An important limitation of conventional league tables is that in a limited space, results may have to be averaged even if analysts have reported results for many different subgroups. Hence, the potential for ICER results to vary at the margin is rarely evident from league tables. However, the approach of constructing a cost-effectiveness database has allowed us to record all baseline cost-effectiveness results reported by analysts, and the inclusion of information on how ICER results vary at the margin is an important feature of our analysis. We discuss three main ways in which ICER results can vary at the margin, illustrated with results from the database.

The first margin we consider is a clinical margin where the ICER may change as a service is expanded/contracted to cover different subgroups of patients with different capacities to benefit from treatment. The importance of recording subgroup analysis as separate baselines is illustrated in *Table 6* using an example from the database which looked at the cost-effectiveness of the implantable cardioverter defibrillator device for treating patients following cardiac arrest.[109] The overall cost-effectiveness of the intervention of £74,100 per life-year masks variation in the cost-effectiveness by subgroup of those patients. Depending on whether patients have a high ejection fraction, inducible arrhythmia and whether inducible arrhythmia can be controlled by drugs, cost-effectiveness can vary from £28,600 to £909,000 per year of life saved.

The second margin of importance we refer to as an intensity margin. At this margin, the same group of patients can receive treatment with greater or less intensity, and cost-effectiveness results should be calculated along this intensity margin. For example, in an analysis of the Oxcheck and British Family Heart Study results, Wonderling *et al.*[110] found that the more intensive British Family Heart Study intervention protocol was expected to generate additional reductions in risk of coronary heart disease over and above those achieved through the less intensive Oxcheck-style intervention. They therefore presented the ICER results for the British Family Heart Study as incremental to the Oxcheck study in order to correctly identify

TABLE 6 *An example of the importance of subgroup analysis – the case of the implantable cardioverter defibrillator for patients surviving cardiac arrest*

High-ejection fraction?	Inducible arrhythmia?	Controlled by drugs?	ICER (£)	Rank
Y	Y	Y	909,001	176
Y	N		212,966	173
N	Y	Y	98,692	168
All patients in the three subgroups			74,100	168[a]
Y	Y	N	48,047	159
N	N		46,749	157
N	Y	N	28,569	141

Y, yes; N, no
[a] *The average across all subgroups was not included in the final analysis: this rank is the rank it would have attained had it been included*

the cost-effectiveness at the intensity margin. Other examples of the intensity margin include the cost-effectiveness of the dose–response relationship for medical interventions, and the results of changing the screening interval in screening interventions.

The final type of margin for cost-effectiveness is a scale or volume margin. For example, Sculpher *et al.*[107] consider the annual utilisation of a laser facility in their cost–utility analysis of laser-assisted angioplasty. They argue that if laser utilisation can increase to over 200 sessions per annum, then the use of the laser will dominate sole reliance on conventional guide-wire angioplasty. To achieve such rates they consider the shared use of laser facilities or the creation of specialist laser centres. The issue of a scale or volume margin typically arises through the use of an expensive piece of capital equipment were the average cost is related to patient throughput. Note, however, in contrast to the clinical and intensity margins illustrated above, this issue is simply an example of technical efficiency. Hence, in an analysis of extracorporeal shock wave lithotripsy (ESWL) for the treatment of stones in the kidney or ureter, Patel *et al.*[111] considered five alternative methods of providing ESWL. The authors concluded that the most (technically) efficient method of provision was to provide second-generation ESWL machines operating at stone centres each serving a population of 12–15 million, since this involved the least use of resources. Therefore, while analysts should be aware of issues related to the volume margin; baseline cost-effectiveness results should not vary at this margin; rather, the most technically efficient arrangement should be the option of choice.

Summary

Cost-effectiveness analysis is a comparative methodology, in which results have meaning primarily in relation to opportunity cost as measured by other cost-effectiveness results. It follows that the greater the number of results available for comparison the more accurately can the relative cost-effectiveness of any particular study be judged. The league table has to date been a common way of making a comparison against other treatments routinely provided in the health service, other treatments which by inference society/ healthcare providers are already revealing a willingness to provide at the calculated cost-effectiveness ratio. However, league tables – or other lists of external comparators – are seldom comprehensive. In our review, the 61% of studies that had referred to external comparators quoted on average just six UK cost-effectiveness results. Thus, assessment of the relative cost-effectiveness of an intervention is generally made on the basis of very incomplete information. This is especially so when analysts are trying to get some grip on mean or median values – what is **routinely** provided and regarded as a currently acceptable norm across the health sector. This scope for subjective opinion and interpretation of cost-effectiveness results has been an important factor in the controversies over research sponsorship.[112]

That the ICERs quoted by analysts when reporting their results may be biased is supported by the observation that 40% of analysts seeking to set their results in the context of other published values for the UK chose to make use, at least in part, of the cost-effectiveness league table used by

Williams in his illustrative cost–utility analysis of coronary artery bypass grafting.[113] This may explain the apparent bimodal distribution of the external ICERs quoted by analysts shown in *Figure 15b*. An alternative explanation might be that analysts are seeking examples of 'good' value for money (at less than £5000 per (QA)LY) and examples of 'not so good' value for money (at around £25,000 per (QA)LY).

Assessing the results of a cost-effectiveness analysis against a structured review, such as that reported here of all UK studies published up to 1996, should allow a better assessment of relative cost-effectiveness. For example, rather than vague and inevitably subjective comments that a particular result 'compares well with existing uses of health-care resources' (see *Table 7* for examples of the types of comment frequently made to describe cost-effectiveness results), analysts (or readers) could place results within a distribution – 'below the median figure for all published UK cost-effectiveness results', or 'within the first decile of published UK cost-effectiveness results'. Of course, it should be noted that our database – as with league tables – is based purely on published results and does not imply that the interventions are necessarily in use. A published ICER should not be equated with a currently accepted use of healthcare resources.

Comparing results in this way requires a relatively high degree of uniformity in the basic cost-effectiveness methodology employed. This structured review has attempted to deal with this by selecting from studies the methodological scenarios that best conform to a reference case. This can be seen as a retrospective application of the prospective 'reference case analysis' approach proposed by the US panel on cost-effectiveness.[3] The acceptance of a more broadly based but methodologically similar set of comparisons across the full spectrum of health-related interventions, as proposed here, might encourage adherence to standards, and meanwhile should help to reduce the amount of subjectivity involved in interpreting results.

TABLE 7 *Analysts' comments on the cost-effectiveness of the interventions under evaluation*

Article identifier[a]	ICER (£)	Rank	Cost-effectiveness comment
Drummond 1988	996	25	'…according to these data the cost per quality-adjusted life year gained for cataract operation compares favorably with those for other health care interventions in the United Kingdom' (p. 1152)
Hart 1993	1054	28	'The cost-effectiveness of enalapril in chronic heart failure is as good as or better than many widely used treatments for cardiovascular disease' (p. 92)
Tubman 1990	1077	29	'…compares favourably with the cost per quality adjusted life year of some forms of treatment for adults in the United Kingdom' (p. 844)
Fenton-Lee 1993	2157	78	'The management of pancreatic necrosis is expensive but justified by the excellent outcome in terms of quality of life' (p. 1579)
Pharoah 1988	3458	86	'It will be for others to decide whether lives and life-years gained at these prices represent good value for money or whether medical resources might be better used' (p. 717)
Ridley 1994	959–13,555	23–121	'The cost/QALY… puts intensive therapy at the higher end of health programmes' (p. 195)
Gournay 1995	42,459	148	'Of treatments for which cost per QALY are available, we do know that the cost per QALY of CPN intervention in our study is at the highest end.' (p. 776)
Anderson 1993	48,047	157	'Use of the [implantable cardioverter defibrillator] in this group currently seems relatively expensive compared to other medical treatments' (p. 90)

[a] *See appendix 3*

Chapter 4

Distribution and variance of cost data

Introduction

As noted above, concerns over the methods and results of economic analyses arise in part because sensitivity analysis normally lacks statistical rigour. For example, when cost data are incorporated in these analyses, it is common to use point estimates of costs, or mean values, and to vary them arbitrarily, with no reference to the actual or presumed underlying variance and distribution of costs and associated confidence intervals. Similarly in relation to outcomes, sensitivity analyses seldom make use of confidence intervals derived from clinical trial data, or from systematic overviews.

To address these complex issues in manageable steps, this chapter begins by examining those studies from the full cost-effectiveness database described in chapter 2 which contain resource use or cost data at the individual patient level, in order to assess the ways in which the variance and distributional form of these data are reported by authors. The second part of this chapter then looks in more detail at five data sets of patient-specific cost information, which we were able to obtain and analyse, in order to examine their distributional form in more detail. The following chapter then considers the handling of uncertainty when cost and effectiveness data are presented as a ratio.

Method

From the 492 published cost-effectiveness or cost–utility studies in the main database, a subset of studies was identified in which patient-specific resource and/or cost data had been reported. Details were then extracted from this subset of studies on the study design (RCT or not); whether or not patient level data had been collected on resource use and on cost (and if so, the sample size used); the size of the trial population from which any resource sample was drawn; the number of arms in a trial; the number of centres from which resource or cost data were collected; and the mean follow-up period. The data sheet then recorded whether the study reported a resource use mean, variance or distributional form; the number of cost components reported; and, for the control and intervention arm(s), the reported mean or median cost, the measures of cost variance reported, any mention of the distributional form of the cost data, any significance tests for cost differences, and, finally, any comments on the studies in a free field.

Results

From the full set of 492 studies, 26 studies were found which had collected patient-specific resource/cost data as part of an RCT, and a further 27 were identified which had collected patient-specific resource/cost data as part of a non-RCT study. In addition, a further 12 studies (three RCT, nine non-RCT) were identified which had collected patient-specific information in the course of the analysis but analysed it in such a way (aggregating resource use in each arm of a trial, applying unit costs and then dividing by n, or variants of this approach) that it was not possible to calculate interpatient cost variance. In total, therefore, 53 of the 492 studies in the database (11%) reported collecting patient-specific resource/cost data in a way which allowed some measure of variance to be reported. These are identified in appendix 5.

Of these 53 studies, 17 reported some statistical measure of variance concerning use of resources, and 25 reported some statistical measure of variance concerning costs. Three studies mentioned the distributional form of resource use data (two normal, one positively skewed). Turning to the measures of cost variance reported, five articles gave a standard error, seven a standard deviation, four gave 95% confidence intervals, two gave an interquartile range, and 11 gave a range. In addition, one study reported an indeterminate measure – of the form 'mean ± x' – which was probably either standard error or standard deviation, but could not be classified. In only four cases did articles report more than one measure of variance: standard deviation and range (two articles), standard error and range (one article), standard error and interquartile range (one article).

In the 26 RCT-related articles, 12 articles reported the value of the mean difference in costs between trial arms, and three of these articles reported some measure of variance in mean cost difference

(95% confidence intervals). Eight articles either reported the *p* value for a significance test of mean cost difference (four articles) or reported that that the difference in mean costs was not statistically significant (four articles). In the 27 non-RCT-related articles, none reported a mean cost difference with associated variance between the patient groups or interventions being compared (one reported a mean cost difference with no measure of variance), and only one article reported a significance test for mean cost difference. These results are shown in *Figure 20*.

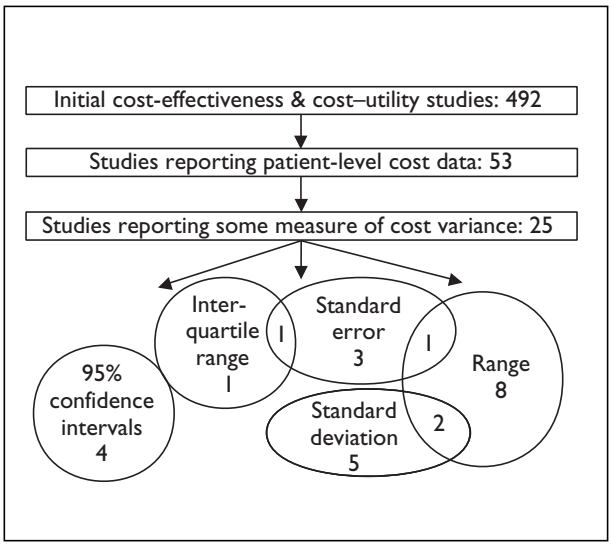


FIGURE 20 *Summary of the handling of cost variance by studies reporting patient level cost data*

In summary, therefore, only a tiny fraction of the published cost-effectiveness analyses retrieved (15/492, or 3%) reported some conventional measure of variance (standard deviation, standard error, 95% confidence interval) around the mean cost estimates they used to calculate cost-effectiveness ratios.

Despite the general lack of information on cost variance in the articles identified, many proceeded to a cost-effectiveness analysis using only point estimates of cost difference. For example, Cantor *et al.*,[114] Castiel *et al.*,[115] Goodwin *et al.*,[116] Jaakkimainen *et al.*[117] and Tramarin *et al.*[118] all use patient-specific cost data for which no information on variance has been reported in cost-effectiveness or cost–utility ratios. To illustrate, Goodwin *et al.*,[36] who were comparing the costs and effectiveness of standard and alternating chemotherapy in small-cell lung cancer, reported a cost per patient of US $16,416 in the standard therapy arm and US $16,866 in the alternating therapy arm, a cost difference of US $450 or < 3%, which almost certainly was not significant, although no measures of variance were reported. They then calculated a cost-effectiveness ratio (US $3371 per life-year gained) and cost–utility ratio (US $4495 per QALY) using this point estimate of cost difference, and in consequence probably seriously understated the degree of uncertainty surrounding their estimated cost-effectiveness ratios.

From the 15 articles identified above as reporting patient-specific mean cost data and conventional statistical measures of variance, a total of 32 mean cost figures with associated standard error, standard deviation or confidence interval were extracted (e.g. a three-arm trial with data for each patient group gave three observations). All variances were then calculated as a standard deviation and coefficient of variation. For these 32 observations, the mean cost was 37,938 (in different denominations), with a mean standard deviation of 40,150; the mean of the corresponding coefficients of variation was 1.01.

A sample size was available for 28 of the 32 observations: the mean sample size was 78 (standard deviation 82, median 37, range 2–279). Given these levels of variance and sample sizes, how much difference in cost would these studies in fact be powered to detect? At a mean of 37,938 and standard deviation of 40,150, a sample size of 78 per arm would be incapable of detecting anything less than a 50% difference in cost. To detect a 10% difference in cost, given this degree of variance in costs, would require a sample size of 1910 patients per arm. *Figure 21* illustrates these results. It therefore seems clear that the majority of cost studies identified in this review are grossly underpowered to detect any but extremely large differences in cost.

Five data sets describing patient level cost data

In this section, five available data sets on cost were analysed to examine the variance and distributional form of the data, and the potential to employ data transformation techniques when analysing and presenting the data. A brief description of each of the five data sets is given below:

- **The anticoagulation example**. These data were taken from an economic evaluation conducted alongside a sequential comparison of a consultant-based anticoagulant clinic service with a nurse specialist clinic service.[119] The objective of the study was to assess differences

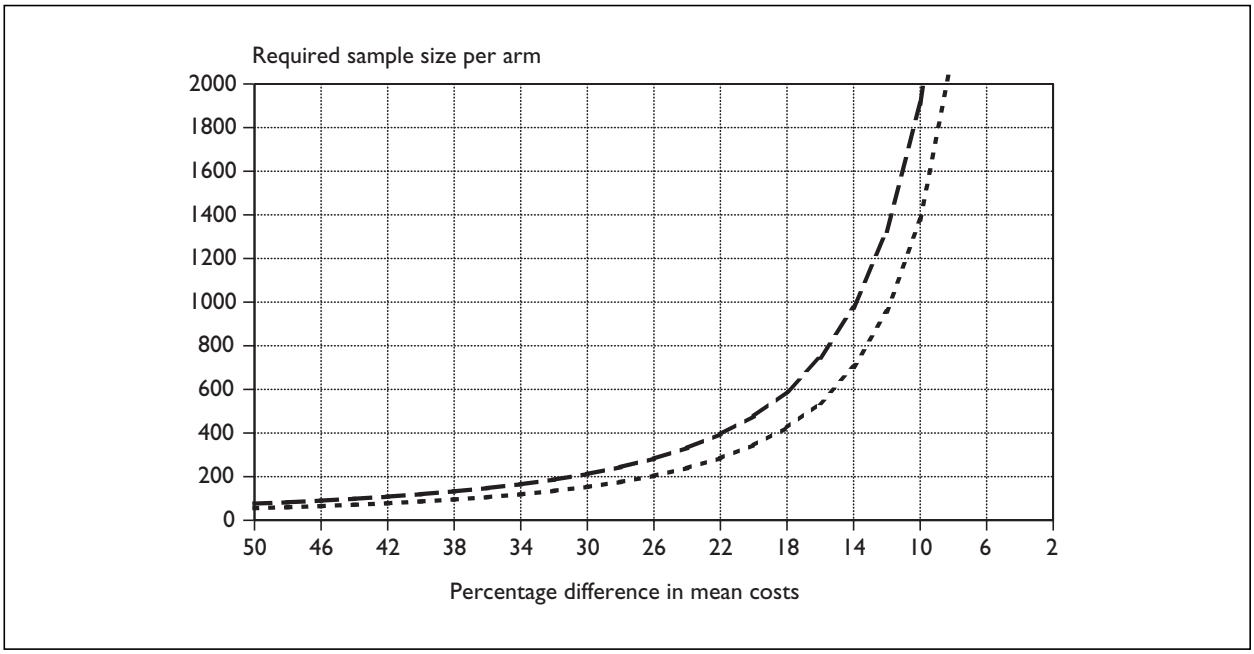


FIGURE 21 *Illustrative power calculations: size of cost difference detectable and required sample size per arm for cost data with a control group mean of 40,836 and a standard deviation of 38,545 (- - -, 80% power and 5% significance; — —, 90% power and 5% significance)*

in the costs to the NHS of the two modes of providing an anticoagulation service, with each service observed for 6 months. Resources used (clinic and domiciliary visits, patient transport, blood tests, general practitioner visits, hospitalisations) were recorded for each patient, and unit costs were then applied to these resource quantities to obtain a total cost per patient for each category of resource use.

- **The antiviral example**. These data were provided by Fenn *et al.*[120] The data originate from a clinical trial that compared a drug therapy treatment group with a placebo control group. Programme costs for each patient were estimated by aggregating recorded resource usage weighted by the prices of those resources. Length of survival for each patient, during the follow-up of the trial, was also recorded. Fewer details are given for this data set since anonymity of the compound employed in the trial is a condition of use.
- **The leg ulcer example**. These data were provided by colleagues from the Sheffield Health Economics Group.[121] The study compared a treatment group of four-layer compression bandaging within clinics to a control group of normal home care for patients with venous leg ulcers. The following components of cost were recorded: (1) treatment visit costs; (2) hospital admission costs; (3) general practitioner costs; (4) other service costs; (5) personal expenditure costs. Just the first four components were employed to give a total NHS cost per patient.
- **The prostate example**. These data were taken from an economic evaluation performed alongside an RCT trial in which 148 patients were randomised to either transurethral resection of the prostate or contact-laser vaporisation of the prostate with the SLT system.[122] All resources associated with the surgical interventions, postoperative hospital stay, community care and reoperations due to treatment failures were identified over a 12 month follow-up period, and the volumes of resources used by each patient were measured. Unit costs were then applied to these resource volumes to obtain costs per patient.
- **The psychiatric example**. These data were taken from an economic evaluation performed alongside an RCT of nurse problem solving as a potential therapy for patients with emotional disorders, compared with conventional general practitioner care.[123] The resources associated with nurse problem-solving – supervision sessions and practice nurse problem-solving sessions – were identified, counted and costed, alongside data on numbers of general practitioner consultations and medications, during the 8 week treatment period, and over the 4 months following the end of the treatment period. Time off work during the study period was also recorded. Unit costs were attached to these volumes to obtain costs per patient.

Summary statistics for cost by control and treatment groups for each of the five data sets described above are given in *Table 8*. The

TABLE 8 *Summary statistics (in £) for each of the five patient level cost data sets*

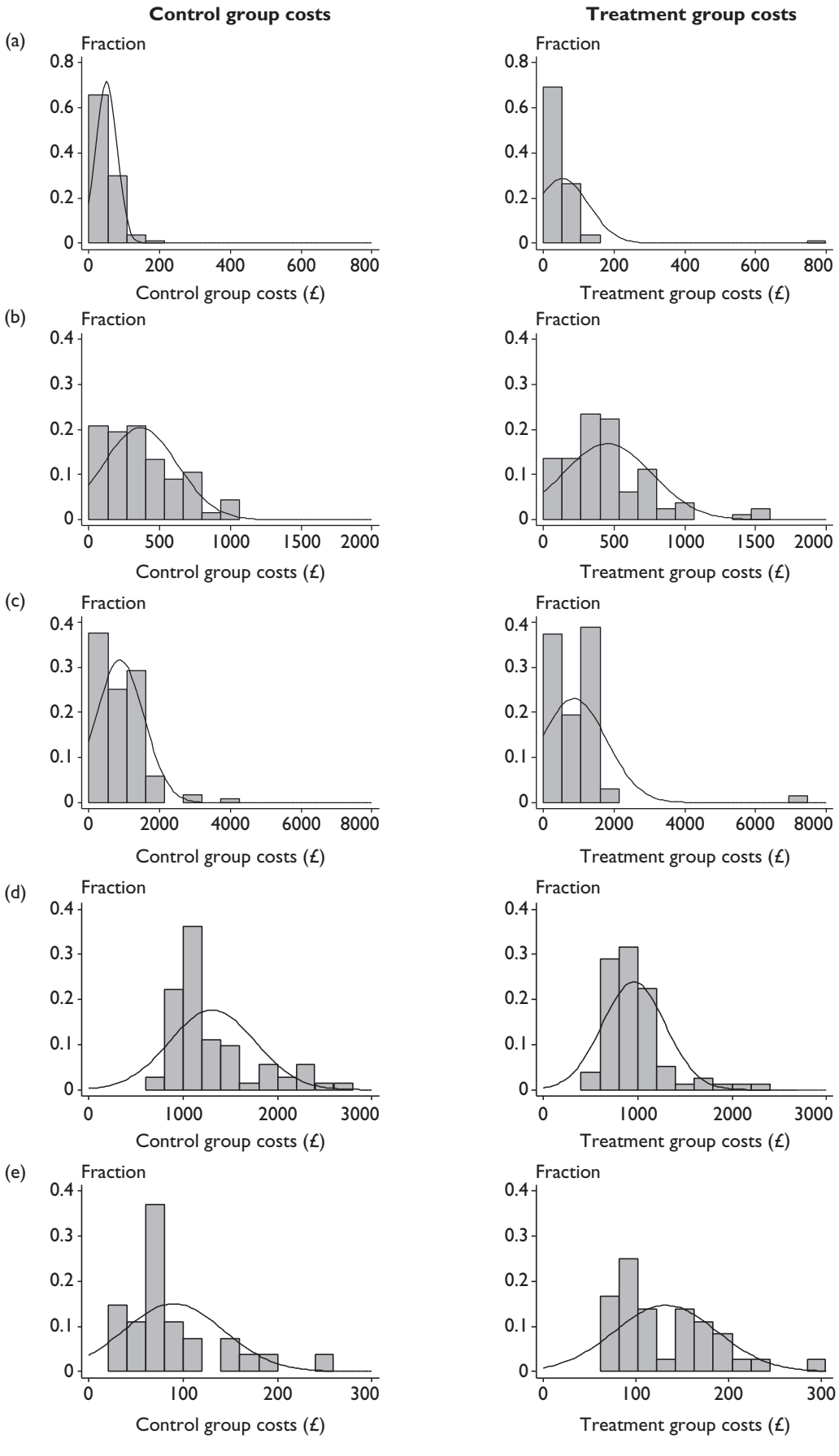
Example and group	Sample size	Minimum	Maximum	Median	Mean	Standard deviation (coefficient of variation)	Standard error (coefficient of variation)	Skew	Kurtosis
Anticoagulation									
Control group	111	10	199	42	47	29.5 (0.63)	2.8 (0.06)	2.12	9.50
Treatment group	113	10	787	43	53	74.02 (1.39)	6.96 (0.13)	8.77	87.10
Antiviral									
Control group	67	1	1004	332	364	260.83 (0.72)	31.86 (0.09)	0.61	2.51
Treatment group	81	4	1557	399	452	316.01 (0.70)	35.11 (0.08)	1.44	5.62
Leg ulcer									
Control group	120	30	4151	680	878	674.56 (0.77)	61.58 (0.07)	1.44	6.87
Treatment group	67	42	7348	904	859	923.71 (1.07)	112.85 (0.12)	5.21	37.58
Prostate									
Control group	72	709	2625	1160	1308	450.31 (0.34)	53.07 (0.04)	1.34	3.82
Treatment group	76	522	2298	854	959	334.55 (0.35)	38.38 (0.04)	2.00	7.52
Psychiatric									
Control group	27	26	243	77	90	53.18 (0.59)	10.23 (0.11)	1.30	4.12
Treatment group	36	65	305	117	132	55.32 (0.42)	9.22 (0.07)	1.07	3.96

