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Sensitivity analysis in economic evaluation: an audit of NICE current practice and a review of its use and value in decision-making

L Andronis, P Barton and S Bryan*

Department of Health Economics, University of Birmingham, UK

*Corresponding author. Present address: Centre for Clinical Epidemiology & Evaluation, University of British Columbia, Vancouver, BC, Canada

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NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

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Abstract

Sensitivity analysis in economic evaluation: an audit of NICE current practice and a review of its use and value in decision-making

L Andronis, P Barton and S Bryan*

Department of Health Economics, University of Birmingham, UK

*Corresponding author. Present address: Centre for Clinical Epidemiology & Evaluation, University of British Columbia, Vancouver, BC, Canada

Objectives: To determine how we define good practice in sensitivity analysis in general and probabilistic sensitivity analysis (PSA) in particular, and to what extent it has been adhered to in the independent economic evaluations undertaken for the National Institute for Health and Clinical Excellence (NICE) over recent years; to establish what policy impact sensitivity analysis has in the context of NICE, and policy-makers' views on sensitivity analysis and uncertainty, and what use is made of sensitivity analysis in policy decision-making.
Data sources: Three major electronic databases, MEDLINE, EMBASE and the NHS Economic Evaluation Database, were searched from inception to February 2008.
Review methods: The meaning of 'good practice' in the broad area of sensitivity analysis was explored through a review of the literature. An audit was undertaken of the 15 most recent NICE multiple technology appraisal judgements and their related reports to assess how sensitivity analysis has been undertaken by independent academic teams for NICE. A review of the policy and guidance documents issued by NICE aimed to assess the policy impact of the sensitivity analysis and the PSA in particular. Qualitative interview data from NICE Technology Appraisal Committee members, collected as part of an earlier study, were also analysed to assess the value attached to the sensitivity analysis components of the economic analyses conducted for NICE.
Results: All forms of sensitivity analysis, notably both deterministic and probabilistic approaches, have their supporters and their detractors. Practice in relation to univariate sensitivity analysis is highly variable, with considerable lack of clarity in relation to the methods used and the basis of the ranges employed. In relation to PSA, there is a high level of variability in the form of distribution used for similar parameters, and the justification for such choices is rarely given. Virtually all analyses failed to consider correlations within the PSA, and this is an area of concern. Uncertainty is considered explicitly in the process of arriving at a decision by the NICE Technology Appraisal Committee, and a correlation between high levels of uncertainty and negative decisions was indicated. The findings suggest considerable value in deterministic sensitivity analysis. Such analyses serve to highlight which model parameters are critical to driving a decision. Strong support was expressed for PSA, principally because it provides an indication of the parameter uncertainty around the incremental cost-effectiveness ratio.
Conclusions: The review and the policy impact assessment focused exclusively on documentary evidence, excluding other sources that might have revealed further insights on this issue. In seeking to address parameter uncertainty, both deterministic and probabilistic sensitivity analyses should be used. It is evident that some cost-effectiveness work, especially around the sensitivity analysis components, represents a challenge in making it accessible to those making decisions. This speaks to the training agenda for those sitting on such decision-making bodies, and to the importance of clear presentation of analyses by the academic community.

Contents

Glossary and list of abbreviations

Glossary

Cost-effectiveness analysis Analysis in which the consequences associated with a health technology are measured in terms of health outcomes such as life-years gained, cases of disease prevented, episode-free days or quality-adjusted life-years.

Cost-effectiveness acceptability curve A method of graphical representation of the results from a cost-effectiveness analysis, which allows assessment of the probability of the assessed interventions being cost-effective at various levels of a decision-maker's willingness to pay for an additional unit of health outcome.

Deterministic sensitivity analysis A form of sensitivity analysis in which the input parameters are assigned point estimate values.

Economic analysis See economic evaluation.

Economic evaluation Analysis that aims to identify, assess and compare the costs and consequences associated with alternative health technologies.

Incremental cost-effectiveness ratio The ratio of the difference in costs between two alternative health technologies to the difference in effectiveness between these two technologies.

Monte Carlo simulation A simulation technique that evaluates the effects of uncertainty by using random numbers. The technique requires running a large number of simulations, for each of which values are drawn from distributions assigned to uncertain parameters, with the aim of constructing an empirical probability distribution for the overall results.

National Institute for Health and Clinical Excellence (NICE) Independent organisation responsible for providing national guidance on promoting good health and preventing and treating ill health. Guidance is aimed towards assisting health-care professionals and patients/ carers to make health-care-related decisions.

NICE Technology Appraisal Committee Independent committee responsible for issuing NICE technology appraisal recommendations and guidance on the use of health technologies.

Net monetary benefit A measure of cost-effectiveness that compares the value that a decision-maker is willing to pay for an additional unit of health benefit accruing from a health technology (e.g. a quality-adjusted life-year) with the additional cost associated with the technology.

Probabilistic sensitivity analysis A form of sensitivity analysis in which probability distributions are applied to the ranges for a model's input parameters, and samples from these distributions are drawn at random to generate an empirical distribution of the relevant measure of cost-effectiveness.

Quality-adjusted life-year(s) A measure of health outcomes that combines quantity and quality of life. It assigns a weight corresponding to health-related quality of life to each year of life.

List of abbreviations

Sensitivity analysis Analysis that aims to assess and determine the influence of input parameters on the outcomes of the economic evaluation study.

5-FU/FA	5-fluorouracil plus folinic acid
AchE	acetylcholinesterase
CEA	cost-effectiveness analysis
CRT-D	cardiac resynchronisation therapy including implantable cardioverter defibrillator
CRT-P	cardiac resynchronisation therapy pacemaker
DMARD	disease modifying antirheumatic drug
EGFR	epidermal growth factor receptor
EMBASE	Excerpta Medica Database
ICD	implantable cardioverter defibrillator
ICER	incremental cost-effectiveness ratio
LDL	low-density lipoprotein cholesterol
LVSD	left ventricular systolic dysfunction
MTA	multiple technology appraisal
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NMB	net monetary benefit
NYHA	New York Heart Association
PCV	procarbazine, lomustine and vincristine
PSA	probabilistic sensitivity analysis
QALY(s)	quality-adjusted life-year(s)
SA	sensitivity analysis
TAR	technology assessment report
TNF-α	tumour necrosis factor-alpha
WHO	World Health Organization

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Introduction

Economic analyses are increasingly being used to inform technology adoption and reimbursement decisions in health care in the UK and in other countries. The growing influence of economic analyses within reimbursement agencies such as the National Institute for Health and Clinical Excellence (NICE) emphasises the importance of methodological rigour in cost-effectiveness work.

The starting point for this work was that the appropriate characterisation of uncertainty is an essential component in an economic analysis of a health technology. However, it is unclear whether good practice is being adopted in such analyses, and the influence of sensitivity analysis, and probabilistic sensitivity analysis (PSA) in particular, on NICE decision-making is unknown.

Research questions

- How do we define good practice in sensitivity analysis in general and PSA in particular? (Phase 1)
- To what extent has good practice been adhered to in the independent economic evaluations undertaken for NICE over recent years? (Phase 2)
- What policy impact does sensitivity analysis have in the context of NICE? (Phase 3)
- What views do policy-makers have on sensitivity analysis and uncertainty, and what use is made of sensitivity analysis in policy decision-making? (Phase 4)

Phase 1: Literature review

Using a review of the literature, the meaning of 'good practice' in the broad area of sensitivity analysis was explored. The literature review revealed that all forms of sensitivity analysis, notably both deterministic and probabilistic approaches, have their supporters and their detractors. The review has summarised arguments for and against alternative approaches, with an outline of good practice (see Recommendations for practice and policy) for each form of analysis.

- Deterministic sensitivity analysis: explanation for the source of ranges used should be provided, along with justification for choice of variables included.
- Analysis of extremes: clear presentation of analysis is required to allow generalisability to be assessed.
- Threshold analysis: A definition of the threshold applied in the analysis must be clearly stated and justified.
- Probabilistic sensitivity analysis: distributional assumptions should be justified and be consistent with any logical bounds on parameter values, and, where correlations are expected, joint distributions should be used.

Phase 2: Audit of cost-effectiveness work for NICE

An audit has been undertaken of the 15 most recent NICE multiple technology appraisal judgements and their related reports. This aspect of the work has reviewed and audited how sensitivity analysis has been undertaken by independent academic teams for NICE. The quality of the PSA has been judged using the criteria defined in Phase 1.

Practice in relation to univariate sensitivity analysis is highly variable, with considerable lack of clarity in relation to the methods used and the basis of the ranges employed. Further, the presentation of such analyses revealed room for improvement with the use of diagrams, such as tornado figures, very rare. In relation to PSA, there is a high level of variability in the form of distribution used for similar parameters, and the justification for such choices is rarely given. Virtually all analyses failed to consider correlations within the PSA, and this is an area of concern.

Phase 3: Review of NICE policy documents

This phase comprised a review of the policy and guidance documents issued by NICE relating to the topics selected in Phase 2. This review aimed to assess the policy impact of the sensitivity analysis and the PSA in particular.

This review found that uncertainty is considered explicitly in the process of arriving at a decision by the NICE Technology Appraisal Committee. The focus of attention is predominantly parameter uncertainty. The cited ranges of incremental cost-effectiveness ratios (ICERs) in the policy documents, and the most value in supporting decision-making, appear to have come from the deterministic analyses. This may, in part, reflect an issue of poor understanding of PSA or may reveal the value of deterministic approaches, especially in the search for subgroups. An association between high levels of uncertainty and negative decisions was suggested in the documents.

Phase 4: Interviews with NICE Committee members

Qualitative interview data from NICE Technology Appraisal Committee, collected as part of an earlier study, have been analysed. This work has assessed the value attached to the sensitivity analysis components of the economic analyses conducted for NICE (see Chapter 5).

The findings suggest considerable value in deterministic sensitivity analysis. Such analyses serve to highlight which model parameters are critical to driving a decision. Strong support was expressed for PSA, principally because it provides an indication of the parameter uncertainty around the ICER value. A concern expressed about PSA was that it can under-report the true level of uncertainty through the selection of a subset of parameters for inclusion in the analysis. Some Committee members expressed the view that where uncertainty is greater, the decision should tend towards a negative. Finally, the communication of sensitivity analysis results is less than optimal. A more detailed and clearer explanation of the sensitivity analysis is required.

Limitations

The focus for this work was on cost-effectiveness work undertaken by the independent academic teams for NICE, and so the cost-effectiveness work from industry, as part of the single technology assessment process, has not been reviewed. The review focused exclusively on documentary evidence – the models underlying the cost-effectiveness analyses were not available for scrutiny. The policy impact assessment was based only on documentary evidence again – observation of Committee discussions, and deliberations and/

or interviews with Committee members around the specific topics might have revealed further insights on this issue. Finally, the interview data were taken from an earlier study in which the scope was broader than sensitivity analysis and uncertainty, and the data were collected in 2003/4, before the 2004 NICE *Guide to the methods of technology appraisal* was published.

Recommendations for practice and policy

In seeking to address parameter uncertainty, both deterministic and probabilistic sensitivity analyses should be used. For methodological and structural uncertainties, repeated analyses should be run using different models in which uncertainties regarding model structure exist or different methods in which there are uncertainties regarding methods.

In terms of the process of conducting and implementing sensitivity analyses, good practice would involve a clear and full justification of the choice of included variables, along with a clear explanation of the information source used to specify the ranges. The use of threshold analysis is to be supported, especially where the value of a particular parameter is indeterminate, but there is a need to provide a clear rationale for, and definition of, the threshold applied.

In relation to PSA, distributions should be placed around all important model parameters, and any excluded parameters must be justified. The distributional assumption for each variable should be justified and should relate to the nature of the variable. The distribution should be consistent with any logical bounds on parameter values given its nature (e.g. utility scores with an upper bound of 1). There might be value in clearer methodology guidelines on which distributions are appropriate for which parameters. Where correlation between variables is expected, joint distributions should be used and independence should not be assumed.

On the use of sensitivity analyses in policy-making, there may be benefits from an explicit recognition of the role of such analyses in supporting the search for subgroups. This issue of the possible association between level of uncertainty and the likelihood of a negative decision requires some further discussion. The data reported here suggest that when the level of uncertainty was high, the NICE Committee was likely to tend towards a

negative decision. Finally, the challenge of effective communication between analysts and policy-makers cannot be ignored. It is evident that some cost-effectiveness work, especially around the sensitivity analysis components, represents a challenge in making it accessible to those making decisions. This speaks to the training agenda for those sitting on such decision-making bodies, and to the importance of clear presentation of analyses by the academic community.

Chapter 1
Introduction

Economic analyses are increasingly being used to inform technology adoption and reimbursement decisions in health care in the UK and in other countries.[1] An important aspect of such decision-making in the UK is the National Institute for Health and Clinical Excellence (NICE), which includes cost-effectiveness analysis (CEA) as a highly integrated component of its technology appraisal process. For every technology it considers, NICE either commissions an independent economic analysis undertaken specifically for its purposes (in the multiple technology stream of work) or receives a CEA prepared by the manufacturer (within the single technology assessment work programme). Thus, it is no surprise that recent research suggests that economic evaluation evidence is a key driver of the final coverage determinations reached by the NICE Technology Appraisal Committee.[2–4]

The influence of economic analyses at NICE emphasises the importance of methodological rigour in the cost-effectiveness work. NICE has recently updated its methodology guide and maintains the requirement for a 'reference case' analysis with a set of methods required as a base case analysis, and is thus highly prescriptive in terms of the approach to economic analysis that it expects to see.[5] One aspect of the NICE reference case concerns the characterisation of potential bias and uncertainty and the requirement that extensive sensitivity analyses, both deterministic and probabilistic, are undertaken. The explicit instruction in the NICE methods guide for the use of probabilistic sensitivity analysis (PSA) is supported by a recent paper, coauthored by a team of leading health economists,[5,6] which makes a strong case in support of the NICE reference case in relation to PSA, arguing that it should not be viewed as an 'optional extra', but that it is central to addressing the decision problems tackled by NICE.

Defining uncertainty

The term uncertainty is defined by the *Oxford English Dictionary* as:

The quality of being indeterminate as to magnitude or value; the amount of variation in a numerical result that is consistent with observation.