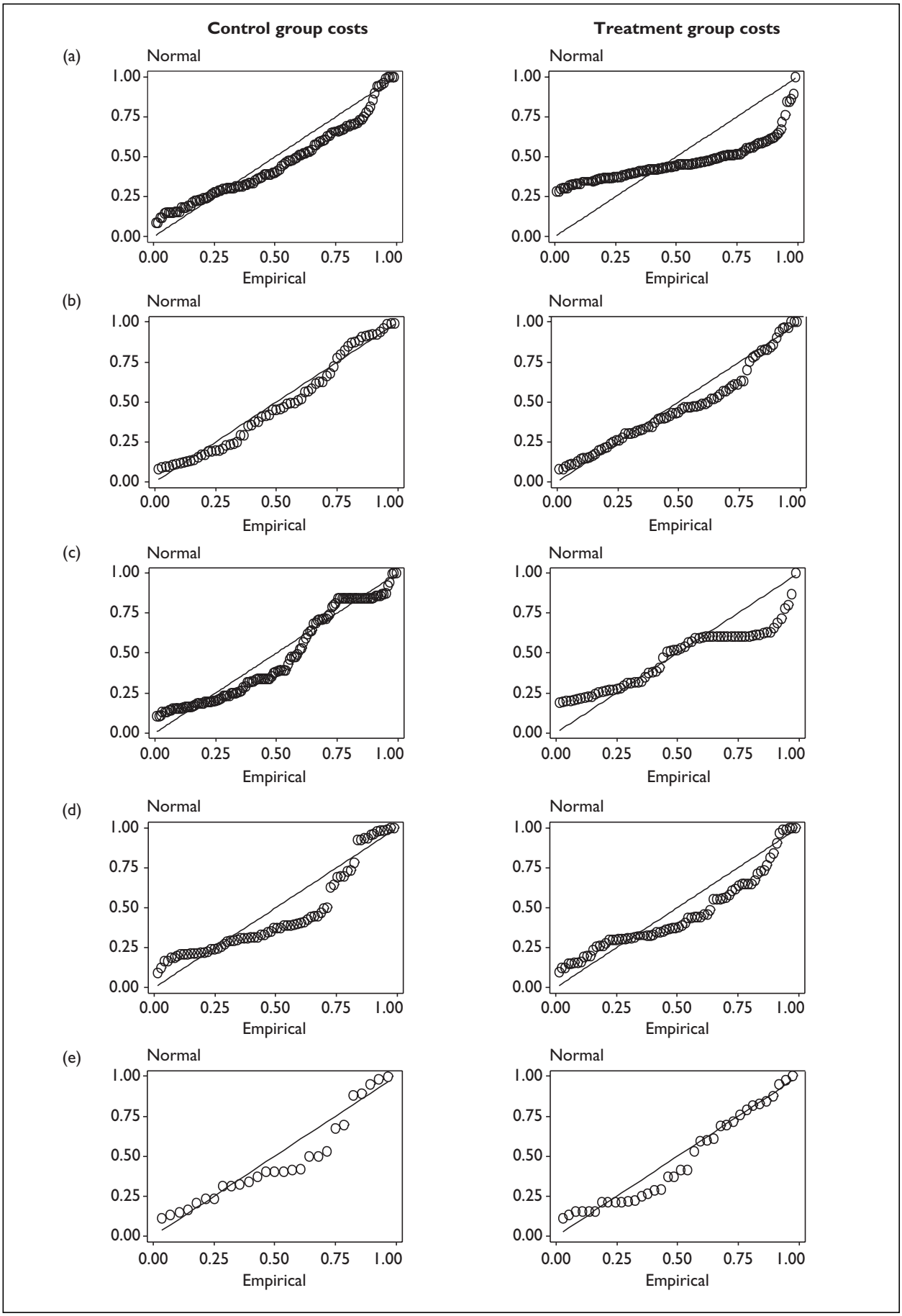
distribution of costs in each data set by treatment group is shown by the histograms in *Figure 22*. Each of the histograms in the figure has the normal distribution with the same mean and variance as the data overlaid for comparison. In addition and as an alternative, *Figure 23* shows normal plots for the same data. If the data are normal, the points in the normal plots are expected to fall along the diagonal line. Hence, systematic departures from the diagonal line in the normal plots indicate departures from normality.

In a cost analysis, it is natural to ask the question 'Is the per patient cost of the treatment group different to the per patient cost of the control intervention?' It is clear from the summary statistics for each of the above data sets given in *Table 8* and the histograms and standardised normal plots presented in *Figures 22* and *23* that these patient level cost data do not seem to follow a normal distribution. Indeed, many of the distributions show evidence of substantial skewness. In the presence of skewed data, it is often common for the median to be used as a measure of central tendency rather than the mean. It should be noted, however, that although median cost provides useful descriptive information (particularly when presented alongside the mean), it is inappropriate to use median costs in a cost analysis. The reason is that we are interested both in the average per patient cost of a particular treatment and the total cost of care for a patient group. In the presence of positively skewed cost data, the median cost will be below the mean. Multiplying the median cost by the number of patients treated will not give the total cost of treatment for that patient group. Since, ultimately, someone will have responsibility for a budget from which total costs of care will have to be met, the appropriate statistic for analysts in economic analyses (and decision makers applying the results of such analyses) is the mean cost per patient. This figure multiplied by the number of patients treated gives the total cost of care for that patient group.

A further problem with median statistics is that convenient measures of dispersion, such as standard deviation or standard error, do not exist as they do for the mean. However, the non-normality of the data presented above causes problems for the parametric statistical tests for the equality of two means. The standard *t* test is based on an assumption of normality of the underlying data and on the assumption that the two population variances are equal. Although the *t* test is known to be robust, that is, moderate failure to meet the assumptions of normality and equal variance will not affect the results very much,[124] it is not clear just how great the departures from normality/equal variance must

RIGHT: FIGURE 22 *Histograms showing the distribution of costs for the control and treatment arms for the five data sets: (a) anticoagulation; (b) antiviral; (c) leg ulcer; (d) prostate; (e) psychiatric. Overlaid are normal distributions with the same mean and variance as the data.*


Control group costs
Treatment group costs
(a)
(b)
(c)
(d)
(e)
Fraction
Control group costs (£)
Treatment group costs (£)


Control group costs
Treatment group costs
(a)
(b)
(c)
(d)
(e)
Normal
Empirical
0.00
0.25
0.50
0.75
1.00

LEFT: FIGURE 23 *Departures from normality for the five data sets are illustrated using a standardised normal probability plot: (a) anticoagulation; (b) antiviral; (c) leg ulcer; (d) prostate; (e) psychiatric*

be before the *t* test becomes inappropriate. It is clear from the central limit theorem, for example, that although the underlying data may not be normally distributed, the sampling distribution of the difference between two means, like the means themselves, will approximate the normal distribution for large sample sizes.[125] A useful result is that the skew coefficient of the population will be reduced by a factor of $\sqrt{n}$ in the sampling distribution of the mean of that population, where n is the sample size.* However, it is still not clear what value of skew in a sampling distribution is 'large enough' to cause concern, such that some of the large skewness observed in the five data sets described above may be problematic despite the sample sizes concerned. We therefore consider two alternatives to the standard parametric approach that might be employed for the analysis and presentation of the above data: the use of transformations to an alternative scale of measurement in order that the data more closely conform to the standard statistical assumptions; and the non-parametric approach of 'bootstrapping', which makes no assumptions concerning the distributional form of the underlying data.

Transformations

The transformation of data from one scale to another can be used to overcome problems associated with non-normality of data and unequal variance. Fortunately, transformations which normalise data will often also provide more equal variances.[126] We consider three of the most commonly used transformations:[125] the (natural) log transformation, the square root transformation and the reciprocal transformation. According to Armitage and Berry:[125] log transformations (defined by the equation $y = \ln(x)$, where x represents the original variable and y the transformed variable) are often appropriate when a variable x is restricted to a positive value and can vary over a wide range; the square root transformation (defined by the equation $y = \sqrt{x}$) is often the appropriate variance-stabilising transformation if $\text{var}(x) = [E(x)]^2$, that is, if the coefficient of variation of x is constant; and the reciprocal transformation (defined by $y = 1/x$) will stabilise variances if $\text{var}(x) = [E(x)]^4$.

In *Table 9*, the data from each of the five studies are presented alongside the results of transforming that data by each of the three transformations outlined above. The second column of the table shows the ratio of the standard deviations (higher to lower) in the treatment and control arms for the untransformed and transformed data. Although the significance of these values could be determined by squaring the ratio (to give the ratio of the variances) and comparing this value to the appropriate critical value from the *F* distribution, just the absolute value of the ratio is presented since the level of significance will be a function of the sample size. The greater the sample size the greater the power to detect differences in the variances as significant, but also the less important are any differences detected. In column three of the tables, the absolute value of the Shapiro–Wilk test statistic for normality for each arm of the studies is given. Normal data take a value of one – so the further the value from 1, the less normal the underlying data. Armitage and Berry[125] suggest that the absolute value of the Shapiro–Wilk statistic is probably more appropriate than its significance due to the effects of sample size (similar to the argument outlined for the variance ratio test above). In the fourth column, the *t* test statistic and *p* value for the test of the equality of the means in each arm on the untransformed and transformed scales are given. This is followed by the 95% confidence limits of the estimated difference on the appropriate scale. Inclusion (exclusion) of 0 between these limits indicates insignificance (significance) at the 5% level. In the final column, the practical implications of the different levels of significance associated with the different scales are indicated by the sample size that would be required to be recruited to each arm of the trial if a further study were to be designed to detect the observed difference based on the observed means and standard deviations at the 90% power and 5% significance level.

In the example of the anticoagulation data, the ratio of the standard deviations shows a wide disparity in the variances, and the Shapiro–Wilk statistics suggest that the data are not normally

* This is a precise result, under standard parametric assumptions, that can be derived from the definition of the skew coefficient.

TABLE 9 *Transformations for each of the five data sets*

Example and transformation	Ratio of standard deviations (high/low)	Shapiro–Wilk test		Two-sample *t* test		95% confidence interval		Sample size
		Control	Treatment	*t* ratio	*p* value	Lower	Higher	
Anticoagulation								
No transformation	2.51	0.83	0.30	–0.49	0.62	–£18.59	£11.18	4874
Natural log	1.07	0.99	0.94	0.23	0.81	–0.13	0.17	22,844
Square root	1.46	0.94	0.65	–0.07	0.94	–0.62	0.58	274,861
Reciprocal	1.00	0.82	0.85	–0.30	0.77	–0.0049	0.0036	13,325
Antiviral								
No transformation	1.21	0.94	0.89	–1.82	0.07	–£183.24	£7.59	229
Natural log	1.19	0.85	0.83	–1.78	0.08	–0.68	0.04	248
Square root	1.00	0.98	0.98	–1.92	0.06	–4.75	0.07	209
Reciprocal	3.44	0.14	0.21	0.90	0.37	–0.02	0.04	1034
Leg ulcer								
No transformation	1.37	0.86	0.52	0.16	0.87	–£213.78	£251.21	38,895
Natural log	1.03	0.95	0.90	0.42	0.67	–0.22	0.34	5158
Square root	1.06	0.96	0.84	0.36	0.72	–2.82	4.07	7275
Reciprocal	1.15	0.43	0.60	–0.26	0.79	–0.0015	0.0011	25,370
Prostate								
No transformation	1.35	0.83	0.80	5.36	< 0.0001	£220.85	£477.69	35
Natural log	1.03	0.91	0.93	6.29	< 0.0001	0.212	0.406	20
Square root	1.18	0.87	0.88	5.85	< 0.0001	3.39	6.86	23
Reciprocal	1.14	0.96	0.98	–6.86	< 0.0001	–0.00039	–0.00021	17
Psychiatric								
No transformation	1.04	0.87	0.90	–3.05	0.0034	–£69.95	–£14.54	35
Natural log	1.42	0.98	0.95	–3.83	0.0003	–0.699	–0.219	24
Square root	1.14	0.94	0.94	–3.46	0.0010	–3.381	–0.906	28
Reciprocal	2.62	0.89	0.96	4.02	0.0002	0.0031	0.0093	23

distributed; in particular, the treatment group looks highly non-normal. Although the reciprocal transformation gives the lowest ratio of standard deviations, the log transformation gives a similarly low ratio and also normalises the data dramatically (as indicated by the values of the Shapiro–Wilk statistic in *Table 9*). This suggests that the greatest confidence can be attached to the results for the log-transformed scale, although in this example it is clear that the difference between the two arms of the study remains highly insignificant whichever transformation is applied.

In the antiviral data, it is clearly the square root transformation that is most appropriate, reflecting that (from *Table 8*) the coefficients of variation in each arm of the study are almost equal. The difference between the arms approaches the standard significance level. However, the improvement in significance or sample size requirement using the transformed scale is unremarkable. This is most likely due to the only moderate violations of parametric assumptions in the underlying data, which may mean that the sample size of the study was sufficient to ensure a near normal-sampling distribution of the difference between the two study arms.

In the leg ulcer example, the log transformation again seems most appropriate (*Table 9*), although the result is still highly insignificant. The sample size requirements emphasise the important consequences for study design of using a transformed scale, with a sevenfold reduction in patient recruitment required to show a difference on the log scale. However, at these levels of sample size requirements it is unlikely that any such study would be attempted.

The prostate data offer an interesting example in that the differences on each of the scales are all deemed highly significant ($p < 0.0001$: *Table 9*). Although the log transformation seems most appropriate again, the gains from transformation are unremarkable in terms of significance or sample size requirement, given the huge absolute difference in cost between the two arms of the study.

Similarly, the psychiatric example shows that the difference on each scale is significant, although not so highly as for the prostate example. The choice of transformation is less clear in this case – the log transformation normalises the data better, but the square root transformation equalises the

variances better. However, it is again clear that the benefits of transformation are unremarkable, given the significance of the difference on the untransformed scale.

Although, in a statistical sense, transformed scales of measurement are no less appropriate for analysing differences between two arms of a study than the untransformed scale, transformation can lead to problems of interpretation for economic analyses. It is not clear what the magnitude of differences mean on the transformed scales, hence analysts are likely to want to back-transform point estimates of central tendency and confidence limits from the transformed scale to the original scale. This is a simple process of using the inverse function for point estimates of the original cost data on the transformed scale.[127] Unfortunately, the cost **differences** observed following a square root transformation or reciprocal transformation are not interpretable when back-transformed.[128] Cost differences under a log transformation do have an interpretation when back-transformed since the difference of two log values is equal to the log of their ratio. The antilog transformation of a log value gives the geometric mean, hence the antilog of the mean log difference gives the ratio of the geometric mean in the control group to the geometric mean in the treatment group. Similarly, the antilog transformation of the confidence limits for the difference in log values gives the confidence limits to this ratio of the geometric means in each group.[128] Hence, a significant result after back transformation is indicated by a confidence interval that excludes unity (i.e. where the ratio of the geometric means is the same).

However, although **an** interpretation is possible after back-transforming results on a log-transformed scale, an **economic** interpretation is still problematic for two reasons. Firstly, the geometric mean is not the appropriate summary statistic for economic analyses, for the same reason the median was argued to be inappropriate above. Secondly, the back-transformation does not result in the original scale of measurement. To interpret results economically, we need to express cost on the original scale (i.e. in pounds and pence). This is particularly so if we intend to combine information on cost with information on effect to produce a cost-effectiveness ratio.

Non-parametric methods

Non-parametric methods are now a widely accepted methodology for handling data analysis situations where the assumptions underlying the standard parametric tests are violated. For the comparison of two independent groups, three tests are commonly employed and can be shown to be exactly equivalent:[125] the Mann–Whitney U test, the Wilcoxon rank sum test and Kendall's S test. These methods are based on comparing the overall ranking of observations from the two samples, rather than comparing the values of the observations. If the samples are drawn from the same distribution, then the expectation is that the average rank of the two samples will be the same. Significant differences in the average rank values leads to rejection of the null hypothesis that the samples are generated from the same distribution.

Unfortunately, there are two main reasons why such non-parametric rank sum tests may be inappropriate for analysing cost data. First, the rank sum tests are better suited to hypothesis testing than estimation – a p value is generated which shows the probability that the two samples are from the same distribution. Although it is quite straightforward to generate estimates of difference and confidence limits for that difference from rank sum tests,[125] such estimates are based on the assumption that the shapes of the distributions of the data are exactly equivalent, and only the locations of the distributions are different. Second, even if such an assumption were justified, economists are interested in mean cost. Rank sum tests effectively test the difference in location between two distributions – where the underlying data are skewed, this location is equivalent to a test of differences between the medians of the two samples. Hence, the estimates of difference and confidence limits generated from rank sum tests would give the difference between the medians, not between the means of the samples.

Fortunately, there exists another approach which does not make distributional assumptions concerning the statistic in question but which does not suffer from the limitations (for economic evaluation) of rank sum methods. The bootstrap approach is a non-parametric method that makes no distributional assumptions concerning the statistic in question. Instead it employs the original data and computing power in a resampling exercise in order to give an empirical estimate of the sampling distribution of that statistic. Suppose a particular population has a real but unobserved probability distribution F from which a random sample $\mathbf{x}$ of n independent observations is taken and the statistic of interest $s(\mathbf{x})$ is calculated. The concern of inferential statistics is to make statements about some population parameter ϑ based on the sample drawn from that population. The bootstrapping approach treats the observed

RIGHT: FIGURE 24 *Histograms with normal distributions overlaid and normal probability plots for the five data sets: (a) anticoagulation; (b) antiviral; (c) leg ulcer; (d) prostate; (e) psychiatric*

random sample as an empirical estimate of the probability distribution of F by weighting each observation in **x** by the probability $1/n$.[129] Successive random samples of size n are then drawn from **x with replacement**[*] to give the bootstrap resamples. The statistic of interest is then calculated for each of these resamples, and these bootstrap replicates of the original statistic make up the empirical estimate of the sampling distribution of the statistic, which can then be used to make inferences about θ.

The validity of the bootstrap approach rests on two asymptotics: (1) as the original sample size approaches the population size so the sample distribution tends to the population distribution; and, given this, (2) as B, the number of bootstrap replications, approaches infinity so the bootstrap estimate of the sampling distribution of a statistic approaches the true sampling distribution.[130]

In the case of the difference between the costs in the treatment and control arms in each of the five studies described above, a simple three-step process to estimating the sampling distribution of the difference in cost was employed:

- n_c costs were sampled, with replacement, from the control group data (where n_c is the size of the sample in the control arm of the study)
- n_t costs were sampled, with replacement, from the treatment group data (where n_t is the size of the sample in the treatment arm of the study)
- The mean of the bootstrapped control group costs, the mean of the bootstrapped treatment group costs and the difference between the two means were then calculated.

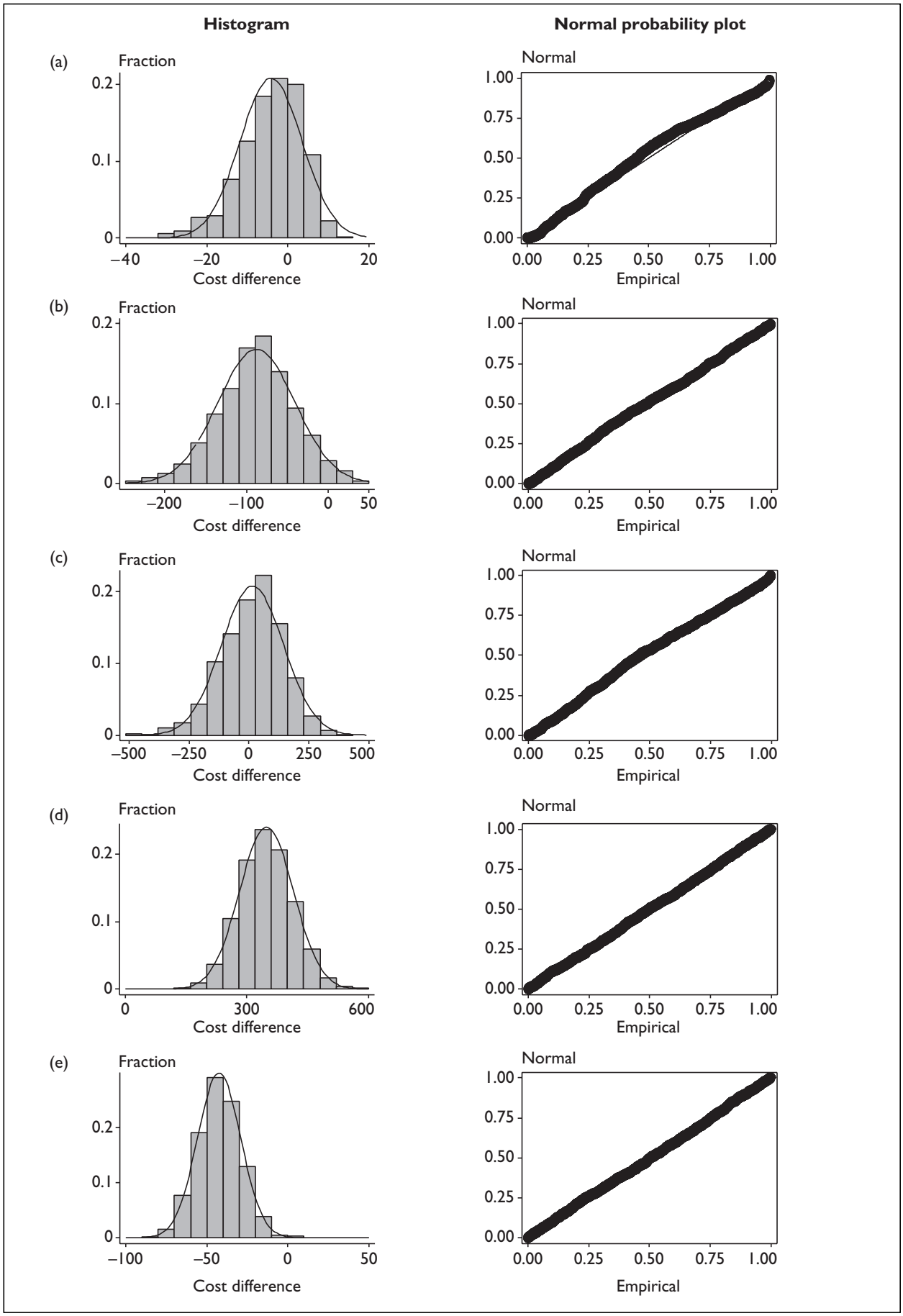
This three-stage process was then repeated 1000 times, to give a vector of bootstrapped cost differences, which is the empirical estimate of the sampling distribution of the difference between the mean costs in each study.

The results of this exercise are presented in *Figure 24*, which shows a histogram of the bootstrap estimate of the sampling distribution of the cost difference and a standardised normal plot for each of the five studies. What the bootstrap estimates of the sampling distributions show is the extent to which, in each case, the sample size of the study is sufficiently large that the assumption of a normal sampling distribution (from the central limit theorem) is justified. Where the sampling distribution approximates the normal distribution, we need not be too concerned about the violations of the assumptions underlying the t test results reported above. It is clear that, for the antiviral example, the prostate example and the psychiatric example, the bootstrap estimate of the sampling distribution closely approximates a normal distribution. Hence, for these studies we are unlikely to want to transform results on to an alternative scale since the sample sizes are sufficient that the untransformed t test results are robust.

By contrast, for the anticoagulation example and the leg ulcer example, the bootstrap results predict substantial non-normality[†] remaining in the sampling distribution due to the relatively small sample sizes in relation to the extreme non-normality of the underlying data. In these examples, there may be a case for transforming the data to ensure that the assumptions underlying the t test results are met. However, the bootstrap method can also be used to estimate confidence limits for the cost difference, which may be preferable to employing parametric techniques on a transformed scale. The most straightforward method of bootstrap confidence interval estimation is the percentile method, by choosing the 2.5th and 97.5th percentile values from the vector of cost differences to represent the 95% confidence interval limits. The bootstrap 95% percentile confidence interval for the anticoagulation data cost difference is –£21.91 to £8.03, while for the leg ulcer data, the 95% percentile confidence interval is –£258.36 to £242.96. These intervals are not symmetrically positioned around the point estimate of cost difference, reflecting the non-normality of the bootstrap estimate of the sampling distribution.

[*] Of course, sampling from **x** without replacement n times, would simply yield **x** itself.

[†] Of course, this judgement based on the visual assessment of histograms and normal plots may be seen as subjective. However, formal tests of **significant** departures from normality are avoided due to the fact that the large number of bootstrap replications gives the power to detect unimportant departures from normality with high levels of significance.