The state of not being definitely known or perfectly clear; doubtfulness or vagueness.

Something not definitely known or knowable; a doubtful point.

(http://dictionary.oed.com)

For the purposes of this report we define uncertainty in a general sense as given above, but will distinguish four categories in the context of economic evaluation in health care.[7]

1. 'Methodological uncertainty' refers to disagreement about the most appropriate analytic methods to use in the evaluation.
2. 'Parameter uncertainty' relates to uncertainty in the estimated values of the parameters that form the inputs for the model.
3. 'Structural or modelling uncertainty' concerns the model structure and uncertainty on the appropriate methodology for combining the input parameters.
4. 'Generalisability' is the issue of the extent to which study results can be applied to another context or setting.

Sensitivity analysis

There is widespread agreement that the appropriate methods for handling uncertainty can be collectively referred to as sensitivity analyses. To ensure a common understanding of terms, we shall define here the alternative forms of sensitivity analysis.

Univariate or one-way sensitivity analysis

This is the simplest type of sensitivity analysis, whereby input values for a parameter are varied

one at a time across a plausible range while the remaining values are held at their baseline values. This provides an assessment of the impact of the change on the results of the analysis.[8–10]

Multivariate sensitivity analysis or scenario analysis

This is an extension of the one-way sensitivity analysis. This analysis recognises that there might be more than one uncertain parameter in the model, and involves varying two or more input values at the same time.[8–10] As 'scenario analysis', the combination of parameters varied is driven by a priori judgement relating to the alternative scenario being considered.

Threshold analysis

The aim of this analysis is to identify the input value, of one or more parameters, above or below which the results of the analysis favour a specific intervention.[11]

Extreme case (worst- and best-case scenario) analysis

Here, the aim is to assess the results of the study under a scenario that involves using the most pessimistic (or optimistic) combination of input values.[8,9]

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis assigns to each input parameter a specified distribution and, by drawing randomly from those distributions, generates a large number of mean cost and effectiveness estimates that can be used to form an empirical joint distribution of the differences in cost and effectiveness between interventions.[7,11–13]

Research questions

Our starting point is that an appropriate characterisation of uncertainty is an essential component in an economic analysis of a health-care technology. Furthermore, we take the view that sensitivity analysis conducted to a high standard can support coverage decision-making in health care. However, it is unclear whether good practice is being adopted in such analyses, and the influence of sensitivity analysis, and PSA in particular, on NICE decision-making is unknown.

Thus, we have addressed the following research questions:

1. How do we define good practice in sensitivity analysis in general and PSA in particular? (Chapter 2)
2. To what extent has good practice been adhered to in economic evaluations undertaken by independent academic teams for NICE over recent years? (Chapter 3)
3. What policy impact does sensitivity analysis have in the context of NICE? (Chapter 4)
4. What views do policy-makers have on sensitivity analysis and uncertainty, and what use is made of sensitivity analysis in policy decision-making? (Chapter 5)

Outline of research methods

Fuller details of research methods will be given in each subsequent chapter, but a brief overview of the methods adopted in this work is given below. There were four phases to the project, and each phase is reported as a separate chapter.

Phase 1 Using a review of the literature, we have explored the meaning of 'good practice' in the broader area of sensitivity analysis, including the subcategory of PSA (Chapter 2).

Phase 2 An audit has been undertaken of the 15 most recent NICE multiple technology appraisal (MTA) judgements and their related reports. This aspect of the work has reviewed and audited how sensitivity analysis has been undertaken by the independent academic teams for NICE, and considered both deterministic approaches and PSA. The quality of the PSA has been judged in relation to the criteria defined as a result of Phase 1 (Chapter 3).

Phase 3 This part of the project comprised a review of the policy and guidance documents issued by NICE relating to the topics selected in Phase 2. This review aimed to assess the policy impact of the sensitivity analysis and the PSA in particular (Chapter 4).

Phase 4 Finally, qualitative interview data from NICE Technology Appraisal Committee members have been analysed. This work has assessed the value attached to the sensitivity analysis components of the economic analyses conducted for NICE (Chapter 5).

Chapter 2
Literature review

Introduction

In order to obtain a view on the use and value of sensitivity analysis as appears in the literature, we developed and carried out a search plan that involved searching major electronic bibliographic databases and scanning the reference list of potentially important studies. As a next step, the retrieved references were filtered according to predetermined criteria, and useful information was extracted.

Search strategy

To facilitate the development of an effective and comprehensive strategy for searching electronic bibliographic databases, the review question under consideration was broken into three different components, namely health technology assessment, decision analytic modelling and uncertainty.

For each of these components, we developed a set of search terms that included text words, synonyms, combinations of expressions and indexing terms derived from each database's thesaurus, if this was available.

The developed search strategies were used to search the following major bibliographic databases: MEDLINE [National Center for Biotechnology Information (NCBI) PubMed, 1950–2008], Excerpta Medica Database (EMBASE) (1980–2008, week 11) and the NHS Economic Evaluation Database (EED) (1996–2008) provided by the Centre for Reviews and Dissemination at the University of York. During the searching process, the set of search terms was modified so as to be consistent with each database's search interface. The searches were not restricted by language or date.

Apart from searching for studies in electronic bibliographic databases, the search strategy also involved searching the reference lists of potentially useful publications and hand-searching selected journals in the area of health economics (*Health Economics*, *Health Technology Assessment*, *Medical Decision Making*, *Pharmacoeconomics*, *Value in Health*).

In addition, we undertook 'related articles' searches in PubMed to identify further references. Details on the search strategy are given in Appendix 1.

Selection of studies

The abstracts and titles retrieved through the literature search were checked against a series of inclusion and exclusion criteria. This process aimed at distinguishing relevant from irrelevant articles and including only those papers that would provide useful input for the review.

Inclusion and exclusion criteria

The inclusion criteria related to:

1. Study design: included studies must be related to the methods for conducting economic evaluations specific to health.
2. Purpose/outcomes: the study must contribute to the methodology that relates to assessing and handling uncertainty in economic evaluations.

Studies published in languages other than English were not included.

Selection process

The process of selecting studies was iterative and involved applying, in the first instance, the inclusion/exclusion criteria liberally, in all the studies identified from the database searches. Selection of studies was carried out by two researchers (SB and LA). Studies that clearly did not meet the inclusion criteria were dropped, while the rest – either obviously useful studies or studies whose abstracts did not provide adequate evidence for exclusion – were forwarded for further consideration. As a next step, the full text of the included articles were retrieved and reviewed against the predetermined inclusion criteria. All the studies that have been selected after the detailed review on the basis of the full text formed the main input for the systematic review. A schematic presentation of the search process is provided in Appendix 2.

Data extraction

Relevant information was obtained through a data extraction form developed for the study. The process of data extraction was undertaken independently by two researchers (SB and LA). Disagreements were resolved through discussion between the involved assessors.

Results

Box 1 lists the 25 papers and reports included in the review.

A taxonomy of uncertainty

Uncertainty is inherent in economic evaluation, as most of the time there is uncertainty about the true values of the input parameters, as well as the structural assumptions and methodology that is used to combine the parameters.

A taxonomy of uncertainty in economic evaluations alongside clinical trials has been proposed by Briggs *et al*.[11] According to this, there are four broad areas of uncertainty in economic evaluation, which relate to:

1. Variability in sample data: this is about the inherent variability that exists in the parameters of interest between patients within a population.
2. Generalisability of results: which relates to the extent to which study results can be applied to another setting or patient group.
3. Extrapolation: which arises from the attempts to extrapolate from an intermediate health outcome to a final outcome, as well as to extrapolate from short to longer time horizons.
4. Analytical methods: this relates to the uncertainty about the most appropriate techniques to be used in economic evaluations.

A slightly different taxonomy of uncertainty has been proposed by Manning *et al*.[10] Here, uncertainty in health economic evaluation is related to:

1. Parameter uncertainty: which is the uncertainty about the true values of the parameters used as inputs in the analysis.
2. Model uncertainty: which can be further distinguished to model structure uncertainty

and modelling process uncertainty. The former relates to uncertainty about the appropriate methodology for combining the input parameters, while the latter is uncertainty introduced by the combination of methods used by the analysts who carry out the analysis, in the sense that if the analysis was conducted again by another team of analysts, the results would be different.

In the context of model-based economic evaluations, uncertainty has been distinguished between parameter, methodological and structural uncertainty.[14]

Parameter uncertainty is defined as the uncertainty that arises from the imperfect knowledge of true values of the parameters that are used in the analysis. Most of the time estimates for the parameters used in the analysis come from sample data and thus they are subject to sampling variability.[10,12]

Methodological uncertainty is defined as the uncertainty caused by the disagreement around the appropriate analytic methods and techniques used in economic evaluations. Commonly cited examples are the disagreement over the appropriate way to incorporate time preference into economic evaluations,[15,16] and the appropriate methods for estimating the opportunity and productivity costs in economic evaluation.[17,18]

Structural uncertainty relates to the uncertainty about the appropriate structural form of the decision model employed for the economic analysis. Imperfect information on the appropriate ways of combining evidence by using different structural assumptions causes uncertainty and is likely to lead to different results.[12]

At this point, a distinction should be drawn between uncertainty and variability or heterogeneity. The former refers to having imperfect information about the precise values of the parameters of interest, while variability refers to the inherent random variation between different subjects, and heterogeneity relates to variation between subjects that can be explained and attributed to specific factors.[12,19]

For the purposes of this review, the focus will now largely be on parameter, methodological and structural uncertainty.

BOX 1 *List of studies/reports included in the systematic review*

Ades AE, Claxton K, Sculpher M. Evidence synthesis, parameter correlation and probabilistic sensitivity analysis. *Health Econ* 2006;**15**:373–81

Barton P, Bryan S, Robinson S. Modelling in the economic evaluation of health care: selecting the appropriate approach. *J Health Serv Res Policy* 2004;**9**:110–18

Bravo VY, Sculpher M. Making decisions under uncertainty: the role of probabilistic decision modelling. *Fam Pract* 2006;**23**:391–2

Briggs A, Sculpher M, Buxton M. Uncertainty in the economic evaluation of health care technologies: the role of sensitivity analysis. *Health Econ* 1994;**3**:95–104

Briggs AH, Gray AM. Handling uncertainty when performing economic evaluation of healthcare interventions. *Health Technol Assess* 1999;**3**:1–134

Briggs A. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics* 2000;**17**:479–500

Briggs A. Probabilistic analysis of cost-effectiveness models: statistical representation of parameter uncertainty. *Value Health* 2005;**8**:1–2

Claxton K, Sculpher M, McCabe C, Brennan A, Briggs A, Claxton K, *et al*. Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra. *Health Econ* 2005;**14**:339–47

Critchfield GC, Willard KE. Probabilistic analysis of decision trees using Monte Carlo simulation. *Med Decis Making* 1986;**6**:85–92

Drummond M, Jefferson T. Guidelines for authors and peer reviewers of economic submissions to the *BMJ*. *BMJ* 1996;**313**:275–83

Felli JC, Hazen GB. Sensitivity Analysis and the Expected Value of Perfect Information. *Med Decis Making* 1998;**18**:95–109

Griffin S, Claxton K, Hawkins N, Sculpher M. Probabilistic analysis and computationally expensive models: Necessary and required? *Value Health* 2006;**9**:244–52

Lord J, Asante MA. Estimating uncertainty ranges for costs by the bootstrap procedure combined with probabilistic sensitivity analysis. *Health Econ* 1999; **8**:323–33

National Institute for Health and Clinical Excellence. *Guide to the methods of technology appraisal*. London: NICE; 2004

National Institute for Health and Clinical Excellence. *Guide to the methods of technology appraisal*. London: NICE; 2008

O'Brien BJ, Drummond MF, Labelle RJ, Willan A. In search of power and significance: issues in the design and analysis of stochastic cost-effectiveness studies in health care. *Med Care* 1994;**32**:150–63

O'Hagan A, McCabe C, Akehurst R, Briggs A, Akehurst R, Buxton M, *et al*. Incorporation of uncertainty in health economic modelling studies. *Pharmacoeconomics* 2005;**23**:529–36

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Strengths and weaknesses of alternative forms of sensitivity analysis

Tables 1–3 report quotes from relevant papers indicating the strengths and weaknesses of four forms of sensitivity analysis; namely deterministic, analysis of extremes, threshold and probabilistic. The main findings of this aspect of the review are discussed below.

Deterministic sensitivity analysis

This section covers all forms of 'simple' sensitivity analysis such as univariate and multivariate analyses. *Table 1* reports quotes from the literature review in respect to this form of analysis.

On the positive side, the literature suggests that such analyses form a natural starting point by which greater understanding of the structure of the CEA can be obtained. In the absence of high-quality sample data, a simple sensitivity analysis can provide insight into the uncertainty regarding a particular parameter. Finally, the suggestion is made that the key drivers of the cost-effectiveness result can best be revealed through univariate analyses.

However, there are important concerns raised in relation to such simple approaches to exploring uncertainty. These include:

- The presentation of the results of multiway analyses is increasingly difficult, as the number of parameters varied simultaneously increases.
- The choice of parameters to include in the analysis is often arbitrary and might be thought of as a form of selection bias.
- Interpretation is highly subjective, as there are no guidelines on what represents a robust result

TABLE 1 *Strengths and weaknesses of 'deterministic' sensitivity analysis*

Publication	Strengths	Weaknesses
Critchfield and Willard, 1986[20]		'One deficiency of n-way sensitivity analysis is that joint effects of variables upon the final decision are difficult both to assess and to present when n is greater than three.'
Briggs *et al.*, 1994[11]	'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 wide-spread use'	'… it becomes progressively more difficult to present the results of multi-way analyses the greater the number of inputs that are varied, and evaluations frequently exhibit uncertainty on more inputs that can feasibly be handled with simple sensitivity analysis … .'
O'Brien *et al.*, 1994[21]		'The analyst has discretion as to which variables and what alternative values are included in the sensitivity analysis, creating the potential for selection bias (conscious or otherwise).'
		'Interpretation of a sensitivity analysis is essentially arbitrary because there are no guidelines or standards as to what degree of variation in results is acceptable evidence that the analysis is "robust".'
		'Variation of uncertain parameters one at a time carries a risk that interactions between parameters may not be captured. For this reason some analysts report two-way or three-way sensitivity analyses. In the clinical decision analysis literature, the limitations of traditional sensitivity analysis have led to the development of probabilistic sensitivity analysis by Monte Carlo simulation methods … .'
Briggs and Gray, 1999[8]		'By failing to allow for interactions and by keeping other variables constant, one-way sensitivity analysis may underestimate the impact of uncertainty … .'
Briggs, 2000[12]		'… by considering the effect of parameters individually, is likely to underestimate overall uncertainty … .'

in terms of the level of variability revealed through such sensitivity analyses.