Histogram
Normal probability plot
(a)
Fraction
0.2
0.1
0
−40
−20
0
20
Cost difference
Normal
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
Empirical
(b)
Fraction
0.2
0.1
0
−200
−100
0
50
Cost difference
Normal
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
Empirical
(c)
Fraction
0.2
0.1
0
−500
−250
0
250
500
Cost difference
Normal
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
Empirical
(d)
Fraction
0.2
0.1
0
0
300
600
Cost difference
Normal
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
Empirical
(e)
Fraction
0.2
0.1
0
−100
−50
0
50
Cost difference
Normal
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
Empirical

Summary

Overall, our results indicate that such cost differences have been poorly reported, suggesting that either the distributional form of cost data and the statistical methods for handling cost data are not well understood or the importance of handling uncertainty appropriately is not appreciated. Recent guidelines may heighten awareness of these problems, and our work seeks to cast light on the appropriate way to handle patient level cost data. Although our results are derived from a small sample of patient level cost data sets that may not be representative, we believe that our analysis does highlight a number of issues that analysts should bear in mind when analysing and presenting such data.

From the data sets presented here, there does seem to be evidence to support the assertion that healthcare costs often follow a skewed distribution. Although some commentators have suggested the transformation of costs in such circumstances,[131] we suggest a cautious approach to analysing cost data on transformed scales. Mean values and confidence limits may be difficult to interpret on the transformed scales, and back-transformation on to the original scale is not possible for cost differences, and therefore such data cannot be used to calculate a cost-effectiveness ratio.

Chapter 5

Confidence intervals for cost-effectiveness ratios

Introduction

The previous chapter has concentrated on the distributional form, variance of healthcare cost, and on the reporting of cost differences in a cost analysis. In practice, however, economic analyses are concerned not simply with cost but also with health outcome. Since it is common that new interventions are both more effective and also more costly than the standard therapy that they seek to replace, the majority of cost-effectiveness analyses report a point estimate of the ICER. Where patient level data are available, it is natural to also present a confidence interval estimate to represent uncertainty due to sampling variation.

It was argued in chapter 2 that analysts will increasingly be in possession of patient level data on both cost and health outcome as more economic analyses are conducted alongside clinical trials. The overall review in chapter 2 found that just 24 studies had attempted any form of statistical analysis in looking at their data, and in only three cases was this analysis related to the ICER itself. Standard statistical methods of confidence interval estimation do not apply to the ICER since the variance of a ratio statistic is intractable. There has been much recent research into possible methods for estimating confidence intervals for the ICER stemming from a seminal paper by O'Brien *et al.*[4] In this chapter, we offer a review* of this recent literature in order to elucidate the strengths and weaknesses of the alternative approaches. Before that, however, we outline the problem of the intractability of the variance for a ratio estimator. Following the review of alternative methods of confidence interval estimation, we consider the use of an alternative approach to representing uncertainty in cost-effectiveness information and discuss the continuing role of sensitivity analysis for handling uncertainty not related to sampling variation.

Statistical analysis and the ICER

Consider a study to determine the additional costs and effects of the therapy under evaluation, say treatment A, compared with the standard therapy, treatment B. On the basis of data collected from two groups of patients receiving the alternative therapies, the ICER can be estimated by

$$\hat{R} = \frac{\bar{C}_A - \bar{C}_B}{\bar{E}_A - \bar{E}_B} = \frac{\Delta\bar{C}}{\Delta\bar{E}} \qquad (2)$$

where $\bar{C}_A$ and $\bar{C}_B$ are the mean costs in the two treatment arms and $\bar{E}_A$ and $\bar{E}_B$ are the mean effects.

The purpose of collecting such data and estimating the ICER statistic is in order to make inferences about the true (but unobservable) population ICER, denoted by

$$R = \frac{\mu_{CA} - \mu_{CB}}{\mu_{EA} - \mu_{EB}} = \frac{\mu_{\Delta C}}{\mu_{\Delta E}}$$

where μ represents a true value for costs (subscript C) and effects (subscript E) for treatment A and treatment B.

Essentially, the estimated ICER statistic from equation (2) is constructed from four sample means (the mean costs and effects from each patient group). Although the underlying data may not follow a well-behaved distribution in general, the central limit theorem states that the means will approach a normal distribution with increasing sample size. Hence, with sufficient sample size and assuming independence,† the relevant estimators can be approximated by normal distributions with the following mean and variance:

* This review did not involve a structured or systematic element for the reason that much of this literature is extremely recent – a structured review of the online databases at the start of this project would not have identified all of the articles reviewed in this chapter.

† The central limit theorem applies to independent observations. Since there is no reason to suppose that there should be any covariant effect between individuals receiving the same therapy, this assumption appears reasonable.

$$\bar{C}_A \sim N(\mu_{CA}, \sigma^2_{CA}/n_A)$$
$$\bar{E}_A \sim N(\mu_{EA}, \sigma^2_{EA}/n_A)$$
$$\bar{C}_B \sim N(\mu_{CB}, \sigma^2_{CB}/n_B)$$
$$\bar{E}_B \sim N(\mu_{EB}, \sigma^2_{EB}/n_B)$$

where σ^2 represents the true population variance for costs and effects for treatment A and treatment B.

As it is known that the sum of two normal variables is itself normally distributed, we can assume that for independent groups* the estimates of the incremental costs and effects, the numerator and denominator of the ICER from equation (2), are distributed,

$$\Delta\bar{E} \sim N(\mu_{EA} - \mu_{EB}, \sigma^2_{\Delta E})$$
$$\Delta\bar{C} \sim N(\mu_{CA} - \mu_{CB}, \sigma^2_{\Delta C})$$

where

$$\sigma^2_{\Delta E} = \frac{\sigma^2_{EA}}{n_A} + \frac{\sigma^2_{EB}}{n_B}$$
$$\sigma^2_{\Delta C} = \frac{\sigma^2_{CA}}{n_A} + \frac{\sigma^2_{CB}}{n_B}$$

It is clear that the estimated ICER statistic in equation (2) is the ratio of two asymptotically normal variables. Wakker and Klaassen suggest that the cost-effectiveness ratio, as a ratio of two normal distributions, will be Cauchy distributed, and comment that the mean of the Cauchy distribution does not exist, rendering the sample mean estimates of Cauchy distributed variables unstable.[132] However, it is the ratio of two independent standard normal distributions, which has a Cauchy distribution.[133] † Since there is no reason to suppose that the cost and effect differences in the numerator and denominator of the ICER will be either independent or standard, the sampling distribution of the ICER will not generally follow a Cauchy distribution, rather the sampling distribution is simply unknown. However, it is clear that there may be a non-negligible probability of obtaining a zero or near zero value on the denominator of the ICER, which suggests that the moments of the ICER may be undefined. For example, in the case of very small differences in treatment effects, the resulting ratio would be very large. In practice this is a very real problem since it is common for clinical trials to be designed to detect the smallest meaningful clinical difference between treatments, which is likely to lead to a large number of results showing differences in treatment effects which are close to 0.[134]

From a statistical point of view, the likely proximity of the effect differences to 0 throws doubt on the wisdom of using the ICER statistic in economic analysis. However, the economic justification for using the ICER rather than, say, the difference between the average cost-effectiveness ratios (which might be expected to be much better behaved statistically) is persuasive.[8,135,136] A similar issue has been addressed in a recent article by Stinnett and Paltiel,[137] examining whether, in the context of a stochastic cost-effectiveness analysis, the 'mean ratio' might be a more appropriate statistic for analysing cost-effectiveness data than the 'ratio of means' embodied by the ICER. Their conclusions were that the ratio of the means had stronger theoretical properties in terms of consistency with the first principles of cost-effectiveness analysis and was internally consistent,‡ compared to a mean ratio statistic. Therefore, despite the intrinsic statistical problems associated with the ICER statistic, the economic argument for the use of the ICER is compelling.

Confidence intervals for cost-effectiveness ratios

In recognition of the problem associated with standard statistical methods for estimating confidence limits for the ICER, a number of analysts have proposed alternative methods, including methods based on confidence boxes, confidence ellipses, the Taylor series expansion, Fieller's theorem, and non-parametric bootstrapping.

* The independence assumption is clearly appropriate for randomised trials; however, for non-randomised trial designs, such as, for example, a before and after study, the independence assumption may not be justified, and the expressions of variance for the incremental costs and effects should incorporate a covariance term.

† Since standard normal variables have zero mean, the Cauchy distribution is symmetric. Relative to a normal distribution, the Cauchy distribution has much fatter tails.

‡ Internal consistency was defined as the absence of preference reversal when the ratio was inverted to give an effectiveness-cost ratio. Their analysis showed that in some circumstances, the use of the mean of ratios could lead to different decisions depending on whether the ratio was cost-effectiveness or effectiveness-cost.

The confidence box

O'Brien *et al.* show how the cost-effectiveness plane can be used to present the confidence limits for the estimate of incremental cost-effectiveness,[4] and a one-sided version of this interval has also appeared in the recent literature.[132] *Figure 25,* which is based on the representation by O'Brien *et al.,* shows the results of a hypothetical prospective economic evaluation on the cost-effectiveness plane. The difference in effect between two therapies is shown on the horizontal axis with mean effect difference $\Delta\bar{E}$ and upper and lower confidence limits for the effect difference ($\Delta\bar{E}^{U}$ and $\Delta\bar{E}^{L}$) represented by the horizontal 'I' bar. Similarly, the difference in cost between the two therapies is shown on the vertical axis with mean cost difference $\Delta\bar{C}$, and upper and lower confidence limits for the cost difference ($\Delta\bar{C}^{U}$ and $\Delta\bar{C}^{L}$) represented by the vertical 'I' bar. These 'I' bars intersect at point ($\Delta\bar{E}$, $\Delta\bar{C}$), hence the ray that connects this point of intersection to the origin has a slope equal to the value of the ICER. The upper and lower limits of the confidence intervals on cost and effect are calculated employing standard parametric assumptions, such that the $(1-\alpha)100\%$ confidence limits on the incremental costs and effects are given by

$$(\Delta\bar{E} - z_{a/2}\sigma_{\Delta\bar{E}}, \Delta\bar{E} - z_{a/2}\sigma_{\Delta\bar{E}})$$
$$(\Delta\bar{C} - z_{a/2}\sigma_{\Delta\bar{C}}, \Delta\bar{C} - z_{a/2}\sigma_{\Delta\bar{C}})$$

where $z_{\alpha/2}$ represents the standardised normal deviate exceeded in either direction with probability α such that for $\alpha = 0.05$, $z_{\alpha/2} = 1.96$.

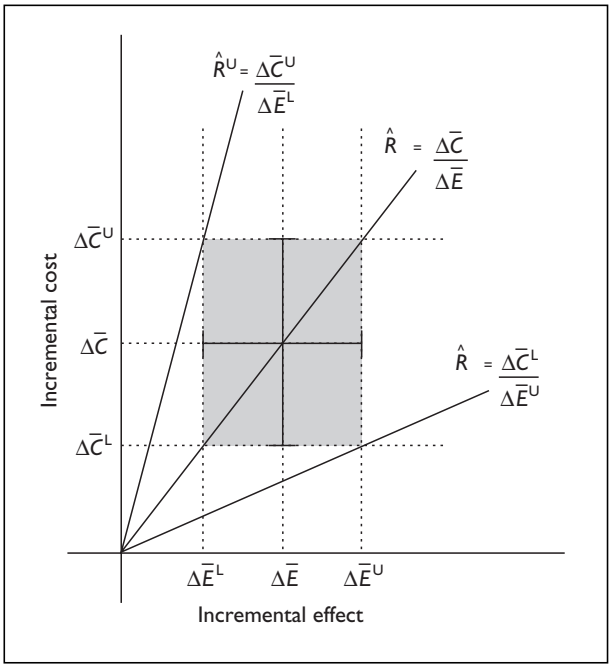


FIGURE 25 *The confidence box*

O'Brien *et al.* argue that combining the limits of the confidence intervals for costs and effects separately gives natural best and worst case limits on the ratio, that is, the upper limit of the cost difference over the lower limit of the effect difference ($\Delta\bar{C}^{U}/\Delta\bar{E}^{L}$) gives the highest values of the ratio (worst case), and the lower limit of costs divided by the upper limit of effects ($\Delta\bar{C}^{U}/\Delta\bar{E}^{L}$) gives the lowest (best) value of the ratio. Thus the approximation to the $(1-\alpha)100\%$ confidence interval employing this method is given by

$$\left(\frac{\Delta\bar{C} - z_{a/2}\hat{\sigma}_{\Delta\bar{C}}}{\Delta\bar{E} + z_{a/2}\hat{\sigma}_{\Delta\bar{E}}}, \frac{\Delta\bar{C} + z_{a/2}\hat{\sigma}_{\Delta\bar{C}}}{\Delta\bar{E} + z_{a/2}\hat{\sigma}_{\Delta\bar{E}}}\right)$$

The area of the shaded box in *Figure 25* represents this combined area of confidence. It is important to note, however, that the confidence level of this area does not correspond to the confidence level on the individual cost and effect differences where those cost and effect differences are independent. The chance of a type I error (usually represented by α) can be interpreted as the proportion of times the true parameter lies outside the estimated interval in repeated sampling. Hence, the chance that the true cost difference is contained within the estimated cost interval is $(1-\alpha)$, as is the chance that the true effect difference is contained within the estimated effect interval. Thus, the chance that both these events occur simultaneously is $(1-\alpha)^2$. Hence, combining the 95% confidence limits for cost and effects individually gives a 90% confidence box in terms of the number of times the true cost and effect differences will appear in the shaded area of *Figure 25* in repeated sampling.

Of course, it is also clear from *Figure 25* that the confidence intervals for the ICER based on the confidence box approach will cover much more than the area of the box (since the box is only part of the area between the rays). Therefore, in practice, the confidence box approach to confidence interval estimation for the ICER will be conservative and give an interval wider than the nominal 95% level.

The Taylor series expansion

O'Brien *et al.* recognise that the representation of uncertainty as box shaped on the cost-effectiveness plane is misleading since, for the case of independence, the chance of observing extreme values for both cost and effect differences simultaneously will be very low. Instead they suggest that con tour lines on the cost-effectiveness plane for which the joint density is constant are likely to be elliptical

in shape.* However, rather than try to estimate confidence limits based on this ellipse, they favour the Taylor series approximation of the variance of a function of two random variables to estimate the variance of a ratio. They argue that the advantage of this method over the confidence box approach is that it accounts for the covariance between the numerator and denominator.

The Taylor approximation shows that where y is a function of two random variables x_1 and x_2, the variance of y can be expressed in terms of the variances and covariance of x_1 and x_2, weighted by the partial derivatives of y with respect to x_1 and x_2. The Taylor series formula is presented below:

$$\text{var}(y) \approx \left(\frac{\partial y}{\partial x_1}\right)^2 \text{var}(x_1) + \left(\frac{\partial y}{\partial x_2}\right)^2 \text{var}(x_2)$$

$$+ 2\left(\frac{\partial y}{\partial x_1}\right)\left(\frac{\partial y}{\partial x_2}\right)\text{cov}(x_1, x_2)$$

This expression can now be solved for the case of the ICER presented in equation (2) by substituting $\Delta\bar{C}$ for x_1 and $\Delta\bar{E}$ for x_2.† Hence the Taylor series approximation of the variance of the ratio estimator, using the sample estimates of the means and variances (since by definition the population values cannot be observed), is given as

$$\text{var}(\hat{R}) \approx \frac{1}{\Delta\bar{E}^2}\text{var}(\Delta\bar{C}) + \frac{\Delta\bar{C}^2}{\Delta\bar{E}^4}\text{var}(\Delta\bar{E}) - 2\frac{\Delta\bar{C}}{\Delta\bar{E}^3}\text{cov}(\Delta\bar{C}, \Delta\bar{E})$$

Taking $\hat{R}^2 = \Delta\bar{C}^2/\Delta\bar{E}^2$ outside on the right-hand side of the above simplifies the expression to

$$\text{var}(\hat{R}) \approx \hat{R}^2 \left(\frac{\text{var}(\Delta\bar{C})}{\Delta\bar{C}^2} + \frac{\text{var}(\Delta\bar{E})}{\Delta\bar{E}^2} - 2\frac{\text{cov}(\Delta\bar{C}, \Delta\bar{E})}{\Delta\bar{C}\,\Delta\bar{E}}\right)$$

and noting that the coefficient of variation‡ for a random variable x is defined $\text{cv}(x) = \sqrt{[\text{var}(x)]}/\bar{x}$ and that the correlation coefficient between two random variables x and y is defined by $\rho = \text{cov}(x, y)/\sqrt{[\text{var}(x)\text{var}(y)]}$ further simplifies the exposition:

$$\text{var}(\hat{R}) \approx \hat{R}^2\left[\text{cv}(\Delta\bar{C})^2 + \text{cv}(\Delta\bar{E})^2 - 2\rho\ \text{cv}(\Delta\bar{C})\text{cv}(\Delta\bar{E})\right] \quad (3)$$

Employing standard parametric assumptions gives the confidence interval as

$$\left(\hat{R} - z_{\alpha/2}\sqrt{[\text{var}(\hat{R})]},\quad \hat{R} + z_{\alpha/2}\sqrt{[\text{var}(\hat{R})]}\right)$$

O'Brien *et al.* argue that although the assumption of a normal distribution may be justified in the case of large samples, it is unlikely that the distribution of a ratio will follow a well-behaved distribution in general. In general they remain cautious about the use of both the Taylor series method and the confidence box method that they examine in their paper.

It was argued above that even though the numerator and denominator of the ratio may follow a normal distribution, the sampling distribution of the ICER may be non-normal due to the non-negligible probability that the denominator of the ratio could take a zero value. Increasing sample sizes in a study will increase the precision of the estimated cost and effect differences, reducing their coefficients of variation and the associated probability of observing a zero value. Hence, it is true that with large sample sizes (or rather small coefficients of variation) the distribution of a ratio may be normal. However, O'Brien *et al.* are correct in remaining cautious of the Taylor series approach. A high coefficient of variation for the denominator of the ratio (i.e. a non-negligible probability of observing a zero value) means that the sampling distribution of the ICER is likely to be non-normal and that the Taylor series will give a poor estimate of variance.[125]

The confidence ellipse

Van Hout *et al.*[138] argue that because the ratio of two normal distributions has neither a finite mean nor a finite variance, the approach of approximating the variance of the ratio using the Taylor series and then assuming a normal sampling distribution is formally incorrect.* Instead, they return to the idea that the joint cost and effect density function might be elliptical in shape, and

* Such elliptical surfaces will be efficient in terms of encompassing the smallest area. The analogy with a 95% confidence interval for a single parameter is that many 95% intervals exist, but the most efficient interval is that with the shortest length.

† The partial derivatives of the ICER with respect to ΔC and ΔE are $1/\Delta E$ and $-\Delta C/\Delta E^2$, respectively.

‡ For an estimator the coefficient of variation is given by the ratio of the standard error to the mean. Coefficients of variation are often defined in terms of the ratio of the standard deviation to the mean. Since this is true for any random variable,[125] and standard errors are equivalent to standard deviations of the estimator, the coefficients of variation for the estimator can be defined in terms of the standard error.

they derive the formula for this ellipse by assuming that the costs and effects follow a joint normal distribution. Employing the previous notation, the joint probability density function can be expressed as

$$f(\Delta\bar{E}, \Delta\bar{C}) = \frac{1}{2\pi\sigma_{\Delta C}\sigma_{\Delta E}\sqrt{1-\rho^2}} \exp(Q) \qquad (4)$$

where the correlation between ΔC and ΔE is given by ρ, and Q is defined as follows:

$$Q = -\frac{1}{2(1-\rho^2)}\left[\frac{(\mu_{\Delta C}-\Delta\bar{C})^2}{\sigma^2_{\Delta C}} + \frac{(\mu_{\Delta E}-\Delta\bar{E})^2}{\sigma^2_{\Delta E}} - \frac{2\rho(\mu_{\Delta C}-\Delta\bar{C})(\mu_{\Delta E}-\Delta\bar{E})}{\sigma_{\Delta C}\sigma_{\Delta E}}\right]$$

The elliptical contour lines on the cost-effectiveness plane are those lines on which the joint density is constant. It is clear that $f(\Delta\bar{C}, \Delta\bar{E})$ is constant if Q is constant, and the locus of such points is an ellipse of equal density centred at $(\mu_{\Delta E}, \mu_{\Delta C})$. They go on to propose that such an ellipse might cover 95% of the integrated probability to give a confidence surface analogous to a confidence interval. Such an ellipse is characterised by setting $Q = \ln(1-\lambda)$, where λ is the value of the integrated probability (0.95 for a 95% confidence surface). An approximation of the 95% confidence interval is given by the rays from the origin of the cost-effectiveness plane that are tangential to the ellipse. Other commentators have also presented the confidence interval to a ratio in terms of the tangents to an ellipse of equal density.[2,66]

The advantage of this method of confidence interval estimation compared with the box method is that it will allow for covariance between the numerator and denominator. *Figure 26* shows the 95% confidence ellipse for (a) the case of independence, (b) negative correlation between the

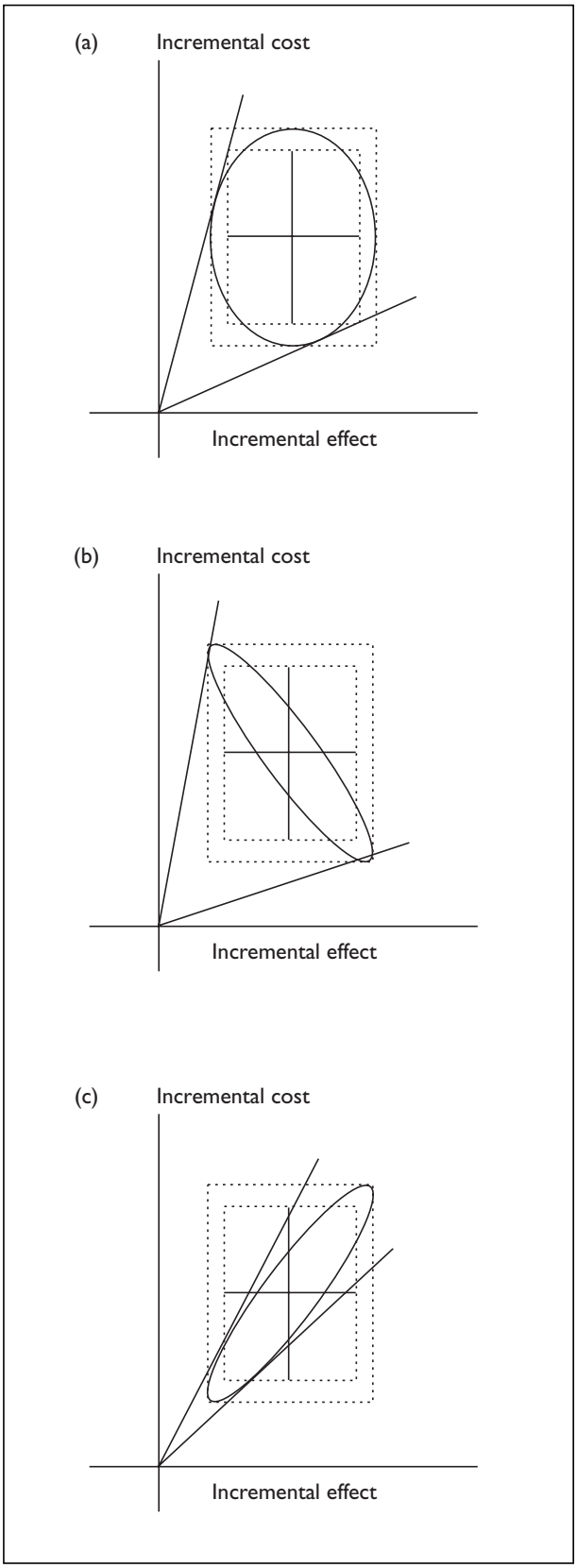


FIGURE 26 *(a) The confidence ellipse for the case of independence between incremental cost and effect. (b) The confidence ellipse for the case of negative covariance between incremental cost and effect. (c) The confidence ellipse for the case of positive covariance between incremental cost and effect*

* In fact, they are mathematically incorrect in the use of this argument (as indicated in the previous section). Armitage and Berry note[125] that the Taylor series approximation will provide a good estimate of the variance of a ratio statistic providing the coefficient of variation of the denominator of the ratio is small. The problem in using the Taylor series for the ICER is not that the ICER is the ratio of two normally distributed random variables but that (as argued above) in practical application the coefficient of variation of the denominator of the ratio is likely to be high.

numerator and denominator of the ICER of –0.9 and (c) positive correlation between the numerator and denominator of 0.9. *Figure 26* clearly shows the dramatic difference in the width of the confidence interval for the ICER for differing levels of covariance between the numerator and denominator. *Figure 26* shows the confidence ellipse neatly contained within a confidence box. However, it is worth noting that, contrary to a recent presentation of confidence ellipses and confidence boxes on the cost-effectiveness plane,[66] the 95% confidence ellipse is not contained within the box defined by the two 95% confidence intervals on cost and effect differences. These intervals and the resulting 90% confidence box are also shown in the figure. It turns out that there is no straightforward relationship between the ellipse and the box. It is a confidence box, constructed from two 98.6% confidence intervals which just contains the 95% confidence ellipse, and which itself covers 97.1% of the integrated probability of the joint density function.

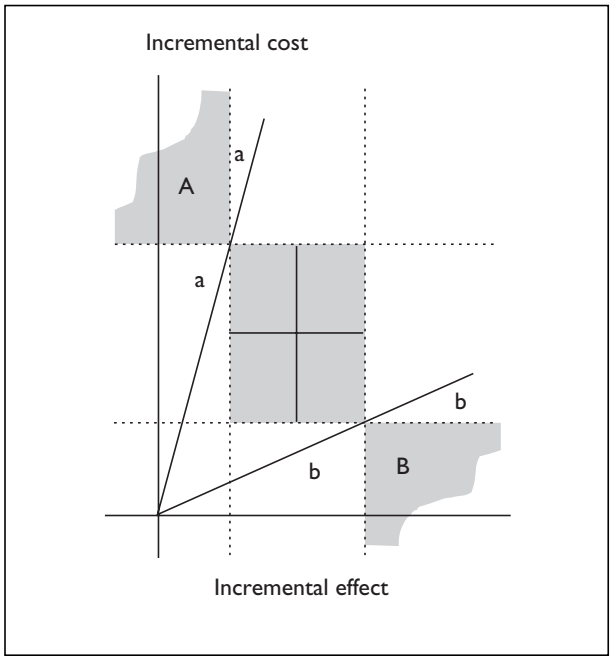


FIGURE 27 *The revised confidence box of Polsky* et al.

The confidence box revisited

In a recent article, Polsky *et al.*[139] attempt to set the individual confidence limits on cost and effect differences such that the confidence interval implied by the combination of the limits as described above generates a more accurate interval for the cost-effectiveness ratio. They suggest that, for the case of independence between costs and effects, the probability that costs are below their lower limit and effects are above their upper limit is $(\alpha/2)^2$. Hence, they argue that combining the limits of two $(1-\alpha)100\%$ confidence intervals on costs and effects generates a $(1-\alpha^2/2)100\%$ interval for the ratio. Therefore, they work backwards from this formula to argue that a 95% interval for the ratio can be generated by two 68.4% confidence intervals on costs and effects, for the case of independence. Unfortunately, this method can perform poorly in many circumstances, even for the case of independence, as can be seen from *Figure 27*. The shaded areas to the north-west and south-east of the confidence box (labelled A and B in *Figure 27*) represent the chance that costs and effects simultaneously take extreme values. For the case of Polsky *et al.*, these areas do indeed correspond to 2.5% probability. However, this does not mean that the interval for the ratio covers $1-(2\times 2.5\%) = 95\%$ of the probability. In fact, the confidence box advocated by Polsky *et al.* is equivalent to only $68.4\%^2 = 46.8\%$ confidence surface. Hence, 49.2% of the probability is not covered by these areas. In terms of *Figure 27*, the important areas not covered are the areas labelled a and b, which lie outside of the interval estimated by the extremes of the individual 68.4% confidence limits on costs and effects. Where the coefficients of variation in the cost and effect differences are high, significant probability may be attached to these areas such that the confidence interval for the ratio performs poorly, even when the cost and effect differences are independent.

Fieller's theorem

As van Hout *et al.* note,[138] the method of calculating the slope of tangents to the 95% probability ellipse gives only an approximation to the 95% confidence interval for the ratio. This is because the area between the rays covers more than 95% of the joint density function. Health economists have been slow to recognise that the problem of estimating confidence intervals for ratio statistics has arisen in other areas of medical research. The statistical properties of ratio statistics and a method of calculating confidence intervals around ratios was described as early as 1932 by Fieller in relation to bioassay.[140,141] This approach has been advocated for use in calculating confidence intervals around ICERs by both Willan and O'Brien[142] and Chaudhary and Stearns.[143]

The advantage of Fieller's method over the Taylor series expansion is that it takes into account the potential skewness in the sampling distribution of the ratio estimator, and may not therefore be symmetrically positioned around the point estimate. In contrast to the Taylor series approximation, Fieller's theorem provides an exact solution, subject to the

assumption of the method that the numerator and denominator of the ratio follow a joint normal distribution, that is, the expression $\Delta\bar{C} - R\Delta\bar{E}$ is normally distributed. Dividing this expression through by its standard deviation, it follows that

$$\frac{\Delta\bar{C} - R\Delta\bar{E}}{\sqrt{[\text{var}(\Delta\bar{C}) + \text{R}^2\,\text{var}(\Delta\bar{E}) - 2R\,\text{cov}(\Delta\bar{C}, \Delta\bar{E})]}} \sim N(0,1)$$

Setting this expression equal to $z_{\alpha/2}$ and rearranging gives the following quadratic equation in R (using the simplified notation from equation (3)):

$$\begin{aligned}&\text{R}^2[1 - z^2_{\alpha/2}\text{cv}(\Delta\bar{E})^2] - 2R\hat{R}[1 - z^2_{\alpha/2}\rho\ \text{cv}(\Delta\bar{C})\text{cv}(\Delta\bar{E})] \\ &\quad +\hat{R}^2\ [1 - z_{\alpha/2}{}^2\,\text{cv}(\Delta\bar{C})^2] = 0\end{aligned} \tag{5}$$

Solving equation (5) for R using the standard quadratic formula gives the confidence interval as

$$\hat{R}\,\frac{\left(\begin{array}{l}1 - z^2_{\alpha/2}\rho\ \text{cv}(\Delta\bar{C})\text{cv}(\Delta\bar{E}) \pm R\,z^2_{\alpha/2}\sqrt{\{\text{cv}(\Delta\bar{C})^2 + \text{cv}(\Delta\bar{E})^2} \\ \quad - 2\rho\ \text{cv}(\Delta\bar{C})\text{cv}(\Delta\bar{E}) - z^2_{\alpha/2}[(1-\rho^2)\text{cv}(\Delta\bar{C})^2\text{cv}(\Delta\bar{E})^2]\}\end{array}\right)}{1 - z^2_{\alpha/2}\text{cv}(\Delta\bar{E})^2}$$

In contrast to the approximate methods discussed above, Fieller's method provides an exact solution subject to the joint normality assumption. However, it has been argued that the assumption of joint normality may be hard to justify, particularly where sample sizes are small.[143] In particular, healthcare costs will often follow a substantially skewed distribution (as was illustrated in chapter 4), which may cause problems for the normality assumption.

The non-parametric bootstrap

Given the unknown nature of the sampling distribution of the ICER, there is reason to be cautious of the parametric approaches to confidence interval estimation. A number of commentators have suggested the non-parametric approach of bootstrapping as a possible method of estimating confidence limits for the ICER,[4,66,134,144] and this approach has been successfully demonstrated using clinical trial data.[143,145,146] The advantage of such intervals is that they do not depend on parametric assumptions of the sampling distribution of the ICER. Rather, bootstrap methods involve building up an empirical estimate of the sampling distribution of the statistic in question by resampling from the original data.

In the case of the ICER, where data on resource use and outcome exists for two groups of patients of size n_A and n_B receiving treatments A and B, respectively, the bootstrap method involves a three-stage process:

- Sample with replacement n_A cost/effect pairs from the sample of patients who received treatment A and calculate the bootstrap estimates C^*_A and E^*_A for the bootstrap sample;
- Sample with replacement n_B cost/effect pairs from the sample of patients receiving treatment B and calculate the bootstrap estimates C^*_B and E^*_B for the bootstrap sample;
- Calculate the bootstrap replicate of the ICER given by the equation:

$$R^* = \frac{\bar{C}^*_A - \bar{C}^*_B}{\bar{E}^*_A - \bar{E}^*_B} = \frac{\Delta\bar{C}^*}{\Delta\bar{E}^*}$$

Repeating this three-stage process many times gives a vector of bootstrap estimates, which is an empirical estimate of the sampling distribution of the ICER statistic. For example, the histogram in *Figure 28* shows the estimated sampling distribution from a previously reported study which used the bootstrap to estimate the sampling distribution of the ICER calculated from data generated by an economic evaluation conducted alongside a clinical trial.[145]

Once the sampling distribution of the ICER has been estimated in this way, several approaches exist to estimate confidence limits using the bootstrap estimate of the sampling distribution. However, for the purposes of this report, we consider only the straightforward percentile method, which employs the $(\alpha/2)100$ and $(1 - \alpha/2)100$ percentiles of the empirical sampling distribution as the estimated confidence limits.

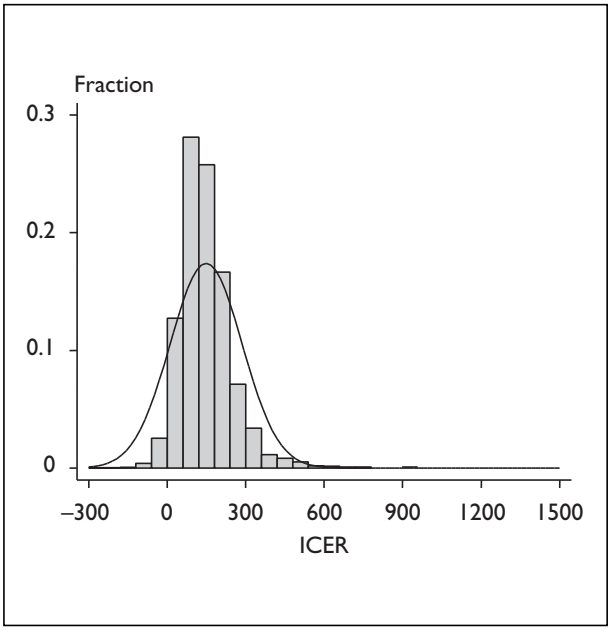


FIGURE 28 *Bootstrap estimate of the ICER sampling distribution*

An example from a clinical trial

Each of the approaches outlined above are illustrated using patient-specific data obtained from a clinical trial that compared a drug therapy treatment group with a placebo control group.[120] (Note that this data set is the same data presented in the Fenn example of chapter 4, but now includes the effectiveness variables.) Programme costs for each patient were estimated by aggregating recorded resource usage weighted by the prices of those resources. Length of survival for each patient, during the follow-up of the trial, was also recorded. The original data are summarised in *Table 10*. In addition to the usual summary statistics, the coefficients of variation for the estimators are also given (the ratio of the standard error to the mean), since it is the value of coefficient of variation that summarises the relative proximity of an estimate to 0 rather than the observed value of a statistic itself. It is clear from the table that while the mean costs and effects in the treatment and control groups are independently very different from 0 (i.e. have low coefficients of variation), the cost and effect differences have much higher coefficients of variation. In fact, the cost differences in *Table 10* have a coefficient of variation greater than 0.5, indicating that they are not significantly different from 0.* The incremental cost-effectiveness of the drug therapy from these data, calculated from equation (2), is 137.18 per year of life gained.

The representation of uncertainty based on each of the methods outlined above is shown in *Figure 29* for the clinical trial data. The horizontal and

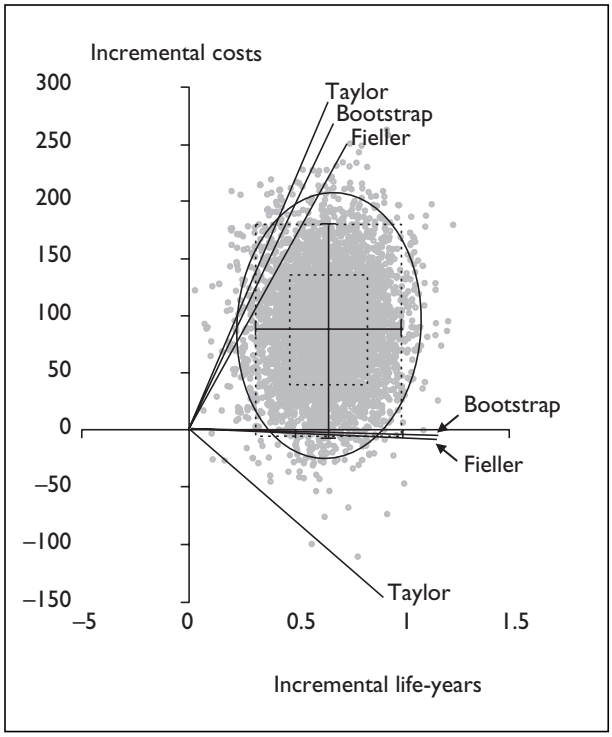


FIGURE 29 *Example of alternative confidence intervals using data from a clinical trial (rays from the origin represent the confidence intervals for the Taylor, Fieller and bootstrap methods; rays representing confidence intervals for the ellipse and box methods are not shown in order to avoid cluttering the figure)*

TABLE 10 *Sample statistics from the empirical data*

Variable	Mean	Standard deviation	Standard error	Coefficient of variation[a]	Correlation coefficient (cost and effect)
Control group (n = 67)					
Cost	363.92	260.85	31.87	0.09	
Effect	1.34	1.15	0.14	0.11	–0.05
Treatment group (n = 81)					
Cost	451.76	316.01	35.11	0.08	
Effect	1.98	0.94	0.10	0.05	0.19
Increments					
Cost difference	87.84	NA	47.42	0.54	
Effect difference	0.64	NA	0.18	0.27	0.05
Sample ICER	137.18	NA	NA	NA	NA

[a] *Coefficient of variation: cv = se($\bar{x}$)/$\bar{x}$, where $\bar{x}$ is the estimator*

NA, not applicable

* A statistic is significantly different from 0 if it has a value greater than approximately two standard deviations. It follows that if the ratio of the standard deviation to the mean is greater than 0.5, then the statistic is not significantly different from zero.

vertical 'I' bars represent the 95% confidence intervals on incremental effects and cost separately, which intersect at the ICER point estimate of 137.18. The dashed box is the confidence box generated by these intervals. The ellipse shown joins points of equal probability (assuming a joint normal distribution) such that the ellipse covers 95% of the integrated probability. Also shown are 5000 bootstrap replications of the incremental effect and incremental cost pairs, and the rays whose slopes correspond to the upper and lower 95% confidence limits of the ICER, as calculated by the Taylor, Fieller and bootstrap (percentile) methods. The confidence limits for each of the different methods, together with the interval length, are shown in *Table 11*.

TABLE 11 *Methods of confidence interval estimation compared: a numerical example*

Method	Lower limit	Upper limit	Interval length
Confidence box			
Standard	–5.2	606.7	611.9
Revised	49.3	290.8	241.5
Taylor series	–162.5	436.6	599.1
Confidence ellipse	–48.7	523.4	572.1
Fieller's theorem	–8.3	380.6	388.9
Bootstrap percentile	–5.9	392.0	397.9

What is immediately apparent from this analysis is that the symmetric nature of the Taylor series method gives a very different balance to the interval than the other methods. All else equal, shorter intervals are preferred to longer intervals and it is clear that the Fieller and bootstrap intervals are considerably shorter than the intervals from the other methods. It is also interesting to observe that, in this example, the interval from the ellipse method is not internal to the interval from the box method, a result that contradicts recent representations in the literature.[2,66]

Figure 29 and *Table 11* emphasise the differences in confidence intervals that can be obtained for the same data when employing different methods. However, on the basis of a single example, it is not possible to judge which method is most appropriate. Recall that the definition of a 95% confidence interval is that the true population parameter will be included in the interval 95% of the time in repeated sampling. In order to estimate the accuracy of the intervals obtained by different methods, simulation experiments, where the true population ICER is defined, can be undertaken. Such experiments involve drawing samples of costs and effects from predefined distributions, calculating confidence intervals for the estimated ICER and recording whether the true value is contained within the interval. This simulation is then repeated a large number of times, and the proportion of times the true value of the ICER is contained within the interval is used to judge the coverage properties of the confidence interval calculation methods.

The results of two such articles have shown that the Fieller method and bootstrap methods outperform the other methods.[139,147] The intuition for this result is that both the Fieller method and the bootstrap method attempt to adjust the interval such that it contains $(1 - \alpha)100\%$ of the joint density, whereas the tangents to the ellipse and rays to the corners of the box cover more than $(1 - \alpha)100\%$ of the joint density. Since the Taylor series method assumes a normal sampling distribution* when there is good reason to believe the sampling distribution is non-normal, it clearly provides an inappropriate interval.

Given that the Monte Carlo evaluation studies show the bootstrap method to be a good overall method, the bootstrap method can be used to show the inaccuracies of the inferior methods from *Table 11* and *Figure 29*. For the Taylor series method, 1.7% of the bootstrap replications gave ICERs that were above the upper estimate of the confidence limit, while 0.6% were below the lower limit, suggesting an overall confidence interval of 97.7%. The ellipse method had an overall confidence interval of 98.4% (0.74% bootstrap replications below the lower limit and 0.84% above the upper limit), a greater over-specification than the standard box method at 96.9% (2.56% below and 0.56% above). The potential pit-falls of the revised box approach are plainly apparent (note that cost and effect differences in *Table 10* are almost independent), since the method gives just an 80% confidence interval: 12.6% of the bootstrap replications fell below the lower limit and 7.3% were above the upper limit.

* Note that the Taylor series method of estimating the variance of a function of two random variables is not based on any assumption of normality. It is the application of that estimate of the variance to the normal distribution to generate confidence intervals that introduces this assumption.

The Monte Carlo evaluation studies also appear to show that the Fieller method outperforms the bootstrap method overall, although in some situations bootstrap methods may be superior (the results are extremely close and in most cases are not statistically significant). This suggests that while the sampling distribution of the ICER is clearly non-normal, the parametric assumption of a joint normal distribution of the numerator and denominator of the ICER may be reasonable.

Problems with confidence intervals

Despite the large volume of research activity directed at methods for estimating confidence limits for ICERs, little has been discussed about how decision makers might use interval estimates for ICERs to make decisions based on cost-effectiveness analysis. It is possible that there may be a number of practical problems associated with the use of confidence intervals for decision making.

In terms of the cost-effectiveness plane introduced in chapter 1 (see *Figure 1*), confidence intervals for the ICER may only be defined in quadrants I and III. A debate is currently in progress concerning the interpretation of negative ICERs.[148–150] Interpretation of negative ICERs may be problematic for two reasons. Firstly, both quadrants II and IV on the cost-effectiveness plane generate negative ICERs; however, the implications for decision making are exactly opposite in each quadrant. Without examining the sign of the numerator and denominator of the ICER, it is impossible to distinguish negative ICERs in quadrant II from negative ICERs in quadrant IV.* Secondly, the magnitude of negative ICERs is meaningless. If an intervention is associated with an increase in life-years of 0.25 years and a cost saving of £1000 it will have an ICER of –£4000 per life-year gained. It is clear that an alternative intervention which generates the same cost savings but which generates a health benefit of 2 years will be preferred, but will have an ICER of –£500 per life-year, which is greater than –£4000. Hence, it is clear that examples can easily be constructed to show that negative ICERs do not obey the transitivity assumption, which means that the magnitude of negative ICERs conveys no useful meaning. Some analysts have proposed the use of cost-effectiveness 'angles' instead of 'slopes', which solves the problem of distinguishing between quadrants of the cost-effectiveness plane. However, such an approach will still suffer from the same problems of transitivity violation in quadrants II and IV of the cost-effectiveness plane.

A second problem with confidence intervals is their close link with hypothesis testing, and in particular the convention that 5% significance is the appropriate level (hence the widespread reporting of 95% confidence intervals). When employing a confidence interval for decision-making purposes, decision makers might compare their own view of the maximum acceptable ICER for a particular intervention with the presented interval. If that ceiling value of the ICER is external to the interval then (assuming 95% embodies an appropriate level of precision) a decision may be possible. The problem comes when the ceiling value of the ICER lies within the interval, since in different situations decision makers may be willing to accept different rates of error in failing to reject the null hypothesis. Although it is known that values towards the centre of a confidence interval are more likely, this aspect of the probability distribution is not quantified. Furthermore, the relevant hypothesis in economic analysis is likely to be a one-sided test, whereas confidence intervals are two sided. In deciding whether the evidence of cost-effectiveness presented in a study is sufficiently strong, decision makers will want to consider the chance that the intervention is not cost-effective (with reference to some ceiling ratio). This is consistent with the one-sided test of hypothesis H_0: $R > R_C$, and suggests that the lower limit of a confidence interval is unlikely to play a practical purpose in decision making. The one-sided nature of hypothesis testing was recognised by Wakker and Klaassen,[132] who advocated the use of the confidence box to calculate what they termed a one-sided interval. Of course, this stated problem of confidence intervals is not one 'of confidence intervals themselves, but of the way they are commonly interpreted'.[151]

Poole has gone on to argue that much more information could be given to a decision maker by presenting the *p* value function in its entirety,

* Note that this can cause problems for the rank ordering of bootstrapped ICERs for the percentile-based methods since negative ICERs relating to negative costs cannot be distinguished from negative ICERs relating to negative effects. This problem was not encountered in the bootstrapping of the data from the clinical trial reported later in the section entitled 'The continuing role of sensitivity analysis'. However, where this problem is encountered, it may undermine the validity of the bootstrap approach.

equivalent to the graph of all possible confidence limits.[151] This would have the simultaneous effect of allowing decision makers to choose the rate of error they regard as most appropriate and encouraging them to think about what that appropriate rate of error might be rather than restricting the information to conventional levels of significance.

Cost-effectiveness acceptability curves

An alternative and much more flexible approach to representing uncertainty has already been advocated by van Hout *et al.*,[138] but has received much less attention than confidence intervals in the recent literature. They refer to the area of the cost-effectiveness plane lying to the right of the ceiling ratio as the acceptability surface, and advocate the construction of a cost-effectiveness acceptability curve on the basis of the probability an intervention is cost-effective in relation to different values of the ceiling ratio from 0 through to ∞ (equivalent to rotating the ceiling ratio line in *Figure 1* from the horizontal through to the vertical).

This approach is illustrated using the data from the clinical trial above. *Figure 30* shows ellipses of equal probability based on these data on the cost-effectiveness plane, assuming a joint normal distribution function as given by equation (4) above. Note, however, that in contrast to using this approach to estimate the confidence limits for the ICER which results in an approximation to the true limits (since tangents to the 95% ellipse cover more than 95% of the joint density function), estimating the proportion of the density function which lies to the left of the line representing the ceiling ratio provides an exact solution (if the assumption of joint normality holds). Van Hout *et al.*[138] give this solution as

$$F(R) = \int_{-\infty}^{\infty} \int_{-\infty}^{R\Delta E} f(\Delta\bar{E}, \Delta\bar{C})\, \mathrm{d}\Delta\bar{C}\, \mathrm{d}\Delta\bar{E} \qquad (6)$$

However, an alternative approach would be to use the bootstrap replications from *Figure 28* as an estimate of the joint probability density function and simply calculate, for different values of the ceiling ratio, the proportion of the bootstrap replications that lie on the acceptable side of the ceiling ratio. Two main advantages are apparent with this non-parametric approach: firstly the relative ease of the approach compared with evaluating equation (6); but perhaps more importantly the fact that the bootstrap approach does not depend on parametric assumptions relating to the joint distribution of the costs and effects. *Figure 31*, shows this bootstrap estimate of the cost-effectiveness acceptability curve for the clinical trial data described in *Table 10*.

Note that the cost-effectiveness acceptability curve does not suffer from the problems of confidence interval estimation identified above. Since it directly

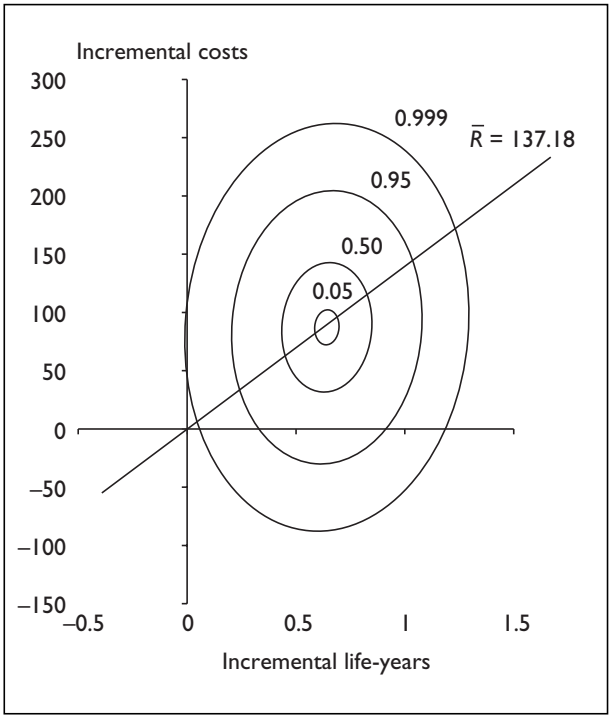


FIGURE 30 *Joint normal distrbution on the cost-effectivness plane*

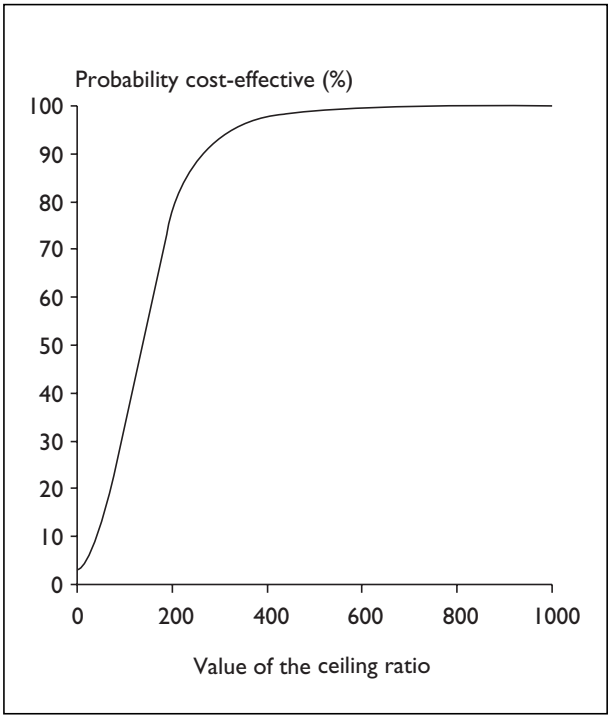


FIGURE 31 *The cost-effectiveness acceptability curve*

addresses the decision-making problem by quantifying the probability that the intervention in question is cost-effective, the issue of negative ICERs in quadrants II and IV of the cost-effectiveness plane does not arise, therefore the problem of different types of negative ICERs for bootstrapping will not arise either. Another advantage is that the cost-effectiveness acceptability curve makes immediately apparent the probability that the intervention in question is not cost-effective (the one-sided hypothesis test most appropriate for decision making). In addition, the cost-effectiveness acceptability curve quantifies this probability for all potential values of the ceiling ratio.