- Interactions and correlations between parameters may not be captured well, and will lead to the true level of uncertainty being under-reported.

Analysis of extremes and threshold analysis

Placing the worst-case (and then best-case) values on all parameters can be useful in providing a sense of the full range of the plausible values for the cost-effectiveness result (*Table 2*). However, this almost certainly overstates the true level of uncertainty, given that the combination of worst-

TABLE 1 *Strengths and weaknesses of 'deterministic' sensitivity analysis (continued)*

Publication	Strengths	Weaknesses
Walker and Fox-Rushby, 2001[22]	'… one-way sensitivity analyses are easy to use and provide flexibility in parameter choice. They are a logical, easy to grasp place to start to understand the structure of a particular cost-effectiveness analysis and provide the natural building blocks to do multi-way sensitivity analyses. They can shed light on whether any piece(s) of research could improve the outcome from a policy decision and whether it is worth waiting for this additional data.' 'Allows more than one parameter to be varied at the same time.' 'Two and three-way sensitivity analyses can be helpful to identify the best scenario likely to appeal to decision-makers with a note of the reliability of such a situation … .' 'The "reference case" as a type of scenario analysis may stimulate an improvement in the comparability and methodological quality of economic evaluations.'	'Looking at one source of uncertainty at a time in the model provides an incomplete and under-estimate of how uncertain the estimated overall cost-effectiveness ratio actually is (Agro *et al*. 1997). There are three related problems: a. The incremental cost and effectiveness depend on multiple parameters, not just one; b. The interaction of particular factors may imply that the total effect could be something quite different from the simple sum of individual contributions; c. The cost-effectiveness ratio is a ratio of two uncertain numbers, with the result that the uncertainty in the ratio may be substantially larger than that of either of its elements.' '… suffer from some of the same problems of one-way sensitivity analyses; namely, that they may be difficult to interpret if the variables used are dependent on each other (Agro *et al*. 1997). In addition, these types of analyses become cumbersome if more than two inputs are varied simultaneously.'
Soto, 2002[23]	'… the best way of managing the uncertainty of multiple parameters is to undertake a multivariate sensitivity analysis.'	
NICE, 2004[24]		'The use of univariate, best/worst case or scenario-based sensitivity analysis to quantify the effect of parameter uncertainty in an analysis cannot incorporate the uncertainty in more than two or three parameters simultaneously … .'
Claxton *et al*., 2005[6]		'… cannot provide enough insight into the scale of decision uncertainty.' '… with a large number of parameters this can be markedly more time-intensive and computer-intensive than PSA. More importantly it is generally very difficult to interpret correctly and becomes impossible if some parameters are correlated.'
Ades *et al*., 2006[25]		'… when model parameters are correlated it can become difficult – even impossible to structure deterministic, scenario-based sensitivity analysis.'
NICE, 2008[5]	'The use of univariate and best/worst-case sensitivity analysis is an important way of identifying parameters that may have a substantial impact on the cost-effectiveness results and of explaining the key drivers of the model.'	'However, such [deterministic] analyses become increasingly unhelpful in representing the combined effects of multiple sources of uncertainty as the number of parameters increase.'

TABLE 2 *Strengths and weaknesses of 'analysis of extremes'/'threshold analysis'*

Publication	Strengths	Weaknesses
Briggs *et al.*, 1994[11]	*Analysis of extremes* 'The use of analysis of extremes can be an efficient way of dealing with uncertainty in data inputs when, for example, experts have been asked to provide a base-case value for a given variable and a plausible range, but the distribution between the outer limits is unknown.'	*Analysis of extremes* '… it is usually the case that approaches cannot reliably be termed optimistic or pessimistic prior to the evaluation being undertaken … .' '… it is very unlikely that, for example, all the pessimistic factors affecting costs will occur simultaneously: there are combinations of factors which are much more likely to take place.'
Walker and Fox-Rushby, 2001[22]		*Analysis of extremes* '… possibly the 'max–min' (i.e. analysis of extremes) is least useful, unless the results are insensitive to the extreme combination of parameter values considered (Agro *et al.* 1997). If the results are sensitive to the extremes, the results are not very useful bounds on the uncertainty in the cost-effectiveness ratio for two reasons: it is highly unlikely that all of the extreme values of key parameters will occur in any particular setting; and, under some circumstances, two or more sources of uncertainty may partially offset each other, due to the inherent structure of the problem.'
Claxton *et al.*, 2005[6]		*Analysis of extremes* '… complex correlation structures between parameters …makes it impossible to locate a fixed (set of) parameter value(s) which can be regarded as "extreme".'
Briggs *et al.*, 1994[11]	*Threshold analysis* '… it lends itself to graphical presentation … .' '… 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 … .'	*Threshold analysis* '… it can only be used to deal with uncertainty in continuous variables, which would normally mean that it is useful only for dealing with uncertainty in data inputs'. 'Cost effectiveness and cost-utility analyses … often seek to estimate incremental cost to effects ratios for which thresholds cannot easily be identified … Although such cut-off points have been suggested, they are not generally accepted.'
NICE, 2008[5]	'The use of univariate and best/worst-case sensitivity analysis is an important way of identifying parameters that may have a substantial impact on the cost-effectiveness results and of explaining the key drivers of the model.'	

case values for all parameters is most unlikely to occur. Further, the process of identifying a fixed set of extreme parameter values is not straightforward if the correlation structure between parameters is considered.

Threshold analysis is seen to be particularly useful in the situation in which the value of a particular parameter is unknown or indeterminate, such as drug price. In the situation of analysis prior to marketing then such sensitivity work can help to identify the maximum price that the reimbursement agency might be willing to accept on the basis of cost-effectiveness. A drawback for threshold work is that a maximum incremental ratio has to be defined as the threshold and although such cut-offs have been suggested they do not necessarily have universal support.

Probabilistic sensitivity analysis

Much of the literature is supportive of the use of PSA to capture parameter uncertainty in cost-effectiveness work (*Table 3*). The suggestion is made that PSA allows the uncertainty in all parameters to be characterised through the use of probability distributions, with this translated through to uncertainty in the mean cost-effectiveness result. Further, where correlation between parameters has been correctly specified in the model, the PSA provides the correct estimates of mean costs and effects even in the situation of non-linear models.

The concerns expressed about PSA relate principally to practice, namely the suggestion that an assumption of independence between parameters is commonly made and that choice of parameter distribution can sometimes be inappropriate.[6] Further, the limitations of PSA are recognised – the broader forms of uncertainty, such as methodology and generalisability, are not captured through PSA.

TABLE 3 *Strengths and weaknesses of probabilistic sensitivity analysis*

Publication	Strengths	Weaknesses
Briggs *et al.*, 1994[11]	It can take into account how likely it is that the uncertain parameter will take a specific value within the specified range (page 101). '… has the potential to be the most comprehensive way of dealing with some forms of uncertainty in economic evaluation.'	'Its value is … likely to be limited to those situations when there is an absence of sample data and the analysis can be used to simulate a distribution in total costs and/or benefits attached to hypothetical patients … .' '… it can only handle uncertainty in data inputs. Therefore analytical uncertainties have to be handled in some other way.' '… unlikely to be of value in dealing with uncertainty relating to the generalisability of results, as decision makers are interested in what happens to the results when data relevant to their context are included, rather than expected results across the whole system … .'
Felli and Hazen, 1998[26]	'… provides a mechanism for the decision maker to directly examine output distributions, such as the payoff for a single alternative or the difference between payoffs for some pair of competing alternatives. Knowledge of the likelihood of each payoff (or payoff difference) over the entire range of possible values enables the decision maker to better assess the risk of an adverse outcome, or, in the case of difference in payoffs between two competing alternatives, select an alternative based upon the likelihood that its payoff will exceed that of its competitor by some specified amount.'	
Lord *et al.*, 1999[27]		'Some types of uncertainty, such as uncertainty over the structural form of a model and uncertainty over basic values, are not amenable to probabilistic sensitivity analysis.'
NICE, 2004[24]	'The use of probabilistic sensitivity analysis (or, where appropriate, stochastic analysis of patient-level data) allows complete characterisation of the uncertainty associated with all input parameters.'	
Briggs, 2005[28]	'… will give a more accurate depiction of the importance of parameter uncertainty for the results of the analysis in comparison, say, to simple sensitivity analysis … .'	

9

TABLE 3 *Strengths and weaknesses of probabilistic sensitivity analysis (continued)*

Publication	Strengths	Weaknesses
Claxton *et al.*, 2005[6]		'… the choice of distribution to represent uncertainty and the common assumption of independence between parameters have been identified as limitations of the probabilistic approach.'
Bravo and Sculpher, 2006[29]	PSA 'allows the uncertainty in the individual parameters … to be fully characterised using probability distributions to reflect their imprecision, and propagated through the model using second order Monte Carlo simulation.' '… probabilistic models allow the joint effect of parameter uncertainty across all input parameters in the model to be translated into uncertainty in the mean cost effectiveness results … .'	
Ades *et al.*, 2006[25]	'Probabilistic methods, however, correctly propagate correlation automatically, providing meaningful sensitivity analysis, and correct computation of expected costs and benefits in non-linear or even multi-linear models, regardless of parameter correlation.'	
Griffin *et al.*, 2006[30]	'… provides a more rigorous approach by requiring that all input parameters in a model be specified as full probability distributions, rather than as point estimates, to indicate the uncertainty of the estimates.'	
NICE, 2008[5]	'This [PSA] enables the uncertainty associated with parameters to be simultaneously reflected in the results of the model. In non-linear decision models, probabilistic methods provide the best estimates of mean costs and outcomes.' 'Within a probabilistic analysis the contribution of the uncertainty in each parameter to overall decision uncertainty and its consequences can be achieved using expected-value-of-information methods.'	

Good practice in sensitivity analysis

Tables 4–6 report quotes from the literature concerning good practice in relation to the appropriate form of sensitivity analysis to address a particular form of uncertainty. A summary of the main points is given below.

- Parameter uncertainty: both deterministic and probabilistic sensitivity analysis should be used.
- Structural uncertainty: repeated analyses should be run using different models where uncertainties regarding model structure exist.
- Methodological uncertainty: repeated analyses should be run using different methods where uncertainties regarding methods exist.

In terms of the process of conducting and implementing sensitivity analyses, the literature review has also uncovered some statements of good practice for each form of sensitivity analysis (*Tables 7–9*). A summary of the main points is given below.

- Deterministic sensitivity analysis:
  - Analysts should provide explanation for the source of ranges used.
  - Analysts should also give a justification for choice of variables included and excluded.
- Analysis of extremes:
  - Analysts should provide clear presentation of analysis, to allow readers to assess the analysis relative to their own context.

TABLE 4 *Statements of good practice – appropriate type of sensitivity analysis to address 'parameter' uncertainty*

Publication	Appropriate type of sensitivity analysis
Briggs *et al.*, 1994[31]	'If the uncertain parameters within an analysis are considered to be independent of each other, then a series of one-way simple sensitivity analysis may be adequate.'
Sonnenberg *et al.*, 1994[32]	'Such uncertainty is best represented by a probability distribution rather than by a point estimate. Monte Carlo analysis (probabilistic sensitivity analysis) can be used to assess the impact of these known variations on the results. However, the most appropriate interpretation of the results of Monte Carlo analysis in decision analysis has not been established.'
Shaw and Zachry, 2002[33]	'Second-order uncertainty needs to be considered in isolation of first-order uncertainty since the implementation of probabilistic sensitivity analysis concurrently with Monte Carlo simulations can lead to misinformed inferences.'
Soto, 2002[23]	'A practical approach would be to perform a simple univariate sensitivity analysis on key values in the model to ascertain under what circumstances uncertainty or lack of agreement about any estimate might have an important impact on the results and conclusions. In addition, the best way of managing the uncertainty of multiple parameters is to undertake a multivariate sensitivity analysis.'
Weinstein *et al.*, 2003[34]	'All modelling studies should include extensive sensitivity analysis of key parameters. Either deterministic (one-way and multiway) or probabilistic sensitivity analyses are appropriate … .'
Barton *et al.*, 2004[35]	'In the special case where the model structure is known to be adequate, and uncertainty about the model parameters can be objectively represented through a joint probability distribution, the effect of uncertainty can be measured using probabilistic sensitivity analysis.'
	'On the other hand, probabilistic sensitivity analysis may not be necessary to guide a decision. If a correctly specified model gives a policy recommendation that is robust to extreme changes in parameter values, then the decision can be made with confidence … In such cases, there is no need to undergo the considerable effort required to produce a joint distribution for model parameters which properly reflects current uncertainty.'
NICE, 2004[24]	'All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis should be used to translate the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared … .'
Philips *et al.*, 2006[14]	'… in the choice between deterministic or probabilistic modelling approaches it should be recognised that the combined effect of parameter uncertainty (in terms of decision uncertainty) is only truly reflected when data are incorporated probabilistically … .'
	'Probabilistic sensitivity analysis is the most appropriate method for handling parameter uncertainty because it facilitates assessment of the joint effect of uncertainty over all parameters. Moreover, it facilitates value-of-information analysis, which can quantify the implications of decision uncertainty explicitly.'
NICE, 2008[5]	'The implications of different estimates of key parameters must be reflected in sensitivity analyses (for example, through the inclusion of alternative scenarios). Inputs must be fully justified and uncertainty explored by sensitivity analysis using alternative input values.'
	'The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.
	The choice of sources of data to include in an analysis may not be clear-cut. In such cases, the analysis should be re-run, using the alternative source of data or excluding the study over which there is doubt, and the results reported separately.'
	'Uncertainty arises from parameter precision, once the most appropriate sources of information have been identified (that is, the uncertainty around the mean health and cost inputs in the model). Distribution should be assigned to characterise the uncertainty associated with the (precision of) mean parameter values. Probabilistic sensitivity analysis is preferred. This enables the uncertainty associated with parameters to be simultaneously reflected in the results of the model. In non-linear decision models, probabilistic methods provide the best estimates of mean costs and outcomes.'
	'Probabilistic sensitivity analysis is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.'

- Threshold analysis:
  - It is important that a definition of the threshold applied in the analysis is clearly stated, and a justification is given.
- Probabilistic sensitivity analysis:
  - The distributional assumption for each variable should be justified and should relate to the nature of the variable.
  - The distribution should be consistent with any logical bounds on parameter values, given its nature (e.g. utility scores with upper bound of 1).
  - When correlation between variables is expected, joint distributions should be used and independence should not be assumed.

Conclusions

The literature review has revealed that all forms of sensitivity analysis have their supporters and their detractors. Furthermore, the review has summarised the arguments for and against alternative approaches, with an outline of good practice. This work is now taken forward in the context of the review of cost-effectiveness work undertaken for NICE in Chapter 3.

TABLE 5 *Statements of good practice – appropriate type of sensitivity analysis to address 'structural' uncertainty*

Publication	Appropriate type of sensitivity analysis
Parmigiani *et al.*, 1997[36]	'Model uncertainty can be approached like parameter uncertainty. In practice however it's harder to handle, and consequently often ignored. Bayesian methods are suited for incorporating such uncertainty.'
Briggs, 2000[12]	'The suggested solution is to run repeated analyses utilising different models and specify prior probabilities of different models across this model space. This is the solution proposed by the US Panel in relation to modelling structure uncertainty by appropriately weighting analyses employing different assumptions concerning the functional form of particular elements of the model structure.'
NICE, 2004[24]	'Sensitivity analysis should be used to deal with sources of uncertainty other than that related to the precision of the parameter estimates. This will include uncertainty about the choice of studies to include in a meta-analysis, and the structural assumptions made in a model. Each alternative analysis should present separate (probabilistic) results.'
Claxton *et al.*, 2005[6]	'… to conduct scenario analysis where the probabilistic analysis is run several times, each scenario conditional on different assumptions about model structure or interpretations of the available evidence. The [NICE] Appraisal Committee is then responsible for making an assessment of which of the scenarios is the most credible.'
Philips *et al.*, 2006[14]	'Whilst no generally accepted method exists for addressing structural uncertainties, guidelines suggest that they should be addressed as sensitivity analyses using alternative model structures. For example, alternative structural assumptions, such as the choice of extrapolation methodology, should be evaluated via sensitivity analysis. This would involve re-running the model with a series of alternative extrapolation techniques and presenting the results under each scenario.'
NICE, 2008[5]	'The impact of structural uncertainty on estimates of cost effectiveness should be explored by separate analysis of a representative range of possible scenarios … .'
	'Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.
	An important element of uncertainty around cost-effectiveness results arises from the uncertainty in the structure of the decision model. The analysis of the uncertainty in all parameters for decision uncertainty assumes that factors such as a model's structure and data inputs are considered to be appropriate. However, these characteristics of the model are also subject to uncertainty, which should be identified and formally examined using sensitivity analysis.'

TABLE 6 *Statements of good practice – appropriate type of sensitivity analysis to address 'methodological' uncertainty*

Publication	Appropriate type of sensitivity analysis
Briggs *et al.*, 1994[11]	'Simple sensitivity analysis can also play an important role in coping with uncertainty in some forms of analytical method: if the data are available, results can be recalculated using alternative approaches.'
Drummond and Jefferson, 1996[37]	'Uncertainties may stem from the existence of alternative analytical methods. Some issues will be avoided by an explicit statement of the approach to be adopted, but others may be usefully handled by using sensitivity analysis – for example, to present results for different discount rates, or with and without indirect costs.'
Lord *et al.*, 1999[27]	'Simple sensitivity analysis might be required in addition to probabilistic analysis to investigate the effect of uncertainty over analytical methods.'
Briggs, 2000[12]	'… the use of a "reference case" of core methods … supplemented by additional analyses employing other methods thought appropriate by the authors.'
NICE, 2004[24]	'Analyses using alternative methods to the reference case should be presented separately from those relating to structure and data.' 'Uncertainty about the appropriateness of the methods used in the reference case can also be dealt with using sensitivity analysis'
Philips *et al.*, 2006[14]	'Methodological uncertainty should be addressed in a similar manner [to structural uncertainty].'

TABLE 7 *Statements of good practice – appropriate implementation of 'deterministic' sensitivity analysis*

Publication	Appropriate implementation of sensitivity analysis
Briggs *et al.*, 1994[11]	'Studies which provide a source of explanation for the ranges used in simple sensitivity analysis are likely to be of more use to decision makers than studies which employ an arbitrary range'
Soto, 2002[23]	'The choice of the variables on which a [deterministic] sensitivity analysis is performed should be justified, and the rationale for the interpretation of the results of such an analysis should be defined clearly.'
Philips *et al.*, 2006[14]	'If data are incorporated as point estimates, the ranges used for sensitivity analysis should be stated clearly and justified … .'

TABLE 8 *Statements of good practice – appropriate implementation of 'analysis of extremes'/'threshold analysis'*

Publication	Appropriate implementation of sensitivity analysis
Briggs *et al.*, 1994[11]	*Analysis of extremes* 'The usefulness of this approach depends on whether the study gives sufficient detail for the reader to be able to determine whether the contexts considered within the analysis are more extreme than their own. This problem can be eased if authors presented clearly the data relating to the various elements of the analysis. For example, resource use and unit costs should be presented separately, thereby enabling local data to be applied to the results of the evaluation.' *Threshold analysis* '… care must be taken in selecting the appropriate threshold for such an analysis. Examples of possible thresholds might be the values of uncertain parameters which cause an intervention just to become more costly than its comparator in a cost-minimisation analysis; just to dominate (more costly and more effective) its comparator in a cost-effectiveness or cost-utility analysis; and just to provide a net benefit in a cost-benefit analysis.'
Soto, 2002[23]	*Analysis of extremes* 'It is advisable to include the best and worst values (extreme values) of the variables and the values of confidence intervals, if available … .'

13

TABLE 9 *Statements of good practice – appropriate implementation of probablistic sensitivity analysis*

Publication	Appropriate implementation of sensitivity analysis
Briggs, 2000[12]	'The distributional assumptions made for each variable [should] relate to the nature of this variable.'
	'In summary, for those parameters of a cost-effectiveness model that could, in principle, be estimated from observed data, consideration should be given to the prior distribution of these parameters to reflect uncertainty. Where possible, this should be based on the available data from studies, supplemented where necessary by expert opinion. The specified prior distributions should relate to second order uncertainty rather than the variability in parameter values, and care should be taken to ensure that the prior distributions chosen are consistent with any logical bounds on the parameter values.'
	'… in some situations it should be very clear that such a relationship [covariant] does exist, in which case these parameters should follow an appropriate joint distribution in a probabilistic analysis.'
Sculpher *et al*., 2000[38]	'… if a stochastic analysis is undertaken, the analyst should be clear about, and justify, their choice of statistical distributions to model the uncertainty.'
Weinstein *et al*., 2003[34]	'If cohort simulation is used, sensitivity analysis may be done using probabilistic (Monte Carlo, second-order) simulation, using the specified probability distributions of parameter inputs.'
	'In specifying those parameter distributions, care should be taken to ensure that interdependence among parameters is reflected properly in the joint distribution of parameters.'
NICE, 2004[24]	'Within a probabilistic analysis it is also helpful to present the contribution of the uncertainty in each parameter to overall decision uncertainty. This can be achieved using expected-value-of-information methods.'
O'Hagan *et al*., 2005[39]	'Formally, we require a joint probability distribution for all the uncertain, parameters. Only in the case where the parameters are statistically independent is it enough to formulate a probability distribution for each parameter separately; otherwise it is necessary to think about correlation between parameters. Although often assumed without comment, independence is a strong assumption.'
Ades *et al*., 2006[25]	'Monte Carlo simulation from the joint posterior distribution [is suggested because it] captures the correlation structure, delivers correct computation of expected costs and benefits based on all the evidence, as well as a correct sensitivity analysis.'
NICE, 2008[5]	'The distributions chosen for probabilistic sensitivity analysis should not be arbitrarily chosen, but chosen to represent the available evidence on the parameter of interest, and the use should be justified. Formal elicitation methods are available if there is a lack of data to inform the mean value and associated distribution of a parameters. If there are alternative plausible distributions that could be used to represent uncertainty in parameter values, this should be explored by separate probabilistic analysis of these scenarios.'
	'Evidence about the extent of correlation between individual parameters should be carefully considered and reflected in the probabilistic analysis. Assumptions made about the correlations should be clearly presented.'

Chapter 3

Review of the use of sensitivity analysis in assessment documents for recent NICE appraisals

This chapter reports the work carried out in the second phase of the project, namely to review the use of sensitivity analysis in general, and PSA in particular, in recent technology assessment reports (TARs) prepared by independent academic teams for NICE. The focus of the work was on the documents available to the NICE Technology Appraisal Committee. The essence of this chapter is a description of what was reported: we reserve comment for Chapter 6.

Methods

The 15 most recent TARs prepared by independent academic teams for NICE were retrieved. (See *Table 10* for brief details of these appraisals, and Appendix 3 for the NICE guidance decisions.) The appraisals spanned NICE technology appraisal waves 8–11, and covered a broad range of interventions and conditions. Seven academic teams were commissioned to undertake review and cost-effectiveness work for NICE, and work from most such teams is featured in this sample.

A preliminary checklist for this review of features of sensitivity analysis to be explored and identified in the TARs was constructed based on the findings of the literature review. This was refined as the process of completing the summaries was undertaken.

We classified the reasons for running the model into three groups, as follows:

- *Parameter uncertainty* involved alternative estimates of the expected costs and outcomes for the same patient group under the same methodological assumptions. This could include the use of different model structures, for example the inclusion or exclusion of a particular effect.
- *Methodological uncertainty* involved estimates of the expected costs and outcomes for the same patient group under different methodological assumptions. This included changing discount rates and time horizons.
- *Alternative patient groups* involved consideration of the expected costs and outcomes for different patient groups. The essence of this type of analysis is to support the possibility of different decisions for the different patient groups. If cost-effectiveness is performed on a population with some sort of case mix, with the expectation that a single decision be made for the population as a whole, then any variation of this case mix would be considered parameter uncertainty for the purposes of this report.

The full list of questions that form the checklist is shown in *Box 2*, and the data extraction form is given in Appendix 4. Clarification of the definitions is given below where appropriate.

Classification of parameters

Model parameters were classified into four groups:

- cost-related parameters: essentially unit costs for treatment
- utility-related parameters: essentially valuations of health states
- patient progression: this covers anything which changes the health status of patients, including transition probabilities, time to event, relative risk, etc.
- other parameters.

Basis for selecting range in deterministic analysis

The basis for selecting the range used in univariate sensitivity analysis could include any of the following:

- use of different estimates from the literature
- percentage changes (including removal of an effect as a special case of this)
- inclusion of an effect not considered in the base case

15

TABLE 10 *Descriptions of the 15 multiple technology appraisals reviewed in this project*

Appraisal number	Published appraisal reports	Population	Interventions	Comparators
TA103[40]	Psoriasis – efalizumab and etanercept	Adults with moderate to severe psoriasis	Efalizumab (Raptiva) Etanercept (Enbrel)	Acitretin, ciclosporin, hydroxycarbamide, methotrexate, fumarates or photo(chemo)therapy
TA105[41]	Colorectal cancer – laparoscopic surgery	People with surgically resectable colorectal cancer	Laparoscopic surgical techniques including: – laparoscopic (or laparoscopically-assisted) colectomy – hand port-assisted laparoscopic colectomy If appropriate comparison will be made between the different methods of laparoscopic surgery	Open colectomy
TA106[42]	Hepatitis C – peginterferon alfa	Adults with mild chronic hepatitis C	Dual therapy (pegylated interferon alfa and ribavirin) Monotherapy (pegylated interferon alfa) (for those who cannot tolerate ribavirin) Non-pegylated interferon alfa and ribavirin	Best standard care, including either treatment without any form of interferon therapy, or (for the pegylated interferon intervention) treatment with non-pegylated interferon, if the evidence allows
TA111[43]	Alzheimer's disease – donepezil, galantamine, rivastigmine (review) and memantine	People with Alzheimer's disease or people whose dementia is considered to be predominately Alzheimer's disease	Drugs for the treatment of Alzheimer's disease including donepezil, rivastigmine, galantamine and memantine, in-line with their marketing authorisation	Management without donepezil, rivastigmine, galantamine or memantine
TA112[44]	Breast cancer (early) – hormonal treatment	Postmenopausal women with early oestrogen-receptor-positive breast cancer (stages I and II of the American Joint Committee on Cancer system)	Aromatase inhibitors for adjuvant treatment: anastrozole, letrozole and exemestane	Comparison will be made with the oestrogen-receptor antagonist, tamoxifen
TA113[45]	Diabetes – inhaled insulin	Adults with Type 1 diabetes mellitus	Inhaled insulin (Exubera)	For Type 1 diabetes mellitus: – injected short-acting insulins or insulin analogues
		Adults with Type 2 diabetes mellitus who require insulin therapy		For Type 2 diabetes mellitus: – injected short-acting insulins or insulin analogues – anti-diabetic regimens without insulin

TABLE 10 *Descriptions of the 15 multiple technology appraisals reviewed in this project (continued)*