This latter attribute is likely to be important for two reasons: clearly because it is known that the appropriate ceiling ratio for decision-making purposes is unknown by the analyst and is likely to vary between decision makers and over time; but also because the appropriate level of acceptable error may vary between therapeutic areas or types of intervention. For example, suppose that two ICERs are identical: $R_A = R_C$ where R_A is the incremental cost-effectiveness of treatment A over treatment B and R_C is the incremental cost-effectiveness of treatment C over treatment D. However, treatment A relates to an extremely rare condition and which may affect only ten patients in the whole country per annum at a total cost of approximately £1000 per patient. By contrast, treatment C relates to the cost-effectiveness of introducing a screening programme which will include a significant proportion of the population, say 1 million per annum, at a cost of say £10 per patient. In the case of treatment A, we may be prepared to accept a relatively high rate of error since the consequences of being wrong are limited to just ten patients and will therefore have little impact on the overall budget for health care. The opposite is true in the case of treatment C: since the resources to be committed to the screening programme constitute a much larger proportion of the available budget for health care the consequences of making an incorrect decision are much higher.

Although it may appear that these advantages of the cost-effectiveness acceptability curve would be apparent through the use of the p value function described above – there is a remaining advantage of using the cost-effectiveness acceptability curve. The problem with estimating confidence intervals for the ICER is that the ICER does not fully describe the decision-making problem since it is only appropriate to consider the ICER when incremental cost and effect differences are simultaneously positive (or negative). Since the cost-effectiveness acceptability curve relates directly to decision making and the confidence surface on the cost-effectiveness plane, it does not suffer from the potential problem associated with being unable to distinguish negative values of the ratio corresponding to different quadrants of the plane.

The continuing role of sensitivity analysis

The focus of this chapter has been the statistical analysis of uncertainty in stochastic cost-effectiveness analysis. However, it is worth remembering that statistical analysis only summarises uncertainty due to sampling variation and that there will be a continuing role for the use of sensitivity analysis to quantify uncertainty in those data requirements of the study for which sample data are not available (as is commonly the case with unit cost information), and for handling uncertainty related to issues of generalisability, extrapolation and methodological considerations, as discussed in chapter 1. It is also worth considering how statistical analysis and sensitivity analysis might be used together. In the case of confidence intervals, sensitivity analyses would generate a number of confidence intervals, which then require interpretation.[152] For example, different methodological scenarios (as described in chapter 3) would each require a separate point estimate of cost-effectiveness and associated confidence interval. Similarly, the study could be made more generalisable by including a different vector of unit cost estimates (representative of another centre or geographical location) and point estimates and confidence intervals re-estimated under these different scenarios. In the example of an economic analysis alongside a clinical trial considered above, the effectiveness measure was life-years gained within the trial period. It could be desirable to extrapolate this result to life-years gained across the lifetime of the patient. If this could be done at the individual patient level then it may still be possible to calculate confidence intervals for the resulting ratio – since this would introduce a deterministic element to the results, alternative assumptions should be tested using sensitivity analysis.*

* If it is not possible to maintain the patient level construct of the data, then the evaluation may become more of a modelling exercise with the trial data representing information to the decision model. Handling uncertainty in a modelling situation is covered in the next chapter.

Therefore the use of sensitivity analysis in addition to statistical analysis implies a series of confidence intervals. If a ceiling ratio value were external to some of these intervals and internal to others, such an approach might be seen to be exacerbating uncertainty in terms of whether a hypothesis should be rejected or not. Sensitivity analyses applied to cost-effectiveness acceptability curves, on the other hand, would generate a range of curves – equivalent to a range of probability that the intervention is cost-effective – for each value of the ceiling ICER. This would seem to be much more readily interpretable.

Summary

A number of alternative methods have appeared in the recent literature for calculating confidence intervals for ICERs. Perhaps due to the fast-moving nature of this field of research, recently published overviews of methods for handling uncertainty in economic evaluation have tended to focus on the confidence box, confidence ellipse and Taylor series methods.[2,66] However, it is clear that these methods are merely approximations to the true interval. Providing the parametric assumption of normality in the numerator and denominator of the ratio holds, Fieller's theorem provides an exact solution to the problem. Where analysts prefer not to rely on these assumptions, the approach of non-parametric bootstrapping will generate the appropriate intervals. The large-scale Monte Carlo simulation experiment reported in this chapter confirms the theoretical arguments in favour of Fieller's theorem when the joint normal distribution assumption holds. The non-parametric bootstrap method was also shown to perform well, and may be preferred to Fieller's theorem when the data show substantial skewness.

The three studies in the database which did employ statistical methods to estimate uncertainty in the ICER point estimates employed the confidence box method,[45] Taylor series approach[153] and a method which is really just a range of cost-effectiveness ratios for individuals.[154] Of course, the literature reviewed above was not available to these analysts. As future economic analyses alongside clinical trials are reported, Fieller's theorem and the non-parametric approach of bootstrapping should be employed when estimating confidence limits in preference to the other methods to have appeared in the recent literature.

However, the focus on confidence intervals as the appropriate method for quantifying uncertainty due to sampling variation does not give adequate weight to the process of decision making. In this chapter is was argued that cost-effectiveness acceptability curves give a better representation of uncertainty in view of continued uncertainty about the appropriate ceiling ratio for decision making and the level of 'confidence' required for decisions to be made.

It should be emphasised, however, that statistical methods for handling uncertainty relate only to uncertainty due to sampling variation and that there is a continuing role for the use of sensitivity analysis to handle other types of uncertainty that will be present in such economic analyses.[154] A further advantage of cost-effectiveness acceptability curves is that given the importance of using sensitivity analysis to handle uncertainty not related to sampling variation, cost-effectiveness acceptability curves are much more easily interpreted than confidence intervals as a series of curves representing different sensitivity analyses.

Chapter 6

Towards the development of guidelines

The purpose of this chapter is to summarise the main findings of the preceding four chapters, while at the same time putting forward some potential guidelines which arise out of the analysis presented in this report. Potential guidance is presented in bold type, and the justifications for these recommendations follow, based on the results of this review. In addition, areas requiring further research arising from this report and the guidelines below are also identified.

Potential guidelines for analysts

Analysts should aim to present results using a methodological reference case in order to increase the comparability of results between studies. By reporting ICERs, analysts are accepting that the ratio from their study should be compared with the results reported by other analysts. Indeed, many analysts make such comparisons directly within their own study. However, such comparisons are hampered by the lack of a consistent methodology – and this has been a common criticism of grouping study results together in so-called cost-effectiveness league tables. In the results of the review of UK studies presented in chapter 3 we employed a retrospective reference case-type approach to improve comparability between results. The prospective application of a reference case during the analysis and reporting of a study would ensure comparability between methods, while still allowing analysts to explore new and innovative methods within the study. In fact, comparison of results using innovative methods with a reference case analysis may serve to elucidate the importance of those new methods. The recent US panel on cost-effectiveness analysis has agreed a reference case.[3] We believe that a similar exercise should be undertaken in the UK to agree a reference case appropriate to the UK context.

Analysts should be aware of the potential for the ICER to vary at the margin. Analysts should attempt to estimate the implications of expanding or contracting a given level of service, since it is at this margin that decisions are likely to be made. At least three different types of margin may be appropriate in cost-effectiveness analysis. First, a clinical margin, where an intervention may cover patients with different age profiles, clinical characteristics or risk levels, such that the capacity to benefit from the intervention varies by patient group. Second, an intensity margin, where an intervention is applied more intensively to the same group of patients, for example by increasing the frequency of a screening programme. Third, a pure volume or scale margin, where a service may be expanded to include more patients with the same characteristics. While analysts should be aware of all three types of margin, baseline cost-effectiveness results should be reported as varying by the clinical and intensity margin. The volume or scale margin, on the other hand, is related to the issue of technical efficiency, and is best handled in the sensitivity analysis.

Analysts should avoid selective comparison of their results with the results from other studies. It is common for analysts to compare the cost-effectiveness results they report with the results from other 'commonly provided' healthcare interventions. However, our analysis in chapter 3 shows firstly, that these comparisons are made on average with only six other results (drawn from an even smaller number of studies), and secondly, that the cost-effectiveness figures chosen for comparison are higher on average than the actual set of reported cost-effectiveness figures for the UK as a whole. Instead, we recommend that analysts locate their results in the appropriate decile of reported cost-effectiveness results.

Analysts should ensure that they consider the potential implications of uncertainty for the results of their analysis. Interval estimates should accompany each point estimate presented. Uncertainty in the economic evaluation of healthcare interventions is pervasive. In addition to point estimates of cost-effectiveness, analysts should seek to provide interval estimates which represent this uncertainty. In the review of published cost-effectiveness studies presented in chapter 2, 17% of studies failed to consider uncertainty at all in their analysis, and a further 3% of studies failed to report the results of any analysis of uncertainty. Furthermore, in the analysis of UK studies in chapter 3, only 133 of 333 baseline results had some form of interval estimate associated with the point estimate, with only 61 baselines having an associated two-sided

range of values representing uncertainty. Analysis of these 61 results showed that their rank ordering changed substantially when the high and low values of the interval estimates were considered. Analysts should aim to report an interval estimate for each point estimate of cost-effectiveness.

Where sensitivity analysis is employed to estimate an interval, analysts should be comprehensive in their inclusion of all variables in the analysis. An examination of the number of variables included in the sensitivity analysis underlying the ranges reported in chapter 3 shows that on average only three variables were included in the sensitivity analysis. This suggests that analysts are not comprehensively including all variables in their sensitivity analysis. Analysts should also be aware that uncertainty in their study is not limited to the data components but also includes issues of generalisability and extrapolation, which should also be explored in any sensitivity analysis.

When reporting sensitivity analysis, analysts should be aware of the probabilistic nature of the reported range. Standard sensitivity analysis methods do not give explicit probabilistic information in the same way as a statistical confidence interval. However, it is clear that intervals based on simple one-way sensitivity analyses underestimate intervals in comparison with confidence intervals due to the lack of consideration of joint variation. By contrast, best/worst-case-type sensitivity analyses will overestimate the interval. More use should be made of multiway analyses to explore the effect of joint uncertainty on the overall interval. Probabilistic sensitivity analysis is also a promising approach, although more research is required to explore exactly how it should be employed in a cost-effectiveness setting.

When reporting patient level cost information, analysts should make more use of descriptive statistics. Our review of studies reporting patient level cost information in chapter 4 showed that only 53/492 (11%) of studies did make use of patient level cost data, and only 25 of these attempted to report some measure of variance for the cost data. Only four of the studies identified attempted to calculate standard statistical confidence intervals. Since the distribution and variance of cost data will have important implications for statistical analysis, analysts should present more descriptive statistics in order to better acquaint the reader with the data. They should not rely solely on range or interquartile range data, the most frequently reported descriptive statistics in this review.

Even when data are skewed, economic analyses should be based on means of distributions. In the presence of skewed cost data, median cost values and the geometric mean of the distribution may provide useful summary information. However, the economic analysis should be based on the standard mean of the distribution since only the mean, when multiplied by the number of patients, will give the total cost of care for a patient group.

When reporting statistical tests of cost differences, analysts should be aware that significance tests may be more powerful on a transformed scale but that confidence limits should be reported on the original scale. Our analysis of five available cost data sets in chapter 4 suggests that cost data are often distributed in a non-normal fashion and that in some cases these distributions may exhibit substantial skewness. Transformation of the original data on to an alternative scale may provide improved power for significance testing by improving the adherence of the data to the assumptions underlying standard statistical tests. However, the interpretation of back transformed values from these scales is fraught with difficulty. An alternative approach of non-parametric bootstrapping can be used to test whether the sample size of the study is sufficient for the central limit theorem of a normal sampling distribution to apply. If it is, then standard parametric methods can be employed on the untransformed scale and confidence intervals can be calculated in the usual way. If it is not, then the bootstrap results can be used to estimate a non-parametric confidence interval on the original scale that will not be symmetric about the point estimate. Since these tests may not have the power of the tests on the transformed scale, but do allow the estimation of point and interval estimates on the untransformed scales, in some situations analysts may want to present the results of both types of test.

Where patient level data on both cost and effect are available, the parametric approach based on Fieller's theorem or the non-parametric approach of bootstrapping should be employed to estimate a confidence interval for the cost-effectiveness ratio. A number of alternative methods for estimating confidence limits for cost-effectiveness ratios have appeared in the recent literature. The review of their statistical properties in chapter 5 and evidence from Monte Carlo simulation studies suggest that the parametric method based on Fieller's theorem and the non-parametric approach of bootstrapping are the most

appropriate methods. The confidence box, as a simple and conservative method, may have a continued role in situations where it is possible to show that when applying a conservative interval (i.e. a wide interval) the results remain cost-effective/cost-ineffective.

Sensitivity analysis has a continuing role in handling uncertainty not related to sampling variation. As the number of economic analyses based on patient level cost and effect data increases, analysts should continue to employ sensitivity analysis to handle those types of uncertainty not related to sampling variation.

Consideration should be given to using cost-effectiveness acceptability curves to present uncertainty in stochastic cost-effectiveness studies. While it is likely that many journals will require confidence limits to be reported for cost-effectiveness, consideration should be given to the use of cost-effectiveness acceptability curves to represent uncertainty due to sampling variation. Cost-effectiveness acceptability curves have the advantage that they present potential decision makers with more information than confidence intervals, since they do not adhere to conventional levels of statistical significance, and they present information over a the whole range of possible ceiling cost-effectiveness ratios appropriate for decision making. Furthermore, cost-effectiveness acceptability curves may be more easily interpreted when used in conjunction with sensitivity analysis compared with confidence intervals.

Areas for future research

Three main areas for future research arise from this review:

- **Agreeing a reference case**. Research is required into the appropriate reference case that could be used in UK studies. A consensus panel approach, such as that used in the USA, could encourage broad acceptance of any agreed reference case and encourage the incorporation of the reference case into emerging economic evaluation guidelines.
- **Probabilistic sensitivity analysis**. Research is required into the promising approach of probabilistic sensitivity analysis. Although this technique has been employed in the medical decision-making literature, its use in economic evaluation has so far been limited. This is most likely due to the complexities of applying the method to the simultaneous comparison of cost and effect and the lack of a clear decision rule in cost-effectiveness analysis.
- **Ceiling cost-effectiveness ratios for decision making**. In the presence of a fixed budget, the maximisation of health outcomes requires that healthcare interventions are implemented in order of cost-effectiveness until the budget for health care is exhausted. This is, in essence, the league table approach, and the last healthcare intervention to receive funding defines the marginal willingness to pay for a unit of effectiveness implied by setting the budget at the given level. The database of UK results developed here represents a systematic attempt to compile a 'league table' for the UK which endeavours to overcome problems associated with simple 'league tables'. Further research could look at which of the studies in the database are currently provided and what this implies about the marginal willingness to pay for health gain in the UK. This could be compared with other forms of estimating willingness to pay for health gain based on consumer surveys or implied from willingness to pay/QALY studies.

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Appendix 1

Key words

Key word proforma

Area	Key words (ring as many as apply)
Funding source	Industry / Non-industry / Not-stated
Countries	
Currency	
Disease	
ICD-9 codes	I / II / III / IV / V / VI / VII / VIII / IX / X / XI / XII / XIII / XIV / XV / XVI / XVII
Intervention	
Type of intervention	Surgical / Diagnostic / Medical / Screening / Health promotion / Prevention
Other type	
Outcomes	Life-years / QALYs
QALY weights	
Study design	Alongside clinical trial Other prospective Secondary analysis of clinical trial results Retrospective evaluation Decision analytic: decision tree model Decision analytic: Markov model Other modelling approach
Patient level data	Patient level health outcomes Patient level resource use
Extrapolation	Intermediate to final Outcomes beyond follow-up Resources beyond follow-up
Handling of uncertainty	Sensitivity analysis not quantitatively reported One-way sensitivity analysis Multiway sensitivity analysis Extreme scenario analysis Threshold analysis Probabilistic sensitivity analysis Statistical analysis No analysis
Article notes	

Keywords in database

Source of article

Ad hoc identification
CINAHL
CRD
EconLit
EMBASE
Gerard (1992)[89]
MEDLINE
OHE–HEED
Secondary identification
SSCI

Funding source

Funding source: Industry
Funding source: Non-industry
Funding source: Not-stated
Funding source: Not clear

Study country

Country: Argentina
Country: Australia
Country: Belgium
Country: Brazil
Country: Burma
Country: Canada
Country: Denmark
Country: Developing countries
Country: European perspective
Country: Finland
Country: France
Country: Germany
Country: Honduras
Country: Ireland
Country: Italy
Country: Japan
Country: Malawi
Country: Mexico
Country: Mozambique
Country: Multinational study
Country: Nepal
Country: New Zealand
Country: Norway
Country: South Africa
Country: Spain
Country: Sweden
Country: Switzerland
Country: Tanzania
Country: The Gambia

Country: The Netherlands
Country: Uganda
Country: UK
Country: Upper Volta
Country: USA
Country: Wales
Country: West Africa
Country: Zambia

Currency of results

Currency: Aus$
Currency: BEF
Currency: Can$
Currency: DFL
Currency: DM
Currency: Dutch guilders
Currency: ECU
Currency: Francs
Currency: IR£
Currency: Kroner
Currency: Lire
Currency: Nepalese rupees
Currency: NLG
Currency: NOK
Currency: NZ$
Currency: Pesatas
Currency: Rand
Currency: SEK
Currency: Sterling
Currency: Swiss francs
Currency: US$
Currency: Yen

Disease or condition

Disease: Abdominal aortic aneurysm
Disease: Acquired abnormal anatomy
Disease: Acute leukemia
Disease: Acute limb ischemia
Disease: Acute myocardial infarction
Disease: Acute necrotising pancreatitis
Disease: Acute pancreatitis
Disease: Adverse cardiovascular events
Disease: AIDS
Disease: Alcoholism
Disease: Alzheimer's
Disease: Anaemia
Disease: Angina
Disease: Aphakia
Disease: Arterial occlusion
Disease: Aspiration
Disease: Asthma
Disease: Back pain
Disease: Bacterial infection
Disease: Barrett's esophagus
Disease: Benign gynaecologic disease
Disease: Benign neoplasm
Disease: Benign prostatic hyperplasia
Disease: Bladder cancer
Disease: Blindness
Disease: Blunt thoracic aortic trauma
Disease: Bone disorders
Disease: Bowel disorders
Disease: Brain metastases
Disease: Brain tumour
Disease: Breast cancer
Disease: Cancer
Disease: Cardiac fibrillation
Disease: Cardiogenic pulmonary oedema
Disease: Cardiopulmonary arrest
Disease: Cardiovascular disease
Disease: Carotid stenosis
Disease: Cataract
Disease: Central nervous system metastases
Disease: Cerebral arteriovenous malformation
Disease: Cerebrovascular disease
Disease: Cervical cancer
Disease: Chemotherapy induced nausea and vomiting
Disease: Chest wound
Disease: Cholesterol related heart disease
Disease: Chronic bronchitis
Disease: Chronic heart disease
Disease: Chronic immune thrombocytopenic purpura
Disease: Chronic lymphocytic leukemia
Disease: Chronic obstructive pulmonary disease
Disease: Cirrhosis
Disease: Colon cancer
Disease: Colorectal cancer
Disease: Coronary artery disease
Disease: Coronary heart disease
Disease: Cutaneous melanoma
Disease: Deafness
Disease: Death by fire
Disease: Dementia
Disease: Dengue
Disease: Depression
Disease: Diabetes
Disease: Diarrhoea
Disease: Digitalis toxicity
Disease: Disability
Disease: E. coli
Disease: End-stage renal disease
Disease: Endometrial cancer
Disease: Endometrial hyperplasia
Disease: Endometriosis
Disease: Epilepsy
Disease: Fatal reactions
Disease: Fibromyalgia
Disease: Foot care related
Disease: Foot disorders
Disease: Gallbladder disease
Disease: Gallstones
Disease: Gastric cancer

Disease: Gastrointestinal disease
Disease: Gaucher's disease
Disease: General infection
Disease: Haemophilus influenzae B
Disease: Haemophilia
Disease: Hand disorders
Disease: Head injury
Disease: Heart disease
Disease: Heart failure
Disease: Helicobacter pylori infection
Disease: Hepatitis
Disease: Hepatitis A
Disease: Hepatitis B
Disease: Hepatitis C
Disease: Hereditary haemochromatosis
Disease: Herniated intervertebral disc
Disease: Herpes
Disease: Herpes zoster
Disease: Hip fracture
Disease: HIV
Disease: HLTV
Disease: Hodgkin's disease
Disease: Hospital acquired infection
Disease: Hypertension
Disease: Immune thrombocytopenic purpura
Disease: Influenza
Disease: Injury
Disease: Intra-abdominal infection
Disease: Intracranial tumour
Disease: Intracranial aneurysm
Disease: Ischaemic heart disease
Disease: Joint disorders
Disease: Kidney stones
Disease: Lead poisoning
Disease: Leukemia
Disease: Liver cancer
Disease: Liver cirrhosis
Disease: Liver disease
Disease: Liver failure
Disease: Low birth weight
Disease: Lung cancer
Disease: Lung failure
Disease: Malaria
Disease: Malignant non-Hodgkin's lymphoma
Disease: Maternal health
Disease: Meningitis
Disease: Menopausal symptoms
Disease: Menstrual disorders
Disease: Mental illness
Disease: Metastatic brain tumour
Disease: Mild hypertension
Disease: Mistransfusion
Disease: Mitral valve disease
Disease: Mitral valve prolapse
Disease: Myeloma
Disease: Myocardial infarction
Disease: Myocardial ischemia
Disease: Nephropathy
Disease: Non-small cell lung cancer
Disease: Obstructive sleep apnea
Disease: Onchocercal blindness
Disease: Orthopaedic disorders
Disease: Osteoarthritis
Disease: Osteoporosis
Disease: Otitis media with effusion
Disease: Ovarian cancer
Disease: Pancreatic cancer
Disease: Parasitical
Disease: Penile cancer
Disease: Peptic ulcer
Disease: Peripheral arterial disease
Disease: Pneumonia
Disease: Polycystic kidney disease
Disease: Prostate cancer
Disease: Prosthetic joint infection
Disease: Pulmonary disease
Disease: Rabies
Disease: Radiation induced cancer
Disease: Renal failure
Disease: Renovascular hypertension
Disease: Renovascular stenosis
Disease: Respiratory disease
Disease: Respiratory distress syndrome
Disease: Respiratory failure
Disease: Retinopathy
Disease: Rh immunisation
Disease: Rheumatoid arthritis
Disease: Road traffic accidents
Disease: Rotavirus
Disease: Schizophrenia
Disease: Sepsis
Disease: Severe burns
Disease: Sleeping sickness
Disease: Smoking related disease
Disease: Spinal disorder
Disease: Stroke
Disease: Subarachnoid haemorrhage
Disease: Surgery induced anxiety
Disease: Tendon disorders
Disease: Tetanus
Disease: Thromboembolism
Disease: Thrombosis
Disease: Thyroid dysfunction
Disease: Trachoma induced blindness
Disease: Trauma
Disease: Tuberculosis
Disease: Typhoid
Disease: Uretal stones
Disease: Urinary tract infection
Disease: Uterine bleeding
Disease: Uterine cancer
Disease: Variceal bleeding
Disease: Varicella
Disease: Whooping cough

ICD-9 code chapter heading

ICD-9: I
ICD-9: II
ICD-9: III
ICD-9: IV
ICD-9: V
ICD-9: VI
ICD-9: VII
ICD-9: VIII
ICD-9: IX
ICD-9: X
ICD-9: XI
ICD-9: XIII
ICD-9: XIV
ICD-9: XV
ICD-9: XVII
ICD-9: Unknown
ICD-9: E (supplement)

Intervention

Intervention: Ablation
Intervention: Adjuvant chemotherapy
Intervention: Amputation
Intervention: Anaesthesia
Intervention: Angiography
Intervention: Angioplasty
Intervention: Antibiotic prophylaxis
Intervention: Antibiotics
Intervention: Anticoagulation therapy
Intervention: Antiemetic drug therapy
Intervention: Antihypertensive drug therapy
Intervention: Antihypertensive management
Intervention: Antimicrobial therapy
Intervention: Arrhythmic monitoring
Intervention: Aspirin
Intervention: Autologous blood donation
Intervention: Autologous bone marrow transplantation
Intervention: Bed net impregnation
Intervention: Behavioural programme
Intervention: Bicycle helmets
Intervention: Bilateral salpingo-ophorectomy
Intervention: Biopsy
Intervention: Bone marrow transplant
Intervention: Breast feeding promotion
Intervention: Bypass surgery
Intervention: Cadaver transplantation
Intervention: Caesarean
Intervention: CAPD
Intervention: Carcinoembyonic antigen
Intervention: Cardiac angiography
Intervention: Care-giver support programme
Intervention: Carotid endarterectomy
Intervention: Cataract removal
Intervention: Chelation therapy
Intervention: Chemoprophylaxis
Intervention: Chemotherapy
Intervention: Child restraints
Intervention: Chiropody
Intervention: Cholesterol lowering therapy
Intervention: Cholesterol screening and reduction programmes
Intervention: Cochlear implants
Intervention: Cognitive therapy
Intervention: Community care
Intervention: Conservative management
Intervention: Contact lens
Intervention: Continuous peritoneal lavage
Intervention: Contrast angiography
Intervention: Coronary angiography
Intervention: Coronary artery bypass graft
Intervention: Coronary care unit
Intervention: Cryotherapy
Intervention: Day care
Intervention: Day care unit
Intervention: Dedicated trauma care unit
Intervention: Degradable starch microspheres
Intervention: Diagnostic tests
Intervention: Dialysis
Intervention: Diet and exercise programme
Intervention: Dietary fat reduction programme
Intervention: Dietary therapy
Intervention: Dilatation and curettage
Intervention: Doppler ultrasound screening
Intervention: Drug prophylaxis
Intervention: Drug therapy
Intervention: Duplex sonography
Intervention: Early cardiac rehabilitation
Intervention: Echocardiography
Intervention: Educational programme
Intervention: Electrocardiography
Intervention: embolectomy
Intervention: Emergency services
Intervention: Endoscopic retrograde cholangiopancreatography (ERCP)
Intervention: Endoscopic surveillance
Intervention: Enzyme replacement therapy
Intervention: Esophagectomy
Intervention: Estrogen therapy
Intervention: Exercise electrocardiography
Intervention: Exercise thallium imaging
Intervention: Fine-needle aspiration biopsy
Intervention: Follow-up care
Intervention: Foot surgery
Intervention: Group living
Intervention: Hand surgery
Intervention: Head CT scan
Intervention: Health check
Intervention: Heart valve replacement
Intervention: High flux dialysis
Intervention: Hip arthroplasty
Intervention: Hip replacement
Intervention: Home care
Intervention: Home dialysis

Intervention: Home dialysis aides
Intervention: Home parenteral nutrition
Intervention: Hormone replacement therapy
Intervention: Hospital dialysis
Intervention: Hospital parenteral nutrition
Intervention: Hospitalisation
Intervention: Hysterectomy
Intervention: Immunisation
Intervention: Immunosuppresion
Intervention: Implantable defibrillator
Intervention: Infection control programme
Intervention: Intensive care
Intervention: Intensive care unit
Intervention: Intensive management
Intervention: Intestinal parasites
Intervention: Intraocular lens
Intervention: Knee replacement
Intervention: Laparoscopic cholecystectomy
Intervention: Laser
Intervention: Leukocyte transfusion
Intervention: Lifestyle interventions
Intervention: Lipid lowering therapy
Intervention: Liver biopsy
Intervention: Living-donor transplantation
Intervention: Low osmolality contrast media
Intervention: Lumbar discectomy
Intervention: Mechanical barrier system
Intervention: Magnetic resonance imaging
Intervention: Malaria control programme
Intervention: Mammography
Intervention: Mastectomy
Intervention: Mechanical ventilation
Intervention: Misoprostol prophylaxis
Intervention: Mobile maternal health service
Intervention: Monitoring
Intervention: Monoclonal antibody
Intervention: Multifactorial risk reduction programme
Intervention: Nasal continuous positive airway pressure
Intervention: Needlecore biopsy
Intervention: Neonatal care
Intervention: Neonatal circumcision
Intervention: Neonatal intensive care
Intervention: Neurosurgery
Intervention: Nicorette nasal spray
Intervention: Nicorette patch
Intervention: Nicotine gum
Intervention: Nicotine patch
Intervention: No smoking programme
Intervention: Open biopsy
Intervention: Open cholecystectomy
Intervention: Orchiectomy
Intervention: Palliative care
Intervention: Palliative chemotherapy
Intervention: Pancreas/kidney transplantation
Intervention: Pancreatic necrosectomy
Intervention: Paramedic emergency medical service
Intervention: Parasite eradication programme
Intervention: Parenteral nutrition
Intervention: Percutaneous transluminal angioplasty
Intervention: Physician awareness campaign
Intervention: Physician counselling
Intervention: Physiotherapy
Intervention: Preservation solution
Intervention: Prophylactic immune globulin therapy
Intervention: Psychotherapy
Intervention: Public awareness programme
Intervention: Pulmonary artery catheterisation
Intervention: Radiation shielding devices
Intervention: Radiation therapy
Intervention: Radiography
Intervention: Radiosurgery
Intervention: Radiotherapy
Intervention: Regular exercise programme
Intervention: Safety codes
Intervention: Safety education programme
Intervention: Screening and early treatment
Intervention: Screening and treatment
Intervention: Screening programme
Intervention: Screening test
Intervention: Shockwave lithotripsy
Intervention: Smoking cessation programme
Intervention: Solvent-detergent treated frozen plasma
Intervention: Spinal discectomy
Intervention: Splenectomy
Intervention: Statin therapy
Intervention: Stenting
Intervention: Supportive care
Intervention: Surfactant therapy
Intervention: Surgery
Intervention: Surgical fixation
Intervention: Surgical implantation
Intervention: Surgical repair
Intervention: Testing and vaccination
Intervention: Thrombolytic therapy
Intervention: Tomography
Intervention: Transplantation
Intervention: Transurethral dilation
Intervention: Transurethral prostatectomy
Intervention: Ultrasonography
Intervention: Ultrasound screening
Intervention: Universal precautions against HIV infection
Intervention: Vaccination
Intervention: Vaccination reminder
Intervention: Varicella zoster immune globulin therapy
Intervention: Vasodilator drug therapy
Intervention: Watchful waiting
Intervention: Wheelchair

Type of intervention
Type of intervention: Ambulatory care
Type of intervention: Anaesthesia
Type of intervention: Care package
Type of intervention: Catheterisation
Type of intervention: Chiropody services
Type of intervention: Cognitive therapy
Type of intervention: Contrast media
Type of intervention: Cryotherapy
Type of intervention: Dedicated care unit
Type of intervention: Dental
Type of intervention: Device
Type of intervention: Diagnostic
Type of intervention: Dialysis
Type of intervention: Health promotion
Type of intervention: Intensive care
Type of intervention: Lithotripsy
Type of intervention: Management
Type of intervention: Maternal health care
Type of intervention: Medical
Type of intervention: Neonatal care
Type of intervention: Palliative care
Type of intervention: Parenteral nutrition
Type of intervention: Physician awareness programme
Type of intervention: Physiotherapy
Type of intervention: Prevention
Type of intervention: Prosthesis
Type of intervention: Psychotherapy
Type of intervention: Public awareness programme
Type of intervention: Radiation therapy
Type of intervention: Rehabilitation
Type of intervention: Resuscitation
Type of intervention: Screening
Type of intervention: Support services
Type of intervention: Surgical
Type of intervention: Surveillance
Type of intervention: Trauma care
Type of intervention: Ventilation

Health outcomes
Outcomes: Life-years
Outcomes: QALYs

QALY weights
QALY weights: Arbitrary
QALY weights: Cambell Index of wellbeing
QALY weights: EuroQol
QALY weights: Health People 2000 – Healthy Years of Life measure
QALY weights: Health status index
QALY weights: Health utility index
QALY weights: Index of HRQoL
QALY weights: Index of wellbeing
QALY weights: Literature
QALY weights: National vital statistics?
QALY weights: NHP
QALY weights: Previously published values
QALY weights: PWFA rating scale
QALY weights: Quality of wellbeing scale
QALY weights: Rosser
QALY weights: SF36
QALY weights: Sickness impact profile
QALY weights: Study specific instrument
QALY weights: Torrance MAUS
QALY weights: Unknown
QALY weights: World Bank DALYs

QALY method to obtain weights
QALY method: SG
QALY method: TTO
QALY method: Unknown
QALY method: VAS

QALY sample employed
QALY sample: Care-givers
QALY sample: Clinician
QALY sample: Clinicians
QALY sample: Experts
QALY sample: Health professionals
QALY sample: Investigators
QALY sample: Patients
QALY sample: Public
QALY sample: Unknown

Study design
Study design: Alongside clinical trial
Study design: Decision analytic model (Markov)
Study design: Decision analytic model (tree)
Study design: Other modelling approach
Study design: Other prospective evaluation
Study design: Retrospective evaluation
Study design: Secondary analysis of clinical trial

Patient level data
Patient-level data: Health outcomes
Patient-level data: Resource use

Extrapolation
Extrapolation: Intermediate to final
Extrapolation: Outcomes beyond follow-up
Extrapolation: Resources beyond follow-up

Handling of uncertainty
Uncertainty: Extreme scenarios
Uncertainty: Multi-way SA
Uncertainty: No analysis
Uncertainty: One-way SA
Uncertainty: Probabilistic SA
Uncertainty: Results of SA not reported
Uncertainty: Statistical analysis
Uncertainty: Threshold analysis

Appendix 2

Full bibliographic listing of articles in the database

Economic assessment of hypertension treatment. *J Intern Med* 1995;**238**(suppl 737):103–15.

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Appendix 4

Full listing of all baseline cost-effectiveness results included in the analysis of UK studies

Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Phillips 1993	1	No mention of discounting for health outcomes	Introduction of the 'Heartbeat Wales' no smoking programme compared with no programme	0	£9	1	2	2		£97
Standing Medical Advisory Committee (SMAC) 1990	2	No averted costs included. Patient costs included. Costs and health outcomes discounted at 5%	Cholesterol testing programme with diet-only therapy compared with no programme for men aged 40–69 years	1	£67	0				
Pickard 1990	3	No averted costs included. Health outcomes not discounted	Dedicated neurosurgery unit compared with no unit for the treatment of extradural haematoma	1	£84	0				
James 1996	4	Health outcomes not discounted	Surgery for the treatment of carpal tunnel syndrome compared with no surgery	1	£90	1	1	1	£35	£331
Rees 1985	5	No averted costs. No mention of discounting costs or health outcomes	Surgery and radiotherapy for the treatment of seminoma (testicular cancer) compared with no treatment	0	£164	0				
Waugh 1996	6	Averted costs not included. Costs discounted at 7%. Health outcomes not discounted	Targeted call of unscreened women in the cervical cancer screening programme for women aged 20–59 years compared with no such targeted call	0	£206	1	1	1	£130	
Rees 1985	7	No averted costs. No mention of discounting costs or health outcomes	Cytotoxic chemotherapy for the treatment of teratoma (testicular/ovarian cancer) compared with no treatment	0	£226	0				
Rees 1985	8	No averted costs. No mention of discounting costs or health outcomes	Outpatient radiotherapy for the treatment of glottic laryngeal carcinoma compared with no treatment	0	£246	0				
SMAC 1990	9	No averted costs included. Patient costs included. Costs and health outcomes discounted at 5%	Cholesterol-testing programme with diet-only therapy compared with no programme for men and women aged 40–69 years	1	£267	0				
Pickard 1990	10	No averted costs included. Health outcomes not discounted	Dedicated neurosurgery unit compared with no unit for the treatment of head injury	1	£310	1	7		£84	d[d]
James 1996	11	Health outcomes not discounted	Spinal discectomy compared with no discectomy to treat disorders of the spine	1	£323	1	1	1	£170	£926

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*
[d] *d, dominance*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Field 1995	12	No averted costs included	Screening strategy for heart disease risk factors with appropriate treatment and cholesterol-loweringdrugs for total cholesterol > 9.5 mmol compared with screening with no cholesterol-lowering drugs for reducing risk factors for heart disease in women	0	£331	0				
SMAC 1990	13	No averted costs included. Patient costs included. Costs and health outcomes discounted at 5%	Cholesterol testing programme with diet and drug therapy (for cholesterol > –6.5 mmol/l) compared with no programme for men aged 40–69 years with a personal history of heart disease	1	£338	1	1	1	£108	
Bryan 1991	14		Domiciliary special chiropody services for patients aged > 75 years	1	£344	1	6			£449
Bryan 1991	15		Domiciliary routine chiropody services for patients aged > 75 years	1	£368	1	6			£429
Pickard 1990	16	No averted costs included. Health outcomes not discounted	Dedicated neurosurgery unit compared with no unit for the treatment of benign intracranial tumours	1	£499	1	7		£304	£1207
Bryan 1991	17		Domiciliary routine chiropody services for patients aged between 60 and 75 years	1	£516	1	6			£687
Pickard 1990	18	No averted costs included. Health outcomes not discounted	Dedicated neurosurgery unit compared with no unit for the treatment of non-metastatic spinal disorders	1	£536	1	7		£156	£977
Rees 1985	19	No averted costs. No mention of discounting costs or health outcomes	Hip replacement for the treatment of hip disorders compared with no hip replacement	0	£554	0				
Bryan 1991	20		Domiciliary special chiropody services for patients aged between 60 and 75 years	1	£573	1	6			£792
Bryan 1991	21		Clinic based routine chiropody services for patients aged > 75 years	1	£608	1	6			£728
Pickard 1990	22	No averted costs included. Health outcomes not discounted	Dedicated neurosurgery unit compared with no unit for the treatment of miscellaneous disorders	1	£630	1	7		£70	£8583
Pickard 1990	23	No averted costs included. Health outcomes not discounted	Dedicated neurosurgery unit compared with no unit for the treatment of subarachnoid haemorrhage	1	£637	1	7		£394	d
Russell 1990	24	No averted costs included. Health outcomes discounted at 5%	Screening for abdominal aortic aneurysm and early repair compared with no screening for men aged 60 years	1	£667	0				
Haigh 1991	25	Costs and health outcomes discounted at 5%	Thrombolytic therapy administered within three hours of onset of symptoms suggesting acute myocardial infarction for patients aged > 65 years compared with no therapy	1	£706	0				

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*
[d] *d, dominance*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
James 1996	26	Health outcomes not discounted	Primary hip replacement compared with no replacement to treat disorders of the hip in patients aged > 40 years	1	£708	1	1	1	£355	£2219
Bryan 1991	27		Clinic based special chiropody services for patients aged > 75 years	1	£728	1	6			£809
Rees 1985	28	No averted costs. No mention of discounting costs or health outcomes	Palliative tamoxifen therapy for carcinoma of the breast compared with no treatment	0	£780	0				
Russell 1990	29	No averted costs included. Health outcomes discounted at 5%	Screening for abdominal aortic aneurysm and early repair compared with no screening for women aged 60 years	1	£796	0				
Wall 1988	30	No averted costs included. Health outcomes not discounted	Low-absorption antiscatter grid for reducing radiation-induced cancers compared with current arrangements	1	£801	1	1	1	£547	£1055
James 1996	31	Health outcomes not discounted	Primary hip replacement compared with no replacement to treat disorders of the hip in patients aged < 40 years	1	£811	1	1	1	£472	£4832
Haigh 1991	32	Costs and health outcomes discounted at 5%	Thrombolytic therapy administered within 3 hours of onset of symptoms suggesting acute myocardial infarction for patients aged between 55 and 64 years compared with no therapy	1	£847	0				
Russell 1990	33	No averted costs included. Health outcomes discounted at 5%	Screening for abdominal aortic aneurysm and early repair compared with no screening for men aged 65 years	1	£849	0				
Parker 1992	34	No averted costs included. No discounting of health outcomes	Operative treatment compared with no treatment for displaced subcapital fracture of the hip	1	£901	0				
SMAC 1990	35	No averted costs included. Patient costs included. Costs and health outcomes discounted at 5%	Cholesterol-testing programme with diet-only therapy compared with no programme for women aged 40–69 years	1	£917	0				
Ridley 1994	36	No averted costs included. Costs and health outcomes discounted at 5%	Intensive care for gastrointestinal conditions compared with zero-cost zero-effect scenario	1	£959	0				
Parkin 1986	37	No averted costs. Health outcomes discounted at 5%. Inappropriate ICER	5-yearly screening programme for women aged 35–65 years plus younger women following third pregnancy compared with an opportunistic screening programme	0	£960	1	1	1	£603	
Russell 1990	38	No averted costs included. Health outcomes discounted at 5%	Screening for abdominal aortic aneurysm and early repair compared with no screening for women aged 65 years	1	£978	0				
Parkin 1986	39	No averted costs. Health outcomes discounted at 5%. Inappropriate ICER	5-yearly screening programme of women aged 35–65 years compared with an opportunistic screening programme	0	£985	1	1	1	£640	

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Drummond 1988	40	Patient costs included. Costs and health outcomes discounted at 5%	Contact lenses in cataract treatment compared with no treatment	1	£996	1	1	1		£1078
Rees 1985	41	No averted costs. No mention of discounting costs or health outcomes	Abdominal resection for the treatment of rectal carcinoma compared with no treatment	0	£1027	0				
Bryan 1991	42		Clinic-based routine chiropody services for patients aged between 60 and 75 years	1	£1041	1	6			£1041
Bryan 1991	43		Clinic-based special chiropody services for patients aged between 60 and 75 years	1	£1041	1	6			£1041
Law 1994	44	No mention of discounting for costs or health outcomes	A programme of screening and early repair of abdominal aortic aneurysms > 6 cm in size for men aged 60–80 years compared with no screening	0	£1053	0				
Hart 1993	45		Angiotensin-converting enzyme inhibitor therapy as an adjunct to diuretic therapy for the treatment of mild-to-moderate chronic heart failure	0	£1054	1	2	6	d	£4425
Tubman 1990	46	No mention of discounting for health outcomes	Surfactant therapy for severe neonatal distress syndrome compared with no therapy	1	£1077	1	1	1		£1319
SMAC 1990	47	No averted costs included. Patient costs included. Costs and health outcomes discounted at 5%	Cholesterol-testing programme with diet and drug therapy (for cholesterol > –6.5 mmol/l) compared with no programme for men aged 40–69 years who are hypertensive (diastolic pressure > 91 mmHg) and who smoke	1	£1080	1	1	1	£344	
Russell 1990	48	No averted costs included. Health outcomes discounted at 5%	Screening for abdominal aortic aneurysm and early repair compared with no screening for men aged 70 years	1	£1092	0				
Tolias 1996	49	Averted costs not included. No mention of discounting for costs or health outcomes	Physician awareness programme relating to sudden agonising headache as a symptom for subarachnoid haemorrhage compared with no awareness programme	1	£1094	0				
Haigh 1991	50	Costs and health outcomes discounted at 5%	Thrombolytic therapy administered between 4 and 6 hours of onset of symptoms suggesting acute myocardial infarction for patients aged between 55 and 64 years compared with no therapy	1	£1129	0				
James 1996	51	Health outcomes not discounted	Repair/replacement of metatarsal joints compared with no surgery to treat disorders of the feet	1	£1173	1	1	1	d	£4463
Field 1995	52	No averted costs included	Screening strategy for heart disease risk factors with appropriate treatment but no cholesterol-lowering drugs compared with no screening for reducing risk factors for heart disease in men	0	£1214	0				

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*
[d] *d, dominance*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
St Leger 1996	53	Costs and health outcomes discounted at 5%	A programme of screening and early repair of abdominal aortic aneurysms > 6 cm in size for men aged 65–74 years compared with no screening	1	£1255	0				
Russell 1990	54	No averted costs included. Health outcomes discounted at 5%	Screening for abdominal aortic aneurysm and early repair compared with no screening for women aged 70 years	1	£1259	0				
Fenn 1991	55	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for men aged 35–39 years following acute myocardial infarction with anterior infarct	0	£1304	0				
Fenn 1991	56	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for men aged 35–39 years following acute myocardial infarction and history of previous myocardial infarction	0	£1304	0				
Smith 1990	57	No averted costs included. Health outcomes not discounted	Programme of controlling hypertension for subjects aged 45–64 years in order to reduce stroke compared with no programme	1	£1312	0				
Fenn 1991	58	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for men aged 55–59 years following acute myocardial infarction with anterior infarct	0	£1365	0				
Field 1995	59	No averted costs included	Screening strategy for heart disease risk factors with appropriate treatment compared with no screening for reducing risk factors for heart disease in men	0	£1368	1	2	3	£563	£1743
Fenn 1991	60	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for men aged 55–59 years following acute myocardial infarction and history of previous myocardial infarction	0	£1380	0				
Russell 1990	61	No averted costs included. Health outcomes discounted at 5%	Screening for abdominal aortic aneurysm and early repair compared with no screening for men aged 75 years	1	£1403	0				
Fenn 1991	62	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for men aged 40–44 years following acute myocardial infarction with anterior infarct	0	£1425	0				
Fenn 1991	63	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for men aged 40–44 years following acute myocardial infarction and history of previous myocardial infarction	0	£1425	0				
Parkin 1986	64	No averted costs. Health outcomes discounted at 5%. Inappropriate ICER	5-yearly screening programme for women aged 30–70 years plus younger women (around 25 years of age for any sexually transmitted disease/contraception/pregnancy consultation) compared with an opportunistic screening programme	0	£1428	1	1	1	£898	

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Parkin 1986	65	No averted costs. Health outcomes discounted at 5%. Inappropriate ICER	5-yearly screening programme for women aged 25–65 years compared with an opportunistic screening programme	0	£1428	1	1	1	£886	
OKelley 1990	66	No mention of discounting costs or health outcomes	An 'ideal' system of eight dedicated trauma centres for dealing with trauma compared with current care arrangements	1	£1428	0				
Williams 1985	67	Costs and health outcomes discounted at 5%	Pacemaker implantation for atrioventricular heart block compared with no pacemaker	1	£1437	0				
Fenn 1991	68	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for women aged 55–59 years following acute myocardial infarction	0	£1516	0				
Williams 1985	69	Costs and health outcomes discounted at 5%	Hip replacement compared with no hip replacement	1	£1540	0				
Fenn 1991	70	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for women aged 65–69 years following acute myocardial infarction	0	£1554	0				
Fenn 1991	71	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for men aged 45–49 years following acute myocardial infarction with anterior infarct	0	£1577	0				
Fenn 1991	72	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for men aged 45–49 years following acute myocardial infarction and history of previous myocardial infarction	0	£1577	0				
Parkin 1986	73	No averted costs. Health outcomes discounted at 5%. Inappropriate ICER	3-yearly screening programme for women aged 35–70 years compared with an opportunistic screening programme	0	£1625	1	1	1	£1009	
Parkin 1986	74	No averted costs. Health outcomes discounted at 5%. Inappropriate ICER	5-yearly screening programme for women aged 35–65 years plus during pregnancy and women attending family planning clinic > 22 years of age not previously screened compared with an opportunistic screening programme	0	£1649	1	1	1	£1009	
Fenn 1991	75	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for men aged 65–69 years following acute myocardial infarction with anterior infarct	0	£1653	0				
Fenn 1991	76	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for men aged 65–69 years following acute myocardial infarction and history of previous myocardial infarction	0	£1653	0				
James 1996	77	Health outcomes not discounted	Primary knee replacement compared with no replacement to treat disorders of the knee	1	£1681	1	1	1	£750	£6821
Fenn 1991	78	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for women aged 60–64 years following acute myocardial infarction with anterior infarct	0	£1683	0				