Appraisal number	Published appraisal reports	Population	Interventions	Comparators
TA114[46]	Drug misuse – methadone and buprenorphine	Opioid dependent adults (≥ 16 years old)	Methadone (oral) and buprenorphine (sublingual)	The interventions are adjuncts to current treatment strategies and therefore the comparator is treatment strategies without methadone (oral) and/or buprenorphine (sublingual)
TA115[47]	Drug misuse – naltrexone	Detoxified, formerly opioid-dependent individuals	Naltrexone (oral)	Any current treatment strategies in the maintenance of detoxified, formerly opioid-dependent individuals without naltrexone
TA117[48]	Hyperparathyroidism – cinacalcet	Adults with hyperparathyroidism secondary to renal failure	Cinacalcet as an adjunct to current standard treatments	Standard management strategies not including cinacalcet If the evidence allows, a comparison may be made with surgical parathyroidectomy, only in the subgroup of patients with very high levels of parathyroid hormone in whom this may be considered an option
TA118[49]	Colorectal cancer (metastatic) – bevacizumab and cetuximab	For bevacizumab: people with untreated metastatic colorectal cancer For cetuximab: people with EGFR-expressing metastatic colorectal cancer who failed irinotecan-including therapy	Bevacizumab (in combination with 5-FU/FA or with irinotecan plus 5-FU/FA) Cetuximab (in combination with irinotecan)	For bevacizumab: – established fluorouracil-containing or releasing regimen For cetuximab: – oxaliplatin in combination with 5-FU/FA by infusion – active/best supportive care (that is without chemotherapy)
TA120[50]	Heart failure – cardiac resynchronisation	People with heart failure (NYHA classification class) with cardiac dyssynchrony and LVSD	Cardiac resynchronisation therapy (biventricular pacing) devices It is intended that cardiac resynchronisation therapy CRT-P devices will be regarded as a class, as will cardiac resynchronisation therapy CRT-D devices	Comparator intervention: – optimal medical treatment For the consideration of cost effectiveness, further comparison of CRT-P, CRT-D and ICD will be required for different subgroups of patients

continued

17

TABLE 10 *Descriptions of the 15 multiple technology appraisals reviewed in this project (continued)*

Appraisal number	Published appraisal reports	Population	Interventions	Comparators
TA121[51]	Glioma (newly diagnosed and high grade) – carmustine implants and temozolomide	People with newly diagnosed high-grade glioma (grades III and IV) for whom surgery and radiotherapy are indicated	Carmustine implants Temozolomide Both are used as adjuncts to surgery and/or radiotherapy	Comparators may include: – surgery with or without radiotherapy alone – surgery, radiotherapy combined with antineoplastic agents other than those listed under interventions (for example nitrosourea-based regimens such as PCV)
TA128[52]	Haemorrhoid – stapled haemorroidopexy	People with haemorrhoids for whom surgery is considered	Stapled haemorrhoidectomy	Milligan–Morgan/Ferguson haemorrhoidectomy
TA130[53]	Rheumatoid arthritis – adalimumab, etanercept and infliximab	Adults (≥ 18 years old) with rheumatoid arthritis	Adalimumab, etanercept and infliximab	Management strategies with or without TNF-α inhibitors Other TNF-α inhibitors
TA132[54]	Hypercholesterolemia – ezetimibe	Adults with primary (heterozygous familial and non-familial) hypercholesterolaemia who are candidates for treatment with statins on the basis of their cardiovascular disease status or risk and: – whose condition is not appropriately controlled with a statin alone or – in whom a statin is considered inappropriate or is not tolerated This appraisal will not consider the use of ezetimibe in people with homozygous familial hypercholesterolaemia	Ezetimibe alone or in combination with a statin	In people with primary (heterozygous and non-familial) hypercholesterolaemia, which is not appropriately controlled with a statin alone, ezetimibe, coadministered with a statin, will be compared with: – optimal statin therapy – treatment with a statin in combination with other lipid regulating drugs, such as nicotinic acid/acipimox, bile acid resins and fibrates In people in whom a statin is considered inappropriate or is not tolerated, ezetimibe monotherapy will be compared with other lipid regulating drugs, including nicotinic acid/acipimox, bile acid resins and fibrates

5-FU/FA, 5-fluorouracil plus folinic acid; CRT-D, cardiac resynchronisation therapy including implantable cardioverter defibrillator; CRT-P, cardiac resynchronisation therapy pacemaker; EGFR, epidermal growth factor receptor; ICD, implantable cardioverter defibrillator; LVSD, left ventricular systolic dysfunction; NYHA, New York Heart Association; PCV, procarbazine, lomustine and vincristine; TNF-α, tumour necrosis factor-alpha.

BOX 2 *Questions used in the technology assessment report (TAR) review forms*

General information about the TAR

Type of model

Measure of health outcomes

Time horizon

Academic team

1. Parameter uncertainty

Does the study consider parameter uncertainty?

If yes, what approaches have been used to deal with parameter uncertainty?

If univariate sensitivity analysis was reported, was justification given for the choice of the parameters to vary and the selected values?

Cost-related parameters

Utility related

Patient progression

Other parameters

If multivariate sensitivity analysis was reported, was justification given for the choice of parameters to vary, and the selected values?

If other types of deterministic sensitivity analysis have been reported, was justification given for the choice of the parameters to vary, and the selected values?

How were the results of the deterministic sensitivity analysis reported?

If PSA was conducted, was justifications given for the choice of the parameter to vary, and the selected values?

Cost-related parameters

Utility related

Patient progression

Other parameters

    For each of the above:

        Type of distribution

        Explanation for the choice of distribution

        Distributions informed by data or by assumptions

Was there any assessment of correlation between model parameters? If parameters were correlated, was this correlation taken into account?

What was the number of replications conducted in the PSA?

How were the results of the PSA reported?

Was there any consideration of value of information?

2. Methodological uncertainty

Did the study address methodological uncertainty?

3. Alternative patient groups.

Did the study assess the cost-effectiveness of the intervention in different patient groups?

4. Additional analysis

- variation in clinical practice
- quantiles of data (including the use of upper and lower quartiles and extreme values)
- expert opinion
- alternative methods of estimation (using different sources or inclusion criteria for data synthesis).

If necessary, the basis was marked as unclear.

Distributions for probabilistic sensitivity analysis parameters

Within PSA, the basis for selection of a particular distribution for each parameter was explored. The issue here was what informed the distribution not the base case value. The options coded were:

- informed by new data available to the assessment group
- based on published values
- assumptions.

However, some cases simply had to be marked as unclear.

Results

Table 11 summarises the answers to the main questions listed in *Box 2*, for each of the 15 independent reports examined. Ten reports used Markov models, three used a decision tree, and one an individual sampling model. One group used the model submitted by the manufacturer rather than developing their own de novo model. However, in that case, the industry model was of a type not clear from public documents. All 15 assessment reports gave analysis outcomes in quality-adjusted life-years (QALYs), with two reports also giving outcomes in life-years gained. Time horizons ranged from 1 year to a lifetime. Reports were produced by six different academic teams.

All 15 reports included deterministic sensitivity analysis, and 13 reports also included PSA. The two exceptions where no PSA was undertaken were the one where the industry model was used and the one based on an individual sampling model.

Features of deterministic sensitivity analysis

The basis for selecting the range used in univariate sensitivity analysis is shown in *Table 12*. A similar table is also included in Appendix 5 (*Table 20*)

documenting which reports are counted in each cell of the table.

Table 12 reveals that the basis for selecting the ranges used in univariate sensitivity analyses was most commonly categorised as 'unclear' for all parameter categories. Practice also commonly included using estimates from the literature, as well as arbitrary percentage changes in the parameter value, or using data quantiles.

Multivariate sensitivity analysis was found in three reports. In all cases, this was a very limited range of combinations of parameters and the basis for selection was not clearly reported.

Other types of deterministic sensitivity analysis included scenario analysis in two reports and threshold analysis in four reports. The usual method of presentation of the deterministic sensitivity analysis was a table showing the new value of the incremental cost-effectiveness ratio (ICER) (occasionally with some other parameters) for each change made. TA117[48] and TA120[50] had graphs showing change in net monetary benefit (NMB). TA132[54] had a tornado diagram.

Threshold analysis (where included) was presented as a graph showing the NMB or ICER as a function of the variable being changed.

Features of probabilistic sensitivity analysis

Table 13 shows the types of distribution used, and *Table 14* shows whether the distribution was informed by data or assumptions. *Tables 21* and *22* in Appendix 5 give an indication of which reports feature in each table cell.

For cost-related parameters, the most common distribution was the lognormal, with gamma and normal also being seen frequently. For utility parameters, the beta distribution was by far the most common, and this distribution was also used widely for patient progression parameters. However, on that latter set of parameters, a wide range of distributions have been used. Explanation for the choice of distribution was clearly stated in only one report, TA121.[51]

For all parameter categories, the source of information for specifying the distribution was published values in the majority of cases. The use of assumptions was also widespread, with data

TABLE 11 *Summary of the 15 independent reports*

Technology appraisal	Academic team	Model type	Time horizon	Parameter uncertainty		Methodological uncertainty	Alternative patient groups
				Deterministic sensitivity analysis	Probabilistic sensitivity analysis		
TA103[40] Psoriasis – efalizumab and etanercept	CRD/CHE Technology Assessment Group, University of York	Markov	1 year	Univariate	Yes	No	Yes
TA105[41] Colorectal cancer – laparoscopic surgery	Health Services Research Unit, University of Aberdeen	Markov	25 years	Univariate Multivariate Threshold analysis	Yes	No	Yes
TA106[42] Hepatitis C – peginterferon alfa	Southampton Health Technology Assessments Centre, University of Southampton	Markov	Lifetime	Univariate	Yes	Yes	Yes
TA111[43] Alzheimer's disease – donepezil, galantamine, rivastigmine (review) and memantine	Southampton Health Technology Assessments Centre, University of Southampton	Markov	5 years	Univariate Multivariate	Yes	Yes	No
TA112[44] Breast cancer (early) – hormonal treatment	School of Health and Related Research, University of Sheffield	Markov	35 years	Univariate	Yes	Yes	Yes
TA113[45] Diabetes – inhaled insulin	Health Services Research Unit, University of Aberdeen	Unclear[a]	20 years	Univariate Multivariate Scenario analysis	No	Yes	Yes
TA114[46] Drug misuse – methadone and buprenorphine	West Midlands Health Technology Assessment Collaboration, University of Birmingham	Decision tree	1 year	Univariate	Yes	Yes	No
TA115[47] Drug misuse – naltrexone	West Midlands Health Technology Assessment Collaboration, University of Birmingham	Decision tree	1 year	Univariate	Yes	Yes	No
TA117[48] Hyperparathyroidism – cinacalcet	Peninsula Technology Assessment Group, University of Exeter	Markov	Lifetime	Univariate Threshold analysis	Yes	Yes	No
TA118[49] Colorectal cancer (metastatic) – bevacizumab and cetuximab	School of Health and Related Research, University of Sheffield	Markov	5 years	Univariate Scenario analysis	Yes	No	No

TABLE 11 Summary of the 15 independent reports (continued)

Technology appraisal	Academic team	Model type	Time horizon	Parameter uncertainty		Methodological uncertainty	Alternative patient groups
				Deterministic sensitivity analysis	Probabilistic sensitivity analysis		
TA120[50] Heart failure – cardiac resynchronisation	Peninsula Technology Assessment Group, University of Exeter	Markov	Lifetime	Univariate Threshold analysis	Yes	Yes	Yes
TA121[51] Glioma (newly diagnosed and high grade) – carmustine implants and temozolomide	Peninsula Technology Assessment Group, University of Exeter	Markov	5 years	Univariate Threshold analysis	Yes	Yes	Yes
TA128[52] Haemorrhoid – stapled haemorrhoidopexy	CRD/CHE Technology Assessment Group, University of York	Decision tree	3 years	Univariate	Yes	No	No
TA130[53] Rheumatoid arthritis – adalimumab, etanercept and infliximab	West Midlands Health Technology Assessment Collaboration, University of Birmingham	Individual sampling model	Lifetime	Univariate	No	No	No
TA132[54] Hypercholesterolemia – ezetimibe	School of Health and Related Research, University of Sheffield	Markov	Lifetime	Univariate	Yes	Yes	Yes

CHE, Centre for Health Economics; CRD, Centre for Reviews and Dissemination.
a The assessment group used the manufacturer's model – the model structure is not described, but refer to the manufacturer's report which is not publicly available.

TABLE 12 Univariate sensitivity analysis (cells indicate number of reports)

Basis for selecting ranges	Parameter categories			
	Cost	Utility	Patient	Other
Estimates from the literature	4	5	2	0
Arbitrary percentage changes	7	3	5	1
Removal of effect	1	0	1	0
Additional effect not included in base case	0	0	1	0
Variation in clinical practice	1	0	0	0
Quantiles of data[a]	3	1	3	0
Expert opinion	1	0	1	1
Alternative methods of estimation[b]	0	1	1	0
Unclear	8	5	6	1

a   Including use of upper and lower quartiles and extreme values.
b   Using different sources or inclusion criteria for data synthesis.

TABLE 13 Distributions used in probabilistic sensitivity analysis (cells indicate number of reports)

Distribution	Parameter categories			
	Cost	Utility	Patient	Other
Gamma	4	2	1	1
Normal	4	2	6	1
Bivariate normal	0	0	2	0
Multinormal	0	1	0	0
Triangular	2	0	2	0
Lognormal	5	0	3	0
Expnorminv	0	0	1	0
Beta	0	8	7	2
Dirichlet	0	0	1	0
Uniform	0	1	1	0
Poisson	0	0	1	0
Not stated	1	1	0	0

TABLE 14 Source of distribution for parameters (cells indicate number of reports)

Source of parameter distribution	Parameter categories			
	Cost	Utility	Patient	Other
Data	0	1	4	0
Published values	9	7	10	1
Assumptions	6	3	6	3
Unclear	2	2	1	0

representing an important source of information for the patient progression parameters.

It was rare for the issue of correlations between parameters to be considered explicitly as part of the PSA. Only one report addressed this issue, TA132, which included the use of joint distributions.[54]

Modelling process and reporting issues

Table 15 shows the distribution of the number of replications used in each technology appraisal model for the PSA.

Table 16 gives the methods of reporting of results. Only two TARs, TA120[50] and TA128[52], included any value of information analysis.

Methodological uncertainty and alternative patient groups

Table 17 shows the different forms of methodological uncertainty that were addressed.