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Fenn 1991	79	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for women aged 60–64 years following acute myocardial infarction and history of previous myocardial infarction	0	£1683	0				
Russell 1990	80	No averted costs included. Health outcomes discounted at 5%	Screening for abdominal aortic aneurysm and early repair compared with no screening for women aged 75 years	1	£1683	0				
Akehurst 1994	81	No averted costs included	Nicorette® nasal spray in addition to general practitioner counselling to help heavy smokers (> 23 cigarettes/day) to quit	0	£1685	0				
Haigh 1991	82	Costs and health outcomes discounted at 5%	Thrombolytic therapy administered within 3 hours of onset of symptoms suggesting acute myocardial infarction for patients aged < 45 years compared with no therapy	1	£1694	0				
Haigh 1991	83	Costs and health outcomes discounted at 5%	Thrombolytic therapy administered between 4 and 6 hours of onset of symptoms suggesting acute myocardial infarction for patients aged > 65 years compared with no therapy	1	£1694	0				
Haigh 1991	84	Costs and health outcomes discounted at 5%	Thrombolytic therapy administered between 7 and 24 hours of onset of symptoms suggesting acute myocardial infarction for patients aged > 65 years compared with no therapy	1	£1694	0				
Sculpher 1996	85		Laser-assisted angioplasty for the treatment of rest pain/ulceration patients aged 70 years with peripheral arterial occlusion compared with standard angioplasty techniques	1	£1702	0				
Fenn 1991	86	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for women aged 35–39 years following acute myocardial infarction	0	£1706	0				
Fenn 1991	87	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for women aged 60–64 years following acute myocardial infarction	0	£1706	0				
Fenn 1991	88	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for women aged 40–44 years following acute myocardial infarction	0	£1820	0				
Fenn 1991	89	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for men aged 35–39 years following acute myocardial infarction	0	£1820	0				
Fenn 1991	90	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for men aged 55–59 years following acute myocardial infarction	0	£1820	0				
Fenn 1991	91	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for men aged 50–54 years following acute myocardial infarction with anterior infarct	0	£1820	0				
Fenn 1991	92	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for men aged 50–54 years following acute myocardial infarction and history of previous myocardial infarction	0	£1820	0				

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Williams 1985	93	Costs and health outcomes discounted at 5%	Valve replacement for aortic stenosis compared with no valve replacement	1	£1848	0				
Lowin 1996	94	No averted costs. Costs and health outcomes discounted at 5%	Counselling and nicotine patches for smoking cessation compared with neither patches nor counselling in men aged 45–49 years	0	£1859	0				
Lowin 1996	95	No averted costs. Costs and health outcomes discounted at 5%	Counselling and nicotine patches for smoking cessation compared with neither patches or counselling in men aged 40–44 years	0	£1867	0				
Haigh 1991	96	Costs and health outcomes discounted at 5%	Thrombolytic therapy administered within 3 hours of onset of symptoms suggesting acute myocardial infarction for patients aged between 45 and 54 years compared with no therapy	1	£1906	0				
Haigh 1991	97	Costs and health outcomes discounted at 5%	Thrombolytic therapy administered between 7 and 24 hours of onset of symptoms suggesting acute myocardial infarction for patients aged between 55 and 64 years compared with no therapy	1	£1906	0				
Russell 1990	98	No averted costs included. Health outcomes discounted at 5%	Screening for abdominal aortic aneurysm and early repair compared with no screening for men aged 80 years	1	£1911	0				
Lowin 1996	99	No averted costs. Costs and health outcomes discounted at 5%	Counselling and nicotine patches for smoking cessation compared with neither patches nor counselling in men aged 50–54 years	0	£1921	0				
Parkin 1986	100	No averted costs. Health outcomes discounted at 5%. Inappropriate ICER	3-yearly screening programme for women aged 25–64 years compared with an opportunistic screening programme	0	£1969	1	1	1	£1218	
Sculpher 1996	101		Laser-assisted angioplasty for the treatment of rest pain/ulceration patients aged 65 years with peripheral arterial occlusion compared with standard angioplasty techniques	1	£1997	0				
Fenn 1991	102	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for women aged 45–49 years following acute myocardial infarction	0	£2002	0				
Fenn 1991	103	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for men aged 40–44 years following acute myocardial infarction	0	£2009	0				
James 1996	104	Health outcomes not discounted	Surgery to release contracture compared with no surgery in the treatment of Dupuytren's contracture (disorder of the hand)	1	£2063	1	1	1	£599	d
Lowin 1996	105	No averted costs. Costs and health outcomes discounted at 5%	Counselling and nicotine patches for smoking cessation compared with neither patches or counselling in men aged 35–39 years	0	£2081	0				

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*
[d] *d, dominance*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Sculpher 1996	106		Laser-assisted angioplasty for the treatment of rest pain/ulceration patients aged 60 years with peripheral arterial occlusion compared with standard angioplasty techniques	1	£2119	0				
Fenn 1991	107	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for men aged 65–69 years following acute myocardial infarction	0	£2123	0				
Lowin 1996	108	No averted costs. Costs and health outcomes discounted at 5%	Counselling and nicotine patches for smoking cessation compared with neither patches nor counselling in men aged 55–59 years	0	£2134	0				
Williams 1985	109	Costs and health outcomes discounted at 5%	Coronary artery bypass graft for patients with severe angina and left main disease compared with medical management	1	£2136	0				
Fenn 1991	110	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for women aged 50–54 years following acute myocardial infarction	0	£2199	0				
Fenn 1991	111	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for men aged 45–49 years following acute myocardial infarction	0	£2237	0				
Fenn 1991	112	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for women aged 60–64 years following acute myocardial infarction	0	£2275	1	1	1		£2428
Russell 1990	113	No averted costs included. Health outcomes discounted at 5%	Screening for abdominal aortic aneurysm and early repair compared with no screening for women aged 80 years	1	£2290	0				
Parkin 1986	114	No averted costs. Health outcomes discounted at 5%. Inappropriate ICER	5-yearly screening programme for women aged 35–65 years plus women with three or more pregnancies and for sexually active women requesting contraceptive advice plus early in pregnancy compared with an opportunistic screening programme	0	£2326	1	1	1	£1391	
Lowin 1996	115	No averted costs. Costs and health outcomes discounted at 5%	Counselling and nicotine patches for smoking cessation compared with neither patches nor counselling in men aged 60–64 years	0	£2454	0				
Rees 1985	116	No averted costs. No mention of discounting costs or health outcomes	Outpatient radiotherapy for the treatment of carcinoma of the breast compared with no treatment	0	£2464	0				
Haigh 1991	117	Costs and health outcomes discounted at 5%	Thrombolytic therapy administered between 4 and 6 hours of onset of symptoms suggesting acute myocardial infarction for patients aged under 45 years compared with no therapy	1	£2470	0				
James 1996	118	Health outcomes not discounted	Flexor tenosynovectomy to free and transfer tendons in the fingers compared with no surgery for the treatment of rheumatoid arthritis	1	£2517	1	1	1	£1174	£11,387
Bulpitt 1993	119	No averted costs included. No mention of discounting	Verapamil drug therapy versus propranolol drug therapy for the treatment of hypertension (patient characteristics not given)	1	£2567	0				

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
James 1996	120	Health outcomes not discounted	Metacarpophalangeal joint replacement compared with no joint replacement for the treatment of arthritis	1	£2568	1	1	1	d	£3888
Fenn 1991	121	Healthcare costs in added years of life included	Thrombolytic therapy compared with placebo for men aged 50–54 years following acute myocardial infarction	0	£2578	0				
Hutton 1996	122		Docetaxal-based chemotherapy compared with paclitaxel-based chemotherapy for the treatment of recurrent metastatic breast cancer	1	£2594	1	1	4	d	£12,639
Dwyer 1996	123	No averted costs included. Health outcomes not discounted	A programme of universal screening for hepatitis B in pregnancy compared with a targeted screening programme	0	£2600	1	1	9	£1814	£5228
Williams 1985	124	Costs and health outcomes discounted at 5%	Coronary artery bypass graft for patients with severe angina and triple vessel disease compared with medical management	1	£2608	0				
James 1996	125	Health outcomes not discounted	Revision hip replacement compared with no replacement to treat failure of primary prosthesis	1	£2608	1	1	1	£1320	£6849
Wall 1988	126	No averted costs included. Health outcomes not discounted	Low-absorption cassettes for reducing radiation-induced cancers compared with current arrangements	1	£2657	1	1	1	£1798	£3517
Williams 1985	127	Costs and health outcomes discounted at 5%	Coronary artery bypass graft for patients with moderate angina and left main disease compared with medical management	1	£2731	0				
FentonLee 1993	128	No averted costs included. Health outcomes discounted at 5%	Surgery for pancreatic necrosis	1	£2801	0				
Hatziandreu 1994	129	Costs and health outcomes discounted at 5%	Selective serotonin reuptake inhibitors compared with tricyclics for preventing suicide in depressed female patients aged 35 years with two previous depressive episodes	1	£2820	1	2	8	£1073	£6830
Haigh 1991	130	Costs and health outcomes discounted at 5%	Thrombolytic therapy administered between 4 and 6 hours of onset of symptoms suggesting acute myocardial infarction for patients aged between 45 and 54 years compared with no therapy	1	£2823	0				
Van Inveld 1993	131	Costs and health outcomes discounted at 5%	Screening programme for breast cancer in women between 50 and 70 years compared with no screening	0	£2823	1	2		£2541	
Patel 1987	132	Patient costs included. Indirect costs included. Costs and health outcomes discounted at 5%	ESWL for treating stones in the kidney or urethra compared with no treatment	1	£2844	0				
Field 1995	133	No averted costs included	Screening strategy for heart disease risk factors with appropriate treatment and cholesterol-lowering drugs for total cholesterol > 9.5 mmol compared with screening with no cholesterol-lowering drugs for reducing risk factors for heart disease in men	0	£2979	0				

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*
[d] *d, dominance*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Parker 1992	134	No averted costs included. No discounting of health outcomes	Operative treatment compared with no treatment for extracapsular fracture of the hip	1	£3012	0				
Sculpher 1996	135		Laser-assisted angioplasty for the treatment of claudicant patients aged 60 years with peripheral arterial occlusion compared with standard angioplasty techniques	1	£3069	0				
Lowin 1996	136	No averted costs. Costs and health outcomes discounted at 5%	Counselling and nicotine patches for smoking cessation compared with neither patches nor counselling in men aged 65–69 years	0	£3126	0				
Lowin 1996	137	No averted costs. Costs and health outcomes discounted at 5%	Counselling and nicotine patches for smoking cessation compared with neither patches nor counselling in women aged 50–54 years	0	£3146	0				
Field 1995	138	No averted costs included	Screening strategy for heart disease risk factors with appropriate treatment but no cholesterol-lowering drugs compared with no screening for reducing risk factors for heart disease in women	0	£3200	0				
Lowin 1996	139	No averted costs. Costs and health outcomes discounted at 5%	Counselling and nicotine patches for smoking cessation compared with neither patches nor counselling in women aged 45–49 years	0	£3201	0				
Lowin 1996	140	No averted costs. Costs and health outcomes discounted at 5%	Counselling and nicotine patches for smoking cessation compared with neither patches nor counselling in women aged 55–59 years	0	£3254	0				
Sculpher 1996	141		Laser-assisted angioplasty for the treatment of claudicant patients aged 65 years with peripheral arterial occlusion compared with standard angioplasty techniques	1	£3354	1	1	13	d	d
Pharoah 1988	142	Other sector costs included. Costs and health outcomes discounted at 5%	Neonatal intensive care compared with no intensive care for the treatment of low birth weight infants (< 1500 g)	1	£3458	0				
Lowin 1996	143	No averted costs. Costs and health outcomes discounted at 5%	Counselling and nicotine patches for smoking cessation compared with neither patches nor counselling in women aged 40–44 years	0	£3468	0				
Ridley 1994	144	No averted costs included. Costs and health outcomes discounted at 5%	Intensive care for trauma compared with zero-cost zero-effect scenario	1	£3476	0				
Wall 1988	145	No averted costs included. Health outcomes not discounted	Low-absorption table top for reducing radiation-induced cancers compared with current arrangements	1	£3615	1	1	1	£2540	£4689
Lowin 1996	146	No averted costs. Costs and health outcomes discounted at 5%	Counselling and nicotine patches for smoking cessation compared with neither patches nor counselling in women aged 60–64 years	0	£3681	0				

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*
[d] *d, dominance*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Lowin 1996	147	No averted costs. Costs and health outcomes discounted at 5%	Counselling and nicotine patches for smoking cessation compared with neither patches nor counselling in women aged 35–39 years	0	£3735	0				
Parker 1992	148	No averted costs included. No discounting of health outcomes	Conservative treatment for patients compared with no treatment for undisplaced subcapital fracture of the hip	1	£3802	0				
Sculpher 1996	149		Laser-assisted angioplasty for the treatment of claudicant patients aged 70 years with peripheral arterial occlusion compared with standard angioplasty techniques	1	£3808	1	1	13	d	d
Haigh 1991	150	Costs and health outcomes discounted at 5%	Thrombolytic therapy administered between 7 and 24 hours of onset of symptoms suggesting acute myocardial infarction for patients aged under 45 years compared with no therapy	1	£3882	0				
SMAC 1990	151	No averted costs included. Patient costs included. Costs and health outcomes discounted at 5%	Cholesterol testing programme with diet and drug therapy (for cholesterol > –6.5 mmol/l) compared with no programme for men aged 40–69 years with no personal history of heart disease	1	£3940	1	1	1	£1260	
Elwes 1996	152	No averted costs	Carbamazepine drug therapy for the treatment of epilepsy compared with no drug treatment	1	£4160	1	1	1	£405	
Haigh 1991	153	Costs and health outcomes discounted at 5%	Thrombolytic therapy administered between 7 and 24 hours of onset of symptoms suggesting acute myocardial infarction for patients aged between 45 and 54 years compared with no therapy	1	£4235	0				
Drummond 1992	154	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Stepped care therapy for male hypertensive patients (100 mmHg) aged 50 years compared with no therapy	1	£4235	1	1	1		£8469
Drummond 1992	155	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Stepped care therapy for male hypertensive patients (100 mmHg) aged 60 years compared with no therapy	1	£4235	1	1	1		£9881
Drummond 1992	156	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Stepped-care therapy for female hypertensive patients (100 mmHg) aged 60 years compared with no therapy	1	£4235	1	1	1		£11,292
Daly 1992	157	Includes costs in added years of life	Oestrogen hormone replacement therapy hysterectomised women with menopausal symptoms	0	£4351	1	1	5	£1200	£31,510

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*
[d] *d, dominance*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Lowin 1996	158	No averted costs. Costs and health outcomes discounted at 5%	Counselling and nicotine patches for smoking cessation compared with neither patches nor counselling in women aged 65–69 years	0	£4543	0				
Williams 1985	159	Costs and health outcomes discounted at 5%	Coronary artery bypass graft for patients with severe angina and double vessel disease compared with medical management	1	£4682	0				
Williams 1985	160	Costs and health outcomes discounted at 5%	Percutaneous transluminal coronary angioplasty for patients with severe angina and single-vessel disease compared with medical management	1	£4928	0				
Williams 1985	161	Costs and health outcomes discounted at 5%	Coronary artery bypass graft for patients with moderate angina and triple vessel disease compared with medical management	1	£4928	0				
Akehurst 1994A	162	No averted costs included	Nicorette® patch in addition to general practitioner counselling to help smokers to quit	0	£4994	0				
Williams 1985	163	Costs and health outcomes discounted at 5%	Coronary artery bypass graft for patients with mild angina and left main disease compared with medical management	1	£5175	0				
Shields 1996	164	Averted costs not included. Health outcomes not discounted	Total parenteral nutrition compared with no total parenteral nutrition in the treatment of non-malignant gastrointestinal disease who are fed for more than 3 weeks	0	£5211	0				
Field 1995	165	No averted costs included	Screening strategy for heart disease risk factors with appropriate treatment compared with no screening for reducing risk factors for heart disease in women	0	£5219	1	2	3	£2163	£6819
Drummond 1992	166	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Diuretic therapy for male hypertensive patients (100 mmHg) aged 50 years compared with no therapy	1	£5646	1	1	1		£9881
Drummond 1992	167	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Stepped care therapy for male hypertensive patients (100 mmHg) aged 40 years compared with no therapy	1	£5646	1	1	1		£12,704
Drummond 1992	168	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Stepped care therapy for female hypertensive patients (100 mmHg) aged 50 years compared with no therapy	1	£5646	1	1	1		£11,292
Dusheiko 1995	169	Costs discounted at 5%. No mention of discounting health outcomes	Interferon-α drug therapy for the treatment of hepatitis C	0	£6067	1	2	2	£2363	£9770

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Williams 1985	170	Costs and health outcomes discounted at 5%	Kidney transplantation (cadaver) compared with no transplantation	1	£6160	0				
SMAC 1990	171	No averted costs included. Patient costs included. Costs and health outcomes discounted at 5%	Cholesterol testing programme with diet and drug therapy (for cholesterol > –6.5 mmol/l) compared with no programme for men aged 40–69 years who are normotensive (diastolic pressure > 91 mmHg) and who do not smoke	1	£6181	1	1	1	£1977	
Pharoah 1996	172	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for males aged 55–64 years with existing heart disease (myocardial infarction) and cholesterol concentrations of ≥ 7.3 mmol/l	0	£6240	1	5	8	£728	£23,920
Forrest 1985	173	Costs and health outcomes discounted at 5%	Breast cancer screening for women aged 50–70 years compared with no screening	1	£6795	1	2	3	£4107	£14,374
Williams 1985	174	Costs and health outcomes discounted at 5%	Percutaneous transluminal coronary angioplasty for patients with moderate angina and single vessel disease compared with medical management	1	£6982	0				
Drummond 1992	175	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Diuretic therapy for male hypertensive patients (100 mmHg) aged 60 years compared with no therapy	1	£7058	1	1	1		£14,115
Drummond 1992	176	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	First-generation β blocker therapy for male hypertensive patients (100 mmHg) aged 50 years compared with no therapy	1	£7058	1	1	1		£9881
Drummond 1992	177	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	First-generation β blocker therapy for male hypertensive patients (100 mmHg) aged 60 years compared with no therapy	1	£7058	1	1	1		£11,292
Wonderling 1996	178	No averted costs	Oxcheck health check programme to reduce cardiovascular risk factors for men aged 50 years compared with no health checks	0	£7256	1	1	1	£960	£22,301
Parker 1992	179	No averted costs included. No discounting of health outcomes	Operative treatment for patients compared with conservative treatment for undisplaced subcapital fracture of the hip	1	£7458	0				
Ridley 1994	180	No averted costs included. Costs and health outcomes discounted at 5%	Intensive care for respiratory conditions compared with zero-cost zero-effect scenario	1	£7459	0				

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Beck 1996	181	Costs and health outcomes discounted at 5%	Zidovudine treatment for AIDS patients compared with no zidovudine	0	£7905	0				
Williams 1985	182	Costs and health outcomes discounted at 5%	Coronary artery bypass graft for patients with moderate angina and double vessel disease compared with medical management	1	£8214	0				
Parker 1992	183	No averted costs included. No discounting of health outcomes	Conservative treatment for patients (in whom surgery is contra-indicated) compared with no treatment for extracapsular fracture of the hip	1	£8363	0				
Waugh 1996A	184	Costs discounted at 7%. Health outcomes not discounted	Cervical cancer screening programme based on 3-yearly screens compared with a programme of 5-yearly screens for women aged 20–59 years	0	£8385	1	1	1	£1697	£16,865
Drummond 1992	185	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Stepped-care therapy for male hypertensive patients (100 mmHg) aged 30 years compared with no therapy	1	£8469	1	1	1		£18,350
Drummond 1992	186	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Stepped-care therapy for female hypertensive patients (100 mmHg) aged 40 years compared with no therapy	1	£8469	1	1	1		£16,939
Ridley 1994	187	No averted costs included. Costs and health outcomes discounted at 5%	Intensive care for 'other' conditions compared with zero-cost zero-effect scenario	1	£8735	0				
Wilkinson 1990	188	No averted costs included	Community care programme for mentally ill patients with schizophrenia compared with no programme	1	£9098	0				
Shields 1996	189	Averted costs not included. Health outcomes not discounted	Total parenteral nutrition compared with no total parenteral nutrition in the treatment of malignant gastrointestinal disease	0	£9214	0				
Williams 1985	190	Costs and health outcomes discounted at 5%	Heart transplantation	1	£10,267	0				
Wonderling 1996	191	No averted costs	British Heart Study health check programme to reduce cardiovascular risk factors for men aged 50 years compared with the Oxcheck health check programme	0	£10,564	1	1	1	£1387	£30,197
Summerfield 1995	192	No averted costs included	Cochlear implants for treating tinitus/deafness in adults compared with no implantation	0	£10,585	1	1	1	£10,172	£10,998
Drummond 1992	193	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Calcium antagonist therapy for male hypertensive patients (100 mmHg) aged 50 years compared with no therapy	1	£11,292	1	1	1		£22,585

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Pharoah 1996	194	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for males aged 55–64 years with existing heart disease (myocardial infarction) and cholesterol concentrations of 6.6–7.2 mmol/l	0	£11,440	0				
Dusheiko 1995	195	Costs discounted at 5%. No mention of discounting health outcomes	Interferon-α drug therapy for the treatment of hepatitis B	0	£11,898	1	2	2	£4899	£18,898
Anderson 1993	196	No averted costs included. Health outcomes not discounted	ICD compared with no ICD for patients with cardiac fibrillation and awaiting cardiac transplantation with ejection fraction less than 25% and stroke volume less than 40 ml	0	£12,077	0				
SMAC 1990	197	No averted costs included. Patient costs included. Costs and health outcomes discounted at 5%	Cholesterol-testing programme with diet and drug therapy (for cholesterol > –6.5 mmol/l) compared with no programme for men and women aged 40–60 years including invitations for those not tested opportunistically	1	£12,131	0				
Daly 1992	198	Includes costs in added years of life	Oestrogen hormone replacement therapy for non-hysterectomised women with menopausal symptoms	0	£12,454	1	1	8	£3901	d
Drummond 1992	199	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	First-generation β blocker therapy for male hypertensive patients (100 mmHg) aged 40 years compared with no therapy	1	£12,704	1	1	2		£21,173
Drummond 1992	200	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	First-generation β blocker therapy for female hypertensive patients (100 mmHg) aged 60 years compared with no therapy	1	£12,704	1	1	1		£21,173
Drummond 1992	201	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Calcium antagonist therapy for male hypertensive patients (100 mmHg) aged 60 years compared with no therapy	1	£12,704	1	1	1		£25,408
Parker 1992	202	No averted costs included. No discounting of health outcomes	Conservative treatment for patients (in whom surgery is contraindicated) compared with no treatment for displaced subcapital fracture of the hip	1	£12,807	0				
Williams 1985	203	Costs and health outcomes discounted at 5%	Coronary artery bypass graft for patients with mild angina and triple vessel disease compared with medical management	1	£12,937	0				
Pharoah 1996	204	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for females aged 55–64 years with existing heart disease (myocardial infarction) and cholesterol concentrations of ≥ 7.3 mmol/l	0	£13,520	0				

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*
[d] *d, dominance*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Glick 1992	205	Costs and health outcomes discounted at 5%	Simvastatin therapy for male of average age 50 years with cholesterol level of 7.5 mmol and smoking and glucose intolerance as coronary risk factors compared with no drug therapy	0	£13,551	0				
Ridley 1994	206	No averted costs included. Costs and health outcomes discounted at 5%	Intensive care for cardiovascular conditions compared with zero-cost zero-effect scenario	1	£13,555	0				
Drummond 1992	207	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	First-generation β blocker therapy for female hypertensive patients (100 mmHg) aged 50 years compared with no therapy	1	£14,115	1	1	1		£21,173
Drummond 1992	208	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Angiotensin-converting enzyme inhibitor therapy for male hypertensive patients (100 mmHg) aged 50 years compared with no therapy	1	£14,115	1	1	1		£26,819
Wonderling 1996	209	No averted costs	Oxcheck health check programme to reduce cardiovascular risk factors for women aged 50 years compared with no health checks	0	£14,192	1	1	1	£1067	£44,602
Wilkinson 1990	210	No averted costs included	Community care programme for mentally ill patients with affective disorder compared with no programme	1	£15,164	0				
Drummond 1992	211	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Angiotensin-converting enzyme inhibitor therapy for male hypertensive patients (100 mmHg) aged 60 years compared with no therapy	1	£15,527	1	1	1		£29,643
Pharoah 1996	212	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for males aged 55–64 years with existing heart disease (myocardial infarction) and cholesterol concentrations of 6.1–6.5 mmol/l	0	£16,640	0				
OBrien 1992	213		ICD for the treatment of ventricula tachycardia/fibrillation compared with medical therapy with amiodarone	0	£16,656	1	2	6	£10,193	£21,738
Drummond 1992	214	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Stepped-care therapy for female hypertensive patients (100 mmHg) aged 30 years compared with no therapy	1	£16,939	1	1	1		£31,054
Simpson 1994	215	No mention of discounting for costs or health outcomes	Adjuctive therapy with zalcitabine compared with zidovudine alone in the treatment of AIDS	0	£18,003	1	1	4	£13,344	£32,223

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Drummond 1992	216	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Calcium antagonist therapy for male hypertensive patients (100 mmHg) aged 40 years compared with no therapy	1	£18,350	1	1	1		£32,466
Drummond 1992	217	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Calcium antagonist therapy for female hypertensive patients (100 mmHg) aged 50 years compared with no therapy	1	£18,350	1	1	1		£35,289
Drummond 1992	218	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Calcium antagonist therapy for female hypertensive patients (100 mmHg) aged 60 years compared with no therapy	1	£18,350	1	1	1		£35,289
Freemantle 1994	219	No averted costs included. Costs and health outcomes discounted at 5%	Newer tricyclics for preventing suicide in depressed patients compared with the older tricyclics	0	£18,395	1	2	3	£9137	
Ludbrook 1981	220	Costs and health outcomes discounted at 7%	A programme of hospital dialysis with home dialysis and transplantation for suitable patients compared with no programme for end-stage renal disease patients aged 15–34 years	0	£18,415	1	2	2	£14,831	£21,999
Pharoah 1996	221	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for males aged 55–64 years with existing heart disease (angina) and cholesterol concentrations of ≥ 7.3 mmol/l	0	£19,760	0				
Ludbrook 1981	222	Costs and health outcomes discounted at 7%	A programme of hospital dialysis with home dialysis and transplantation for suitable patients compared with no programme for end-stage renal disease patients aged 35–44 years	0	£20,145	1	2	2	£16,808	£23,482
Ludbrook 1981	223	Costs and health outcomes discounted at 7%	A programme of hospital dialysis with home dialysis and transplantation for suitable patients compared with no programme for end-stage renal disease patients aged 55–64 years	0	£20,516	1	2	2	£16,561	£24,471
Anderson 1993	224	No averted costs included. Health outcomes not discounted	ICD compared with no ICD for patients with cardiac fibrillation awaiting cardiac transplantation	0	£20,777	0				
Pharoah 1996	225	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for males aged 55–64 years with existing heart disease (myocardial infarction) and cholesterol concentrations of 5.5–6.0 mmol/l	0	£20,800	0				
Drummond 1992	226	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Angiotensin-converting enzyme inhibitor therapy for male hypertensive patients (100 mmHg) aged 40 years compared with no therapy	1	£21,173	1	1	2		£39,523

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Drummond 1992	227	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Angiotensin-converting enzyme inhibitor therapy for female hypertensive patients (100 mmHg) aged 50 years compared with no therapy	1	£21,173	1	1	1		£42,346
Drummond 1992	228	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Angiotensin-converting enzyme inhibitor therapy for female hypertensive patients (100 mmHg) aged 60 years compared with no therapy	1	£21,173	1	1	1		£43,758
Glick 1992	229	Costs and health outcomes discounted at 5%	Simvastatin therapy for male of average age 50 years with cholesterol level of 7.5 mmol and smoking as a coronary risk factor compared with no drug therapy	0	£21,314	0				
Daly 1992	230	Healthcare costs in added years of life included	Oestrogen hormone replacement therapy with added progestogen for non-hysterectomised women with menopausal symptoms	0	£21,607	1	1	8	£4952	d
Ludbrook 1981	231	Costs and health outcomes discounted at 7%	A programme of hospital dialysis with home dialysis and transplantation for suitable patients compared with no programme for end-stage renal disease patients aged 45–54 years	0	£21,628	1	2	2	£18,044	£25,212
Williams 1985	232	Costs and health outcomes discounted at 5%	Percutaneous transluminal coronary angioplasty for patients with mild angina and single vessel disease compared with medical management	1	£22,013	0				
Williams 1985	233	Costs and health outcomes discounted at 5%	Haemodialysis at home compared with no dialysis	1	£22,588	0				
Pickard 1990	234	No averted costs included. Health outcomes not discounted	Dedicated neurosurgery unit compared with no unit for the treatment of central nervous system metastases	0	£22,861	1	7			
Pharoah 1996	235	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for males aged 45–54 years with existing heart disease (myocardial infarction) and cholesterol concentrations ≥ 7.3 mmol/l	0	£22,880	0				
Pharoah 1996	236	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for females aged 55–64 years with existing heart disease (myocardial infarction) and cholesterol concentrations of 6.6–7.2 mmol/l	0	£22,880	0				
Drummond 1992	237	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Calcium antagonist therapy for male hypertensive patients (100 mmHg) aged 30 years compared with no therapy	1	£23,996	1	1	1		£45,170

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*
[d] *d, dominance*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Williams 1985	238	Costs and health outcomes discounted at 5%	Coronary artery bypass graft for patients with mild angina and double vessel disease compared with medical management	1	£25,874	0				
Ludbrook 1981	239	Costs and health outcomes discounted at 7%	A programme of hospital dialysis with home dialysis for suitable patients compared with no dialysis for end-stage renal disease patients aged 15–34 years	0	£26,819	1	2	2	£25,212	£28,426
Drummond 1992	240	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Calcium antagonist therapy for female hypertensive patients (100 mmHg) aged 40 compared with no therapy	1	£26,819	1	1	1		£47,993
Ludbrook 1981	241	Costs and health outcomes discounted at 7%	A programme of hospital dialysis with home dialysis for suitable patients compared with no dialysis for end-stage renal disease patients aged 35–44 years	0	£27,066	1	2	2	£25,459	£28,673
Ludbrook 1981	242	Costs and health outcomes discounted at 7%	A programme of hospital dialysis with home dialysis for suitable patients compared with no dialysis for end-stage renal disease patients aged 45–54 years	0	£27,190	1	2	2	£25,459	£28,920
Ludbrook 1981	243	Costs and health outcomes discounted at 7%	A programme of hospital dialysis with home dialysis for suitable patients compared with no dialysis for end-stage renal disease patients aged 55–64 years	0	£27,561	1	2	2	£25,707	£29,414
Drummond 1992	244	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Angiotensin-converting enzyme inhibitor therapy for male hypertensive patients (100 mmHg) aged 30 years compared with no therapy	1	£28,231	1	1	1		£53,639
Drummond 1992	245	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Angiotensin-converting enzyme inhibitor therapy for male hypertensive patients (90 mmHg) aged 40 years compared with no therapy	1	£28,231	1	1	1		£32,466
Anderson 1993	246	No averted costs included. Health outcomes not discounted	ICD compared with no ICD for patients with cardiac fibrillation and inducible arrhythmia not suppressed by drugs plus low ejection fraction	0	£28,569	0				
Williams 1985	247	Costs and health outcomes discounted at 5%	Haemodialysis in hospital compared with no dialysis	1	£28,748	0				
SMAC 1990	248	No averted costs included. Patient costs included. Costs and health outcomes discounted at 5%	Cholesterol-testing programme with diet and drug therapy (for cholesterol > –6.5 mmol/l) compared with no programme for men and women aged 40–69 years	1	£28,811	1	1	1	£20,471	

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Drummond 1992	249	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	First-generation β blocker therapy for male hypertensive patients (100 mmHg) aged 30 years compared with no therapy	1	£29,643	1	1	1		£42,346
Drummond 1992	250	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Angiotensin-converting enzyme inhibitor therapy for female hypertensive patients (100 mmHg) aged 40 years compared with no therapy	1	£29,643	1	1	1		£57,873
Drummond 1992	251	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	First-generation β blocker therapy for male hypertensive patients (90 mmHg) aged 40 years compared with no therapy	1	£29,643	1	1	1		£29,643
Field 1995	252	No averted costs included	Screening strategy for heart disease risk factors with appropriate treatment and cholesterol-lowering drugs for total cholesterol > 8.5 mmol compared with screening with cholesterol-lowering drugs for total cholesterol > 9.5 mmol for reducing risk factors for heart disease in women	0	£30,121	0				
Anderson 1993	253	No averted costs included. Health outcomes not discounted	ICD compared with no ICD for patients with cardiac fibrillation and with non-sustained ventricular tachycardia and inducible arrhythmia not suppressed by drugs	0	£30,516	0				
Pharoah 1996	254	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for females aged 55–64 years with existing heart disease (myocardial infarction) and cholesterol concentrations of 6.1–6.5 mmol/l	0	£31,200	0				
Field 1995	255	No averted costs included	Screening strategy for heart disease risk factors with appropriate treatment and cholesterol-lowering drugs for total cholesterol > 6.5 mmol compared with screening with cholesterol-lowering drugs for total cholesterol > 7.5 mmol for reducing risk factors for heart disease in women	0	£32,217	0				
Glick 1992	256	Costs and health outcomes discounted at 5%	Simvastatin therapy for male of average age 50 years with cholesterol level of 7.5 mmol and no other risk factors compared with no drug therapy	0	£32,324	0				
Rees 1985	257	No averted costs. No mention of discounting costs or health outcomes	Palliative chemotherapy for the treatment of carcinoma of the bladder compared with no therapy	0	£32,855	0				

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Field 1995	258	No averted costs included	Screening strategy for heart disease risk factors with appropriate treatment and cholesterol-lowering drugs for total cholesterol > 7.5 mmol compared with screening with cholesterol-lowering drugs for total cholesterol > 8.5 mmol for reducing risk factors for heart disease in women	0	£33,210	0				
Pharoah 1996	259	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for males aged 55–64 years with existing heart disease (angina) and cholesterol concentrations of 6.6–7.2 mmol/l	0	£33,280	0				
Drummond 1992	260	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	First-generation β blocker therapy for female hypertensive patients (100 mmHg) aged 40 years compared with no therapy	1	£35,289	1	1	1		£53,639
Pharoah 1996	261	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for females aged 55–64 years with existing heart disease (angina) and cholesterol concentrations of ≥ 7.3 mmol/l	0	£35,360	0				
Rees 1985	262	No averted costs. No mention of discounting costs or health outcomes	Palliative chemotherapy for non-small-cell bronchogenic carcinoma compared with no therapy	0	£36,962	0				
Pharoah 1996	263	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for males aged 45–54 years with existing heart disease (myocardial infarction) and cholesterol concentrations of 6.6–7.2 mmol/l	0	£37,440	0				
Wilkinson 1990	264	No averted costs included	Community care programme for mentally ill patients with neurotic disorder compared with no programme	1	£37,910	0				
Pharoah 1996	265	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for females aged 55–64 years with existing heart disease (myocardial infarction) and cholesterol concentrations of 5.5–6.0 mmol/l	0	£38,480	0				
Gournay 1995	266	No averted costs included	Community psychiatric nursing programme compared with standard general practitioner care for mental health conditions	1	£42,459	0				
SMAC 1990	267	No averted costs included. Patient costs included. Costs and health outcomes discounted at 5%	Cholesterol-testing programme with diet and drug therapy (for cholesterol > –6.5 mmol/l) compared with no programme for men and women aged 25–39 years	1	£43,308	1	1	1	£13,858	
Field 1995	268	No averted costs included	Screening strategy for heart disease risk factors with appropriate treatment and cholesterol-lowering drugs for total cholesterol > 8.5 mmol compared with screening with cholesterol-lowering drugs for total cholesterol > 9.5 mmol for reducing risk factors for heart disease in men	0	£44,133	0				

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Ludbrook 1981	269	Costs and health outcomes discounted at 7%	Hospital dialysis compared with no dialysis for end-stage renal disease patients aged 15–34 years	0	£44,987	1	2	1	£34,852	£55,121
Ludbrook 1981	270	Costs and health outcomes discounted at 7%	Hospital dialysis compared with no dialysis for end-stage renal disease patients aged 35–44 years	0	£45,110	1	2	1	£34,852	£55,368
Ludbrook 1981	271	Costs and health outcomes discounted at 7%	Hospital dialysis compared with no dialysis for end-stage renal disease patients aged 45–54 years	0	£45,234	1	2	1	£35,099	£55,368
Ludbrook 1981	272	Costs and health outcomes discounted at 7%	Hospital dialysis compared with no dialysis for end-stage renal disease patients aged 55–64 years	0	£45,481	1	2	1	£35,347	£55,615
Pharoah 1996	273	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for males aged 55–64 years with existing heart disease (angina) and cholesterol concentrations of 6.1–6.5 mmol/l	0	£45,760	0				
Anderson 1993	274	No averted costs included. Health outcomes not discounted	ICD compared with no ICD for patients with cardiac fibrillation and non-inducible arrhythmia plus low-ejection fraction	0	£46,749	0				
Anderson 1993	275	No averted costs included. Health outcomes not discounted	ICD compared with no ICD for patients with cardiac fibrillation and surviving myocardial infarction with: reduced heart rate variability; ten ventricular extrasystoles per hour; positive-signal average electrocardiogram	0	£47,398	1	1	3	£24,673	£70,123
Drummond 1992	276	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Calcium antagonist therapy for female hypertensive patients (100 mmHg) aged 30 years compared with no therapy	1	£47,993	1	1	1		£87,516
Anderson 1993	277	No averted costs included. Health outcomes not discounted	ICD compared with no ICD for patients with cardiac fibrillation and inducible arrhythmia not suppressed by drugs plus high-ejection fraction	0	£48,047	0				
Pharoah 1996	278	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for males aged 45–54 years with existing heart disease (myocardial infarction) and cholesterol concentrations of 6.1–6.5 mmol/l	0	£50,960	0				
Pickard 1990	279	No averted costs included. Health outcomes not discounted	Dedicated neurosurgery unit compared with no unit for the treatment of cerebral metastases	1	£51,417	0				
Field 1995	280	No averted costs included	Screening strategy for heart disease risk factors with appropriate treatment and cholesterol-lowering drugs for total cholesterol > 7.5 mmol compared with screening with cholesterol-lowering drugs for total cholesterol > 8.5 mmol for reducing risk factors for heart disease in men	0	£53,401	0				

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Drummond 1992	281	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Angiotensin-converting enzyme inhibitor therapy for female hypertensive patients (100 mmHg) aged 30 years compared with no therapy	1	£55,050	1	1	1		£105,866
Pharoah 1996	282	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for males aged 55–64 years with existing heart disease (angina) and cholesterol concentrations of 5.5–6.0 mmol/l	0	£55,120	0				
Anderson 1993	283	No averted costs included. Health outcomes not discounted	ICD compared with no ICD for patients with cardiac fibrillation and with non-sustained ventricular tachycardia and inducible arrhythmia	0	£55,319	0				
Anderson 1993	284	No averted costs included. Health outcomes not discounted	ICD compared with no ICD for patients with cardiac fibrillation and destined for CABG with ejection fraction less than 40% and a positive-signal average electrocardiogram	0	£57,137	0				
Mangtani 1995	285	No averted costs included	Universal preadolescent vaccination against hepatitis B compared with no vaccination	0	£57,171	1	1	4	£16,917	£87,349
Pharoah 1996	286	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for females aged 45–54 years with existing heart disease (myocardial infarction) and cholesterol concentrations of ≥ 7.3 mmol/l	0	£57,200	0				
Pharoah 1996	287	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for females aged 55–64 years with existing heart disease (angina) and cholesterol concentrations of 6.6–7.2 mmol/l	0	£57,200	0				
Freemantle 1994	288	No averted costs included. Costs and health outcomes discounted at 5%	Selective serotonin reuptake inhibitors for preventing suicide in depressed patients compared with the older tricyclics	0	£60,998	1	2	3	£22,895	£203,936
Pharoah 1996	289	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for males aged 45–54 years with existing heart disease (angina) and cholesterol concentrations of ≥ 7.3 mmol/l	0	£61,360	0				
Richards 1996	290		Home parenteral nutrition compared with no feeding in patients with intestinal failure aged < 44 years	1	£62,137	0				
Pharoah 1996	291	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for males aged 45–54 years with existing heart disease (myocardial infarction) and cholesterol concentrations of 5.5–6.0 mmol/l	0	£62,400	0				
Field 1995	292	No averted costs included	Screening strategy for heart disease risk factors with appropriate treatment and cholesterol-lowering drugs for total cholesterol > 6.5 mmol compared with screening with cholesterol-lowering drugs for total cholesterol > 7.5 mmol for reducing risk factors for heart disease in men	0	£66,751	0				

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Pharoah 1996	293	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for males aged 55–64 years with no existing heart disease and cholesterol concentrations of ≥ 7.3 mmol/l	0	£67,600	0				
Richards 1996	294		Home parenteral nutrition compared with no feeding in patients with intestinal failure aged 41–54 years	1	£73,599	1	1	3	£58,403	£202,152
Pharoah 1996	295	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for females aged 55–64 years with existing heart disease (angina) and cholesterol concentrations of 6.1–6.5 mmol/l	0	£76,960	0				
Pharoah 1996	296	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for females aged 45–54 years with existing heart disease (myocardial infarction) and cholesterol concentrations of 6.6–7.2 mmol/l	0	£91,520	0				
Pharoah 1996	297	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for females aged 55–64 years with existing heart disease (angina) and cholesterol concentrations of 5.5–6.0 mmol/l	0	£93,600	0				
Drummond 1992	298	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Diuretic therapy for male hypertensive patients (100 mmHg) aged 40 years compared with no therapy	1	£95,985	1	1	1		£151,036
Anderson 1993	299	No averted costs included. Health outcomes not discounted	ICD compared with no ICD for patients with cardiac fibrillation and inducible arrhythmia suppressed by drugs plus low-ejection fraction	0	£98,692	0				
Pharoah 1996	300	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for males aged 45–54 years with existing heart disease (angina) and cholesterol concentrations of 6.6–7.2 mmol/l	0	£98,800	0				
Anderson 1993	301	No averted costs included. Health outcomes not discounted	ICD compared with no ICD for patients with cardiac fibrillation and with non-sustained ventricular tachycardia	0	£103,237	0				
Pharoah 1996	302	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for males aged 55–64 years with no existing heart disease and cholesterol concentrations of 6.6–7.2 mmol/l	0	£109,200	0				
Pharoah 1996	303	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for females aged 45–54 years with existing heart disease (myocardial infarction) and cholesterol concentrations of 6.1–6.5 mmol/l	0	£122,720	0				
Pharoah 1996	304	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for males aged 45–54 years with existing heart disease (angina) and cholesterol concentrations of 6.1–6.5 mmol/l	0	£133,120	0				

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Richards 1996	305		Home parenteral nutrition compared with no feeding in patients with intestinal failure aged > 55 years	1	£135,370	0				
Mangtani 1995	306	No averted costs included	Selective vaccination of high-risk adults against hepatitis B compared with no vaccination	0	£137,671	1	1	5	£84,418	£210,335
Pickard 1990	307	No averted costs included. Health outcomes not discounted	Dedicated neurosurgery unit compared with no unit for the treatment of malignant intracranial tumours	1	£141,060	1	7		£1618	£821,404
Pharoah 1996	308	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for females aged 45–54 years with existing heart disease (angina) and cholesterol concentrations of ≥ 7.3 mmol/l	0	£146,640	0				
Pharoah 1996	309	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for females aged 45–54 years with existing heart disease (myocardial infarction) and cholesterol concentrations of 5.5–6.0 mmol/l	0	£148,720	0				
Leese 1992	310	No mention of discounting costs or health outcomes	Erythropoietin therapy for the treatment of anaemia in end-stage renal disease patients	1	£156,407	1	2	2	£100,271	
Pharoah 1996	311	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for males aged 45–54 years with existing heart disease (angina) and cholesterol concentrations of 5.5–6.0 mmol/l	0	£160,160	0				
Pharoah 1996	312	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for males aged 45–54 years with no existing heart disease and cholesterol concentrations of ≥ 7.3 mmol/l	0	£194,480	0				
Anderson 1993	313	No averted costs included. Health outcomes not discounted	ICD compared with no ICD for patients with cardiac fibrillation and non-inducible arrhythmia plus high-ejection fraction	0	£212,966	0				
Anderson 1993	314	No averted costs included. Health outcomes not discounted	ICD compared with no ICD for patients with cardiac fibrillation and surviving myocardial infarction with ejection fraction < 40%	0	£220,757	0				
Rees 1985	315	No averted costs. No mention of discounting costs or health outcomes	Palliative chemotherapy for advanced, previously treated non-small-cell bronchogenic carcinoma compared with no therapy	0	£229,987	0				
Pharoah 1996	316	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for females aged 45–54 years with existing heart disease (angina) and cholesterol concentrations of 6.6–7.2 mmol/l	0	£234,000	0				
Fenn 1996	317		Infant vaccination programme against hepatitis B compared with no programme	0	£267,888	1	1	7	£48,946	£592,754
Pharoah 1996	318	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for males aged 45–54 years with no existing heart disease and cholesterol concentrations of 6.6–7.2 mmol/l	0	£308,880	0				

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Pharoah 1996	319	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for females aged 45–54 years with existing heart disease (angina) and cholesterol concentrations of 6.1–6.5 mmol/l	0	£312,000	0				
Pharoah 1996	320	Averted costs not included. Costs and health outcomes discounted at 5%	Statin therapy compared with no statin therapy for females aged 45–54 years with existing heart disease (angina) and cholesterol concentrations of 5.5–6.0 mmol/l	0	£375,440	1	5	8	£160,160	£950,560
Anderson 1993	321	No averted costs included. Health outcomes not discounted	ICD compared with no ICD for patients with cardiac fibrillation surviving myocardial infarction with ejection fraction < 40% and a positive-signal average electrocardiogram	0	£740,186	0				
Anderson 1993	322	No averted costs included. Health outcomes not discounted	ICD compared with no ICD for patients with cardiac fibrillation and inducible arrhythmia suppressed by drugs plus high-ejection fraction	0	£909,001	0				
Mangtani 1995	323	No averted costs included	Universal infant vaccination against hepatitis B compared with universal preadolescent vaccination	0	d	0				
Mason 1993	323		Screening for abdominal aortic aneurysm and early repair compared with no screening for men aged 70 years	0	d	0				
Patel 1987	323	Patient costs included. Indirect costs included. Costs and health outcomes discounted at 5%	Surgery compared with ESWL for treating stones in the kidney or urethra	1	d	0				
Drummond 1992	323	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Diuretic therapy for male hypertensive patients (100 mmHg) aged 30 years compared with no therapy	1	d	1	1	1		d
Drummond 1992	323	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Diuretic therapy for female hypertensive patients (100 mmHg) aged 30 years compared with no therapy	1	d	1	1	1		d
Drummond 1992	323	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Diuretic therapy for female hypertensive patients (100 mmHg) aged 40 years compared with no therapy	1	d	1	1	1		d
Drummond 1992	323	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Diuretic therapy for female hypertensive patients (100 mmHg) aged 50 years compared with no therapy	1	d	1	1	1		d

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*
[d] *d, dominance*

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Article identifier[a]	Rank	Deviations from reference case	Intervention description	QALY?[b]	ICER	Range?[b]	Method[c]	No. of parameters	Low ICER	High ICER
Drummond 1992	323	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	Diuretic therapy for female hypertensive patients (100 mmHg) aged 60 years compared with no therapy	1	d	1	1	1		d
Drummond 1992	323	No averted costs included. Costs and health outcomes discounted at 5%. Not clear whether appropriate incremental analysis was undertaken	First-generation β blocker therapy for female hypertensive patients (100 mmHg) aged 30 years compared with no therapy	1	d	1	1	1		d
Parkin 1986	323	No averted costs. Health outcomes discounted at 5%. Inappropriate ICER	5-yearly screening programme for women aged 35–65 years plus during pregnancy and women attending family planning clinic aged > 22 years not previously screened plus all women at sexually transmitted disease clinics compared with an opportunistic screening programme	0	d	1	1	1	d	d
Wonderling 1996	323	No averted costs	British Heart Study health check programme to reduce cardiovascular risk factors for women aged 50 years compared with the Oxcheck health check programme	0	d	1	1	1	d	d

[a] *See appendix 3*
[b] *0, no; 1, yes*
[c] *Method of obtaining range of sensitivity analysis: 1, one way; 2, multiway; 3, threshold; 4, extreme; 5, probabilistic; 6, no analysis; 7, statistical*
[d] *d, dominance*

Appendix 5

Full bibliographic listing of articles reporting patient level resource/cost data

Trial based studies reporting patient-level resource/cost data

Backhouse ME, Mauskopf JA, Jones D, Wold DE, Schumacher R, Cotton R, *et al.* Economic outcomes of colfosceril palmitate rescue therapy in infants weighing 1250g or more with respiratory distress syndrome: results from a randomized trial. *PharmacoEconomics* 1994;**6**(4):358–69.

Bourne RB, Rorabeck CH, Laupacis A, Feeny D, Tugwell PS, Wong C, *et al.* Total hip replacement: the case for noncemented femoral fixation because of age. *Can J Surg* 1995;**38**(suppl 1):S61–6.

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Cook J, Richardson J, Street A. A cost utility analysis of treatment options for gallstone disease: methodological issues and results. *Health Econ* 1994;**3**(3):157–68.

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Gournay K, Brooking J. The community psychiatric nurse in primary care: an economic analysis. *J Adv Nursing* 1995;**22**(4):769–78.

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Jonsson B, Johannesson M, Kjekshus J, Olsson AG, Pedersen TR, Wedel H. Cost-effectiveness of cholesterol lowering. Results from the Scandinavian Simvastatin Survival Study (4S). *Eur Heart J* 1996;**17**(7):1001–7.

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Levin LA, Jonsson B. Cost-effectiveness of thrombolysis – a randomized study of intravenous rt-PA in suspected myocardial infarction. *Eur Heart J* 1992;**13**(1):2–8.

Mark DB, Hlatky MA, Califf RM, Naylor CD, Lee KL, Armstrong PW, *et al.* Cost effectiveness of thrombolytic therapy with tissue plasminogen activator as compared with streptokinase for acute myocardial infarction. *N Engl J Med* 1995;**332**(21):1418–24.

Mauskopf JA, Backhouse ME, Jones D, Wold DE, Mammel MC, Mullett M, *et al.* Synthetic surfactant for rescue treatment of respiratory distress syndrome in premature infants weighing from 700 to 1350 grams: impact on hospital resource use and charges. *J Pediatr* 1995;**126**(1):94–101.

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Non-trial-based studies reporting patient level resource/cost data

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