TABLE 15 *Number of replications*

Number of replications	TAR numbers
1000	117,[48] 120,[50] 121,[51] 128,[52] 132[54]
2000	118[49]
5000 or 10,000	112[44]
10,000	105,[41] 114,[46] 115[47]
Not found	103,[40] 106,[42] 111[43]

TABLE 16 *Reporting of results*

Method for reporting results	TAR numbers
Tables for specific thresholds	103,[40] 106[42]
Scatterplots	111,[43] 112,[44] 114,[46] 115,[47] 117,[48] 118,[49] 120,[50] 121,[51] 128[52]
Cost-effectiveness acceptability curve	105,[41] 106,[42] 111,[43] 112,[44] 114,[46] 115,[47] 117,[48] 118,[49] 120,[50] 121,[51] 128,[52] 132[54]

TABLE 17 *Methodological uncertainty*

Aspect of methodological uncertainty explored	TAR numbers
Discount rates	106,[42] 111,[43] 112,[44] 120,[50] 121,[51] 132[54]
Time horizons	113,[45] 117,[48] 120,[50] 121,[51] 132[54]
Societal perspective	114,[46] 115,[47] 117[48]

Eight reports explored the issue of generalisability by providing estimates of costs and effects for alternative patient groups. The TAR numbers, along with the alternative groups considered, are listed as follows:

- TA103 – poor baseline quality of life.[40]
- TA105 – different stages of cancer.[41]
- TA106 – start age of the cohort and proportion of genotype I.[42]
- TA112 – different start age.[44]
- TA113 – different age and different duration of diabetes.[45]
- TA120 – starting age.[50]
- TA121 – groups with different prognoses.[51]
- TA132 – gender, age groups, primary or secondary cardiovascular disease, baseline low-density lipoprotein (LDL) cholesterol level.[54]

Conclusions

Practice by the commissioned academic teams in relation to univariate sensitivity analysis is highly variable, with considerable lack of clarity in relation to the methods used and the basis of the ranges employed. Further, the presentation of such analyses revealed room for improvement, with the use of diagrams, such as tornado figures, being very rare. In relation to PSA, the variability in the form of distribution used for similar parameters is surprising, and it is concerning that the justification for such choices is rarely given. The failure to consider correlations within PSA is another area of concern worthy of highlight. Chapter 4 will explore how the reported uncertainty was considered and used in the context of making coverage policy.

Chapter 4
Review of the NICE guidance documents

Introduction

The next stage of the work was to explore how uncertainties in the CEAs were handled by NICE in the process of making coverage decisions. In particular, we wished to assess the value placed on the sensitivity analysis components of the economic analyses, and identify any particular issues or concerns with the PSA components.

Methods

For all 15 NICE technology appraisals studied in this research, the Final Appraisal Determination guidance has been reviewed. The objective was to assess the policy impact of the sensitivity analysis, and of the PSA in particular. Given this focus, the review concentrated entirely on the section in the guidance document entitled 'Consideration of the evidence'. Issues of uncertainty and reporting of the sensitivity analyses were contained in all guidance documents as part of the evidence overview sections.

All documents were read by one member of the research team (SB), and selected text was extracted where reference was made to uncertainty in the context of the economic analysis, sensitivity analyses or a range of results for the CEA.

Across all 15 appraisal topics, the extracted text was then reviewed to identify themes relating to uncertainty and the use of sensitivity analyses.

Results

Seven themes relating broadly to uncertainty and sensitivity analyses were identified and are listed as follows:

- *Acknowledgement of uncertainties in data and/ or analyses* The issue of uncertainties around the analysis results was acknowledged and discussed explicitly in several documents.
- *Uncertainties regarding data inputs to the analysis* Concerns relating to the appropriate

or correct value to attach to specific model parameters were also raised.
- *Range of results* This refers to instances when a range of results from a sensitivity analysis is reported in the discussion.
- *Uncertainty and the coverage decision* In some instances, the issue of uncertainty is raised in the context of the coverage decision and the influence of the uncertainty on the Committee's willingness to make a positive decision.
- *Value attached to deterministic sensitivity analysis* Explicit reference is made in some documents to the usefulness of the sensitivity analysis, particularly the deterministic component.
- *Search for subgroups* The sensitivity analysis served as a route for identifying subgroups of patients, with quite different cost-effectiveness results, in many reports.
- *Structural uncertainties* Where the Committee was concerned about the appropriateness of the model structure, sensitivity analysis was seen as a route to provide supporting information.

Table 18 gives an indication of which themes were identified in relation to which technology appraisal. It is clear that some themes, notably the data uncertainties and subgroups, were prevalent in most appraisals, whereas others, such as structural uncertainties and use of ICER ranges, were very limited in their coverage.

This section of the chapter is structured by theme, with introductory text to introduce the theme and then quotes from the guidance document as evidence. The parenthesised number at the end of each quote is the number of the technology appraisal to which the quote relates.

Acknowledgement of uncertainties in the data and/or analyses

In many of the guidance documents, the issue of uncertainty was raised and acknowledged explicitly. It is evident that the Committee was aware of the fact that the cost-effectiveness estimates presented

TABLE 18 *Distribution of themes across appraisal topics*

Theme	TARs where theme identified
Acknowledgement of uncertainties in the data and/or analyses	103,[40] 112,[44] 115,[47] 118,[49] 130,[53] 132[54]
Uncertainties regarding data inputs to the analysis	103,[40] 105,[41] 106,[42] 111,[43] 112,[44] 113,[45] 118,[49] 120,[50] 121,[51] 128,[52] 130,[53] 132[54]
Range of results	111,[43] 132[54]
Uncertainty and the coverage decision	130,[53] 132[54]
Value attached to deterministic sensitivity analysis	111,[43] 112,[44] 113,[45] 121[51]
Search for subgroups	103,[40] 111,[43] 112,[44] 113,[45] 115,[47] 117,[48] 120,[50] 121,[51] 132[54]
Structural uncertainties	111,[43] 117[48]

to it were, in some instances, quite uncertain, and the wording of the guidance documents serves to emphasise this point repeatedly.

> The Committee was mindful that all the cost-effectiveness estimates were associated with uncertainty. (TA132[54])

> The Committee noted that these factors introduced considerable uncertainty into the estimates of cost effectiveness in all the models. (TA130[53])

> The Committee also noted that these estimates were associated with a high level of uncertainty …. (TA118[49])

> In considering the economic modelling the Committee recognised that there was considerable uncertainty in the estimates of cost effectiveness that had been produced. (TA103[40])

Uncertainties regarding data inputs to the analysis

The principal focus of the discussion of uncertainty was in terms of the key data inputs into the cost-effectiveness model or analysis. Such uncertainties, very commonly in relation to effectiveness data, were expressed as a concern and clearly led to some degree of caution on the part of the Committee in reaching a positive judgement. A broad range of parameter types are referred to where uncertainties in data were mentioned, notably the longer-term effectiveness of the technologies, the health state utilities and side-effect profiles.

> It [the Committee] was aware of the lack of data for ezetimibe on cardiovascular outcomes

and the possibility that future adverse events relating to ezetimibe might become apparent with extended use over time. (TA132[54])

> The Committee considered that there were significant uncertainties relating to the assumptions in the models, most notably about long-term disease progression and stabilisation while responding to tumour necrosis factor-alpha (TNF-α) inhibitors and conventional DMARDs [disease modifying antirheumatic drugs] in patients with established disease. (TA130[53])

> The Committee recognised that there were few data to inform estimates of long-term disease progression. (TA130[53])

> Furthermore, the Committee understood that, because there was little direct evidence, there remains uncertainty over the precise utility values associated with pain and the overall benefits of stapled haemorrhoidopexy. (TA128[52])

> The Committee considered there to be insufficient evidence on the effectiveness of CRT in patients with heart failure associated with atrial fibrillation for it to make recommendations for this group … . (TA120[50])

> The Committee discussed the uncertainties around the estimates of utility for patients with metastatic colorectal cancer. (TA118[49])

> This uncertainty related principally to estimates of the efficacy of the alternative interventions and treatment regimens and the evidence on long-term outcomes. (TA103[40])

Range of results

Despite the explicit acknowledgement of uncertainty in the guidance documents, very few of those reviewed explicitly discussed the impact of the uncertainty on the cost-effectiveness results. Note that this review was limited to the 'Consideration of the evidence' section, and the report of the evidence always included detail of the base case and sensitivity analysis results. Nevertheless, only two of the guidance documents reported a range of results in the use of evidence section, where discussion focused on how the Committee made use of the evidence to arrive at a coverage decision. The ranges reported in the two cases came from deterministic sensitivity analyses and not from PSAs.

> The Committee noted that the incremental costs per QALY gained of ezetimibe … ranged from £24,000 to £43,000 … . (TA132[54])

> It further noted that the incremental costs per QALY gained for ezetimibe monotherapy versus no treatment, assuming a baseline LDL cholesterol concentration of 3.5 mmol/litre, ranged from £24,000 to £30,000 between the ages of 45 and 65 years and from £33,000 to £42,000 at age 75 years. (TA132[54])

> It noted that the new estimates of cost effectiveness would then be in the range of 36,000 to 50,000 per QALY gained. (TA111[43])

> A one-way sensitivity analysis on the augmented base case plus the element for carer benefits was associated with cost-effectiveness estimates ranging from 31,000 to 43,000 per QALY gained. (TA111[43])

Uncertainty and the coverage decision

In two of the appraisals, uncertainty was raised explicitly as a factor having direct influence on the Committee's deliberations around the coverage decision itself. Specifically, uncertainties around the cost-effectiveness results were cited as one of the factors leading the Committee to make a decision not to recommend the technology in question. In both cases, uncertainty was associated with a decision not to recommend use of the technology in the NHS.

> Given the uncertainty around the range of incremental cost-effectiveness ratios (ICERs) for this scenario … the Committee agreed that

ezetimibe coadministered with a statin should not be recommended. (TA132[54])

> Taking into consideration clinical practice and the uncertainties in the estimates of cost effectiveness of TNF-α inhibitors, the Committee was not persuaded that the use of TNF-α inhibitors after the failure of one conventional DMARD would be an appropriate use of NHS resources. (TA130[53])

Value attached to deterministic sensitivity analysis

Where reference was made explicitly to the sensitivity analysis part of the assessment report, in all cases it was the deterministic sensitivity analysis, and not the PSA, that was cited. Further, when such references were made, the comments always indicated that the deterministic analysis was helpful to the Committee. The indication appears to be that such sensitivity analyses supported the Committee in identifying where the focus needs to be for the discussion and for challenging of the evidence and assumptions. Where the sensitivity analysis was able to demonstrate that the cost-effectiveness result was insensitive to plausible variation in a particular parameter value or to a structural model assumption, this appears to have provided considerable reassurance to the Committee.

> The Committee noted that in both models the main influence on the ICERs was the utility estimates used. (TA128[52])

> It was also aware that a sensitivity analysis demonstrated that the model was not sensitive to this time-dependency assumption. It also concluded that the results of the sensitivity analyses showed that the overall gain from treatment would have to increase considerably for the ICERs to decrease substantially. (TA121[51])

> The Committee concluded that the ICERs remained high for the whole study population when these alternative measures of progression-free survival were used in the analysis and were also subject to considerable uncertainty. (TA121[51])

> The Committee additionally considered the Assessment Group's economic modelling of improved uptake of insulin or intensification in type 2 diabetes (in the absence of any utility

gain) and were persuaded that this sensitivity analysis indicated that, even if earlier uptake were assumed, this effect alone was insufficient to provide support for a cost-effective use off this technology for most patients. (TA113[45])

It heard from the clinical specialists that the 'benefits maintained' scenario, used by the Assessment Group in a sensitivity analysis, provides the most relevant analysis. Therefore, the Committee based its discussion on the cost-effectiveness analysis using the 'benefits maintained' assumption, and it noted that the incremental cost per QALY gained for aromatase inhibitors, compared with tamoxifen, was less than £20,000 for all treatment strategies. It further noted that the incremental cost per QALY gained did not increase to more than £20,000 when the predicted fracture risk was increased. (TA112[44])

After hearing testimony from clinical and patient experts, the Committee considered a number of issues that might alter the estimates of the cost effectiveness of the AChE [acetylcholinesterase] inhibitors from the base case presented by the Assessment Group. At the Committee's request the NICE secretariat provided an augmented base case with additional sensitivity analyses for consideration by the Committee … .(TA111[43])

Search for subgroups and the role of deterministic sensitivity analyses

One of the principal roles of the deterministic sensitivity analyses was in the search for subgroups of patients for whom the technology might represent better (or worse) value for money for the NHS. This is a demonstration of the Committee seeking to deliver on its charge and formal remit around cost-effectiveness. This role was expressed repeatedly in the guidance documents and reflects its desire to make the most use of the available evidence.

The Committee was persuaded that this ICER was a conservative figure that underestimated the cost effectiveness of naltrexone in people who were highly motivated to remain abstinent and who were enrolled in a supervised treatment programme. (TA115[47])

The Committee therefore explored other factors that could potentially improve the cost effectiveness of inhaled insulin. Additionally,

the Committee explored if there were any subgroups of people with diabetes who would gain greater clinical benefit from inhaled insulin. (TA113[45])

For some technologies where the CEAs in general terms indicated a negative decision, the subgroup search, facilitated by the deterministic sensitivity analysis, occasionally allowed a positive recommendation to be made for a subgroup of patients. The following examples indicate that formal subgroup analyses, when alternative cost-effectiveness estimates were provided through the sensitivity analysis, were potentially influential in the Committee's decision-making.

The Committee noted that the incremental costs per QALY gained of ezetimibe plus simvastatin compared with atorvastatin were all below £4600 regardless of age, sex and CVD history. (TA132[54])

It [the Committee] further noted that the incremental costs per QALY gained for ezetimibe monotherapy versus no treatment, assuming a baseline LDL cholesterol concentration of 3.5 mmol/litre, ranged from £24,000 to £30,000 between the ages of 45 and 65 years and from £33,000 to £42,000 at age 75 years. (TA132[54])

The Committee noted that the ICER from the Assessment Group's economic analysis based on measures of functional status was £23,100 per QALY gained in the subgroup of patients in whom 90% or more tumour resection had been achieved. It concluded that carmustine implants would be cost effective for this subgroup of patients. (TA121[51])

The Committee noted that the Assessment Group's economic analysis showed a substantial difference in the estimates of cost effectiveness of temozolomide for patients with a WHO performance status of 0 and patients with a WHO performance status of 1. … The Committee considered the uncertainty around the treatment effects for these two subgroups and noted that the confidence intervals overlapped. It heard from the Assessment Group that if this uncertainty was taken into account in the economic analysis, confidence intervals around the ICERs were likely to overlap. The Committee concluded that it was not appropriate to distinguish between these two subgroups. (TA121[51])

The Committee considered that if the high risk of adverse consequences and the poor quality of life experienced by the subgroup of patients described in 4.3.7 (in whom surgical parathyroidectomy is not possible) were taken into account, it was unlikely that the ICER for cinacalcet would be reduced to the extent that it could be considered a cost-effective use of NHS resources. (TA117[48])

The Committee was, however, persuaded that inhaled insulin could be cost effective in those people with diabetes who are unable to inject because they experience marked and persistent fear of injections or because they cannot find suitable injection sites (for example, due to severe lipohypertrophy) which cannot be overcome by patient support and education or by injection site rotation. Furthermore, the Committee agreed that it was likely that the utility gain in this patient group would be sufficiently high to make the use of inhaled insulin cost effective. This judgement was based on the modelling provided by the Assessment Group, which showed that the use of a utility gain of 0.04 for inhaled insulin led to ICERs of less than £25,000. (TA113[45])

It therefore considered whether it might be possible to define, prospectively, subgroups of people with Alzheimer's disease who might benefit more than average, and for whom AChE inhibitors might be a relatively cost-effective treatment. In accepting the subgroup analyses using severity of cognitive impairment, the Committee reviewed the estimates of cost-effectiveness. It noted that for people with moderate Alzheimer's disease these estimates ranged from 23,000 to 35,000 depending on the choice of AChE inhibitor and by including carer benefits in the augmented base case. Conversely, the Committee noted that for the subgroup of people with mild Alzheimer's disease estimates of cost effectiveness ranged from 56,000 to 72,000 depending on the choice of AChE inhibitor and by including carer benefits in the augmented base case. (TA111[43])

Structural uncertainties causing problems in making a decision

In a small number of cases, the guidance document highlights the difficulties that the Committee faces when dealing with structural uncertainties. That is, in situations where the structure of the model was

perceived to be out-of-line with clinical practice or excluded a parameter deemed to be of importance to the question at hand, then the Committee faced the prospect of making a decision using suboptimal analyses. Again, the value of deterministic sensitivity analyses in these circumstances is highlighted.

Although accepting the Assessment Group's approach to modelling the decision problem, the Committee recognised that the ranges of PTH [parathyroid hormone] levels that defined health states in the model were arbitrary and were not intended to define the goals of a treatment strategy. The Committee therefore considered that the use of these ranges by the manufacturer in defining treatment strategies did not reflect clinically appropriate treatment goals and was not consistent with the does-titration regimen described in the SPC [study protocol]. (TA117[48])

Benefits to carers

The Committee decided that it was reasonable to add to the modelling of the augmented base case a utility benefit of 0.01 for carers. It noted that the new estimates of cost effectiveness would then be in the range of 36,000 to 50,000 per QALY gained. (TA111[43])

Behavioural symptoms in Alzheimer's disease

On balance, the Committee decided that it would be appropriate to include an effect of AChE inhibitors on behavioural symptoms associated with dementia. A one-way sensitivity analysis on the augmented base case plus the element for carer benefits was associated with cost-effectiveness estimates ranging from 31,000 to 43,000 per QALY gained. (TA111[43])

Conclusions

Caution is required when interpreting these findings. The method employed assumes that the text of the guidance document (i.e. the arguments and information used to justify decisions) accurately reflects the thinking of the Committee on the day of the decision (i.e. the information that actually informed the decision). It would be wrong to think that the guidance documents provide a direct window into the factors which actually led to a particular decision. The documents are drafted by the NICE secretariat who, although

present during all discussions, has the unenviable task of capturing the essence of the discussion and determining what the key 'considerations of the evidence' were. Further, even if the document accurately captures the issues discussed by the Committee, it is a further leap to assume that the document gives insight into the value placed on different components of the analysis (e.g. sensitivity analysis).

This review of the policy documents indicates that uncertainty appears to be considered explicitly in the process of arriving at a decision, and the focus tends to be on parameter uncertainty predominantly. The cited ranges in the policy documents and the most value in supporting decision-making appear to have come from the deterministic analyses rather than from the probabilistic approaches. This may in part reflect an issue of poor understanding of PSA (explored further in Chapter 5) or may reveal the value of deterministic approaches, especially in the search for subgroups. The apparent association between high levels of uncertainty and negative decisions will be explored further in Chapters 5 and 6.

Chapter 5

The views of policy-makers on sensitivity analysis: data from interviews with members of the NICE Technology Appraisal Committee

Introduction

The next stage of the project was to explore the views of those charged with making use of CEAs (including the sensitivity analysis components) in order to formulate technology coverage policy at NICE, namely the members of the NICE Technology Appraisal Committee. In particular, we wished to assess their views on how uncertainty was handled in the assessment reports, the value they place on the sensitivity analysis components of the economic analyses conducted for NICE, and any particular issues they might have with the PSA components.

Methods

The original plan was to conduct a small number of new interviews with members of the Committee. This path was not followed for two reasons. First, there were practical constraints around ethical approvals, coupled with time pressures for this small project. Second, interviews with members of the Committee had recently (2003/4) been undertaken by a Birmingham-based research team exploring the use of CEA in decision-making by NICE.[1] In a desire to maximise the value from existing data and not wanting unnecessarily to burden Committee members further, we made a decision to interrogate the existing qualitative data rather than conduct a further round of interviews.

The NICE interview data have been written up and published elsewhere,[1–3] and so only brief details of the data collection methods are given here. Research ethics committee approval was obtained from the West Midlands Multi-Centre Research Ethics Committee. Interviews were conducted with a sample of 28 NICE Technology Appraisal Committee members, focusing on the use of economic analyses in the appraisal determination. *Table 19* gives a breakdown of the interview sample, indicating that broad coverage of the different groupings represented on the Committee was

achieved. Interviewees were required to provide written consent to involvement in the research, and all interviews were tape recorded. With a single exception, all of those approached for interview consented. A pre-established semi-structured interview schedule was used (see Appendix 6).

In the original research, the primary research questions concerning the use of CEA formed an initial structure for categorising data, and then new themes and subthemes were identified as data were collected and analysed. Analysis of all data was performed by two researchers operating independently who compared their findings and discussed any differences in the themes each had identified. The research team conducted 'open coding', whereby the vast majority of research data were placed into categories. These coded data were then taken for use in the current work on sensitivity analysis. Through a process of review of codes and of all raw data, comments and views relating to uncertainty in the CEAs, and to sensitivity analysis in particular, were identified and further classified.

Results

Relevant quotes were identified in 11 interview transcripts. Interviewees categorised as 'methodologist', including health economists, contributed the majority of the data (6 of the 11 interviewees) (see *Table 19*). In the remainder of the transcripts ($n = 17$), there was no discussion of uncertainty relating to the cost-effectiveness work in general or to sensitivity analysis in particular.

The themes identified from the transcripts in which uncertainty was discussed are listed below:

* support for deterministic sensitivity analysis
* support for PSA
* concerns about partial coverage of uncertainty
* challenges relating to the interpretation of sensitivity analysis.

This section of the chapter is structured by theme, which is introduced by explanatory text and then quotes from the interviews are given as evidence. The number in square brackets at the end of each quote is the number of the interviewee, given in order to indicate quotes from the same person.

Support for deterministic sensitivity analysis

The interviewees spoke repeatedly of the value of univariate and multivariate deterministic sensitivity analysis in highlighting which issues or model parameters are critical to driving a decision, and which can largely be ignored. They point to the process by which deterministic sensitivity analysis helps in focusing the discussion and questioning of experts at the Committee meetings and helps in the process of reaching a coverage decision.

> I think sometimes when we have settled on an economic model it's sort of believed as if it's gospel. And clearly you could change one or two assumptions a small amount, and the whole thing changes. Now normally the assessment team has done some of that sensitivity analysis to illustrate it for us. But I think perhaps a bit more clear presentation of that kind of thing would be useful. Yeah, perhaps a bit more simple and clear presentation of the sensitivity analysis and of the things that, with small changes, might make major differences to the model. And it helps you look at targeting and other things then if you realise that … . [1]

> I think we were all happy with the modelling and it gave a nice cost-effectiveness figure – about ten thousand. … and as the report said that was very robust to changing assumptions in the sensitivity analysis, it was very robust. … And in this particular case they did a sensitivity analysis showing that whether you assume that there was about a 0.75 quality of life or whether it was down to about 0.33 didn't actually make that much difference as to whether it was cost-effective at that threshold level so we're talking about quite large differences in the quality if life figure not actually changing our view on whether it's cost-effective. [2]

> The most useful thing about the economic analysis is it focuses the discussion on what actually matters. … What is it that can actually switch a decision on this? And do we believe that there are plausible scenarios that could be run which might switch us? If there are maybe

we should go off and ask them to be done. And I think sometimes … those things only become clear in the committee. Things become clear during the scoping and the TAR teams … provide us with a series of sensitivity analyses and they look at industry submission and so we do get quite a lot. But sometimes its only in the process of that argument and discussion with the experts and seeing all the other submissions that it becomes clear that really this all swings on maybe one or two issues. [3]

Support for probabilistic sensitivity analysis

Strong support was also expressed for PSA by several members of the Committee. The principal argument put forward is that it provides an indication of the parameter uncertainty around the ICER value, and so the Committee is not then making decisions on the basis of point estimate cost-effectiveness values. One of the interviewees quoted below indicates explicitly that the level of uncertainty, and hence the width of the confidence interval around an ICER, should matter when making technology coverage decisions. Thus, a higher mean ICER with narrow confidence limit might be more attractive than a lower mean ICER with a very wide confidence interval. Thus, for some members of the Committee, probabilistic analyses were seen as key to informing such decisions.

> I think the difficulty with this was partly the problem around uncertainty and the extent of the uncertainty around the estimates. I didn't think they'd really demonstrated that really well. You know, confidence intervals are obviously problematic anyway, but they didn't really do any kind of proper probabilistic analysis. [4]

> I think it's very good to have probabilistic sensitivity analysis to include uncertainty around your parameter estimates at the distribution, rather than just take … point estimates … and then do sensitivity analysis around that. I think that's nice. It's not always done but I think it is helpful … I think having that in there is great – to have some confidence intervals around those final cost per QALY figures. So that's important. [2]

> … if you're going for a cost per QALY of say, for example say £30k, if you get one that comes in … with a cost per QALY of £28k but what

they're actually saying is, given the uncertainty this could be anything from perhaps even £12k to £60k. And if you put that through, you're accepting that there may be a very high cost per QALY. Something else comes in at £31k per QALY but actually because the evidence is very good you know it really is between 28 and 33, that might be less risk. And that is an issue, that if you've got a slightly expensive thing with very tight limits, you might be willing to accept it because you're not taking a big risk. [1]

We usually come up with some cost per QALY … with sensitivity analysis. What I'm saying is quite often it won't be stochastic, won't have a CEAC [cost-effectiveness acceptability curve], and these are natural consequences of capacity in the TAR industry at the moment. But NICE should be actually saying 'This is what we want as our output, our model and we're going to fund it properly'. [5]

Concerns about partial coverage of uncertainty

Some concerns were raised about the extent to which the probabilistic analyses captured the full level of uncertainty in the model. The selection of some parameters around which to place distributions for the PSA, with others not being included, is highlighted in a quote below. The implication is that the PSA, when conducted in such a partial manner, might under-report the true level of uncertainty around the cost-effectiveness result.

I don't always necessarily believe the confidence intervals that come up from the modelling are actually… I think sometimes there're too narrow because they don't take in to account all the uncertainties that we have and so the confidence can be so wide that really I would prefer not to make any decisions at all. So I think the health economist don't take enough … cognisance of uncertainty. [6]

I probably would have had a quibble with the model that probably there wasn't enough uncertainty and there were certain bits of it where I think they took a rather narrow range of figures, certainly for some of the costs. I don't think there was enough uncertainty in there, for example when we discussed this issue, if you have a lot more people needing infusion and it takes six hours, almost a whole day for the first infusion you might have to

build a few more facilities to do that so there is a bit of uncertainty in there which wasn't reflected … . [2]

Challenges in the interpretation of sensitivity analyses

The interviewees raised issues around the fact that the communication of the results from sensitivity analyses were less than optimal. This applied to traditional deterministic sensitivity analysis, but more particularly to PSA. There is a message for a more detailed and clearer explanation of the analyses to ensure that the significant implications are well understood by all members of the Committee. In relation to the PSA, there was an honest reflection by Committee members on the need for more people on the Committee to understand the PSA analyses and results, including those with a health economics background. Further, there seems to be confusion around how to use the cost-effectiveness acceptability curve in arriving at a coverage decision, with the suggestion made that consideration needs to be given to what represents an agreed threshold or cut-off probability value. Further, the suggestion is made again that there might be value in reporting the PSA as a conventional confidence interval around the ICER where that is possible. However, when the scatter of cost-effectiveness points spans several quadrants on the cost-effectiveness plane then the confidence interval estimation is more problematic. To our knowledge, the best attempt to define confidence intervals outside the north-east quadrant has been by Cook and Heyse,[55] but even this does not give satisfactory answers when the distribution covers all four quadrants of the cost-effectiveness plane.

… the sensitivity analysis that they did is all in the bag, but I think the significance of it wasn't really brought out in the document. [4]

I mean they do the sensitivity models but it's very difficult to get your head around that, I think, as a non-health economist. [7]

The other area which … has come up in the past – and people do struggle with – is uncertainty. And I don't think anybody quite knows how to handle cost-effectiveness acceptability curves at the moment. For some people it's a technical problem of understanding what they are. For those who understand what they are, they still don't understand what they should do with it. You know, most people understand 95% confidence

TABLE 19 *Composition of interview sample from the NICE Technology Appraisal Committee*

Area of expertise	Number of Committee members interviewed	Number of interviewees providing material
Medical (e.g. GP, physician, surgeon)	13	3
Other clinical (e.g. nurse, pharmacist)	3	0
Methodologists (e.g. health economist, statistician)	6	6
Managers	2	1
Patient 'advocate'	3	1
Manufacturer 'representative'	1	0

intervals, or I think they do. But I think very few people are quite sure what to do with CEACs [cost-effectiveness acceptability curves], particularly when you have several interventions. It starts getting very complicated … and there's no agreed threshold or cut-off for anything. And so, often they're presented but nobody is really much the wiser. … And I don't think we [health economists] have answered their questions very well so far. I think we've fudged it a bit to be honest. [4]

I'm not sure it [graphical representation of the CEAC] adds… I mean if you just simply give the confidence interval that you pick out from that cost-effectiveness acceptability curve, that probably would do. I'm not sure about those curves. People didn't really pick up on it. … I prefer, just as a personal preference I think the cost-effectiveness plane is more helpful… Different people have different levels of understanding and I'm sure there are people on the committee who wouldn't really understand the details of what that means although I think they would understand that 'Look if you take the 5th percentile and the 95th percentile then you have a nice confidence interval' type of thing. That's all that we really get out of that. [2]

Discussion

The main messages coming through from the interview data are:

- There is considerable value attached to conventional univariate and multivariate deterministic sensitivity analysis. Such analyses serve to highlight which model parameters are critical to driving a decision, and which

can largely be ignored. This supports the Committee in giving focus to the process of questioning the experts and challenging the data.
- Among those who commented on PSA, there is strong support for this approach principally because it provides an indication of the parameter uncertainty around the ICER value.
- In general, those Committee members who mentioned the issue expressed the view that the level of uncertainty should be a consideration when making a technology coverage decision. When uncertainty is greater, the decision would tend towards a negative.
- A concern expressed about PSA was that it can under-report the true level of uncertainty through the selection of a subset of parameters for inclusion in the analysis.
- The communication of sensitivity analysis results is less than optimal. A more detailed and clearer explanation of the sensitivity analysis is required to ensure that the significant implications are well understood by all Committee members. In particular, the PSA appears not to be well understood by Committee members and, even for those who have insight into the method, there is confusion around how to use the cost-effectiveness acceptability curve in arriving at a coverage decision.

The data drawn on in this chapter come from an earlier research project – new interviews with members of the NICE Technology Appraisal Committee have not been undertaken. A drawback of this approach is that the interviews asked rather general questions about CEA and did not focus specifically on uncertainty and sensitivity analyses. Further, the interviews were conducted in 2003/4 and so reflect views on technology appraisal methods being used at that time. For the majority

of the interviews, the data were collected before the launch of the April 2004 NICE *Guide to the methods of technology appraisal*,[5,24] which made the use of PSA mandatory. It is, of course, possible that the more widespread use of PSA after 2004 has led to a different appreciation of its weaknesses and strengths for decision-making. However, the limited resource available to the current project meant that only a very small number of new interviews would be possible, and so the gains in terms of volume and quality of data were thought to outweigh the negatives.

Chapter 6
Discussion and conclusions

Introduction

As indicated at the outset of the report, we believe that an appropriate characterisation of uncertainty is an essential component in an economic analysis of a health-care technology. Thus, the intention behind the work reported here is to provide recommendations on how sensitivity analyses and work relating to exploring uncertainty in CEAs can be strengthened.

Thus, the research addressed the following questions:

- How do we define good practice in sensitivity analysis in general and PSA in particular?
- To what extent has good practice been adhered to in economic evaluations undertaken by independent academic teams for NICE over recent years?
- What policy impact does sensitivity analysis have in the context of NICE?
- What views do policy-makers have on sensitivity analysis and uncertainty, and what use is made of sensitivity analysis in policy decision-making?

This chapter will initially review the main findings from each component of the project, and comment on the strengths and weaknesses of our work. The chapter will then draw together the principal recommendations both for the practice of sensitivity analysis and further methodological research.

Main findings

The review work (see Chapter 2) has provided considerable support for traditional deterministic sensitivity analysis, indicating an important role as a natural starting point for the investigation of uncertainty in cost-effectiveness work. This form of analysis provides a route through which some of the key drivers of the cost-effectiveness results can best be revealed. However, there are important concerns raised in relation to simple approaches to exploring uncertainty, such as: selection bias in the choice of parameters; difficulties in relation

to their interpretation, as there are no guidelines on what represents a robust result in terms of level of variability; and the failure to easily capture interactions and correlations between parameters. Threshold analysis is seen to be particularly useful in the situation in which the value of a particular parameter is unknown or indeterminate, such as drug price.

Much of the literature is also supportive of the use of PSA to capture parameter uncertainty in cost-effectiveness work. Further, where correlation between parameters has been correctly specified in the model, the PSA provides the correct estimates of mean costs and effects even in the situation of non-linear models. The concerns expressed about PSA relate partly to practice, namely the suggestions that an assumption of independence between parameters is commonly made and that choice of parameter distribution can sometimes be inappropriate.[6]

Through the examination of the TARs relating to 15 NICE technology appraisals (see Chapter 3), it is evident that extensive sensitivity analyses are being conducted. All 15 reports included deterministic sensitivity analysis, and 13 reports also included PSA. However, practice in relation to this aspect of the analyses was variable. For example, in the work on deterministic sensitivity analysis the basis for selecting the ranges used in univariate analyses was commonly unclear. Multivariate sensitivity analysis was found in only three reports and, in all cases, this included a very limited range of combinations of parameters and the basis for selection was not clearly reported.

In relation to PSA, a wide range of distributional functions have been used for the same parameter category. In many cases the choice has probably not materially affected the results, but this would be interesting and important to explore. Encouragingly, for all parameter categories, the source of information for specifying the distribution was published values in the majority of cases. However, only one report explicitly considered the issue of parameter correlation as part of the PSA.

An alternative to making assumptions about distributions around parameters is to employ a resampling technique such as bootstrapping. In settings in which data are available, such methods do represent a real alternative, but the context of the work explored here (i.e. systematic reviews and decision analytic models for NICE) is not one where original data to inform model parameters are typically available. Thus, in work for NICE, the option of using resampling techniques does not generally exist, as evidenced by the fact that none of the reports reviewed in Chapter 3 used such methods.

Issues around structural uncertainty have not been explored to any great extent in the context of the work for NICE. Given the time constraints on such work and the policy rather than methodological focus, this is not surprising. Similarly, uncertainties relating to methodological issues have also been largely ignored, aside from time horizon, discount rates and perspective. The proscriptive nature of the NICE methods guidance again makes it unsurprising that such uncertainties tend not to be the concern of analysts commissioned by NICE.

The review of guidance documents (see Chapter 4) has revealed that uncertainty is a factor considered by the Institute and the Technology Appraisal Committee in arriving at coverage decisions. The main uncertainties documented in the guidance report concern data inputs on effectiveness, utilities, etc. It is evident that the results of deterministic sensitivity analyses are valued, and where ranges of results were given in the 'Consideration of the evidence' section, these were always from deterministic analyses. The main use of such sensitivity analyses appears to be in the search for subgroups of patients for whom the intervention in question might prove most cost-effective. In two of the appraisals, uncertainty was raised explicitly as a factor having direct influence on the Committee's deliberations around the coverage decision itself. Specifically, uncertainties around the cost-effectiveness results were cited as one of the factors leading the Committee to make a decision not to recommend the technology in question. The question of how uncertainty should play out in relation to the technology coverage decision is important and unresolved. The data reported here suggest that uncertainty is seen as a reason for caution and thus tends to be associated with a negative decision.

The interview data reported in Chapter 5 reveal that a minority of interviewees raised issues around uncertainty or sensitivity analysis. Possible interpretations of this are that such issues are not of concern because they are being capably handled in assessment reports or that the importance of uncertainty issues is not appreciated by those making decisions. Those who did share views on uncertainty issues indicated support for deterministic sensitivity analysis from the users of the analyses, i.e. decision-makers at NICE. Similarly, a strong endorsement for PSA was also revealed, although the practice of PSA and the partial coverage of parameters was a concern raised by some interviewees. Finally, it is clear that the challenge of effectively communicating results of sensitivity analyses, especially for more sophisticated analyses such as PSA, has not been overcome, and some interviewees honestly admitted to a lack of understanding of the analyses being presented. However, related to this is the lack of clarity concerning the appropriate interpretation of PSA outputs, such as cost-effectiveness acceptability curves, in the context of making a coverage decision. Clear guidance on interpretation of outputs from PSAs would be welcomed.

Strengths and weaknesses of the work

Strengths

- Comprehensive and systematic literature review.
- In-depth review of 15 TARs prepared for NICE as part of the technology appraisal programme.
- Detailed review of the guidance documents in order to explore the policy impact of the sensitivity analysis in each of the 15 cases studied.
- Interview data analysed from 28 members of the NICE Technology Appraisal Committee to explore how economic evaluations are viewed, their strengths and weaknesses, and any opinions on the issue of uncertainty and the sensitivity analysis methods.

Weaknesses

- Principally based upon literature identified through formal searches, therefore textbooks have not been included.
- Focus was on cost-effectiveness work undertaken by the independent academic teams for NICE, and so the cost-effectiveness work being undertaken for industry, as part of

the single technology assessment process, has not been reviewed.

- The review of the TARs focused exclusively on the documentary evidence – access to the models or analyses was not requested as part of this work.
- The policy impact assessment is based only on documentary evidence again – observation of Committee discussions and deliberations and/ or interviews with committee members around the specific topics might have revealed further insights on this issue.
- The interviews were not undertaken as part of this project but relate to earlier work by one of the authors (SB). Thus, the focus of the interviews was not uncertainty, and the interviews were conducted in 2003/04. For the majority of the interviews, the data were collected before the launch of the April 2004 NICE Methods Guidance, which made the use of PSA mandatory. It is, of course, possible that the more widespread use of PSA after 2004 has led to a different appreciation of its weaknesses and strengths in decision-making.
- The focus of this work has been NICE technology appraisal. This is narrow, and so caution must be taken in attempting to extrapolate to other decision-makers in the health-care sector in the UK or elsewhere. It is acknowledged that other decision-makers need to understand uncertainties in economic analyses, but this small project had to restrict its scope for pragmatic reasons.

Recommendations for the practice of probabilistic sensitivity analysis and for policy-making

In seeking to address parameter uncertainty, both deterministic sensitivity analysis and PSA should be used. Traditional univariate and multivariate analysis can play an important role as a starting point in understanding the cost-effectiveness model and the main aspects of uncertainty. This form of analysis provides a route through which some of the key drivers of the cost-effectiveness results can best be revealed. For methodological and structural uncertainties, repeated analyses should be run using different models where uncertainties regarding model structure exist or different methods where there are uncertainties regarding methods.

In terms of the process of conducting and implementing sensitivity analyses, good practice would involve the following components. For deterministic sensitivity analyses, a clear and full justification for choice of included variables should be given, along with a clear explanation of the information source used to specify the ranges. When the sensitivity analysis involves an analysis of extremes, the analysts should justify the extreme values chosen and provide a clear presentation of the analysis in order to allow the reader to assess the analysis relative to their own context. The use of threshold analysis is to be supported, especially when the value of a particular parameter is indeterminate, but there is a need to provide a clear rationale for, and definition of, the threshold applied.

In relation to PSA, partial coverage of parameters is commonly seen, but this is poor practice. Distributions should be placed around all important model parameters and any excluded parameters must be justified. The distributional assumption for each variable should be justified and should relate to the nature of the variable. The distribution should be consistent with any logical bounds on parameter values given its nature (e.g. utility scores with upper bound of 1). There might be value in clearer methodology guidelines on which distributions are appropriate for which parameters. When correlation between variables is expected, joint distributions should be used and independence should not be assumed. These recommendations are consistent with, and build upon, those reported in Philips *et al.*[14]

In relation to the use of sensitivity analyses in policy-making, there may be benefits from an explicit recognition of the role of such analyses in supporting the search for subgroups where the cost and effect results are more or less favourable. Given that such analyses are used in this way by the Committee, tasking the analysts to prepare sensitivity analyses to answer this question is appropriate. The identification of structural concerns with the model at the point of the NICE Technology Appraisal Committee meeting is clearly problematic. The recognition that sensitivity analysis can provide critical information in the situation of structural uncertainties should encourage earlier identification of such structural issues, thus facilitating the development of appropriate sensitivity analysis by the analysts.

This issue of the possible association between level of uncertainty and the likelihood of a negative decision requires some further discussion. The data reported in Chapters 4 and 5 suggest that when the level of uncertainty was high then the Committee was likely to tend towards a negative decision. Assuming a threshold at some value (e.g. £20,000 per QALY), the theoretical argument is that if the mean-based estimate of the ICER is above the threshold, the answer to the question 'Should the technology be used in routine practice?' should always be 'no'. If the Committee says 'yes' with such an ICER, they are in effect saying that there are other considerations that merit the use of a higher threshold in that case. If there is a substantial probability that further research might bring the ICER below the threshold, then it would be appropriate to recommend that such research be carried out.

If the mean-based ICER is below the threshold, the 'irrelevance of inference' argument is that the decision should always be 'yes' regardless of uncertainty.[56] This would be agreed by most if the ICER is robustly below the threshold. However, if there is a serious probability that the ICER is above the threshold, the basis for the 'irrelevance of inference' argument is questionable. If there is no possibility of resolving the relevant uncertainty, or the value of information is below the cost of appropriate future research, then there is sufficient evidence to give an outright 'yes'. However, if there is potential for future research to be efficient, then there is a strong case for saying 'no' in routine practice (an 'only in research' recommendation) on two grounds. First, that it is difficult to change a 'yes' into a 'no' should the inclusion of future research move the mean-based estimate of the ICER to a value just above the threshold, particularly if the change in the mean-based ICER is within the range of random error. Second, making the technology available in routine practice may itself preclude recruitment to future trials.

Finally, the difficulties surrounding effective communication between analysts and policy-makers cannot be ignored. It is evident that some cost-effectiveness work, especially around the sensitivity analysis components, represents a challenge to become accessible to those making decisions. There has been recent debate on the issue of presentation, with some[57] arguing in favour of scatter diagrams and intervals around incremental net benefits, and others[58] arguing for cost-effectiveness acceptability curves and frontiers, especially in the case of more than two treatment options. While we acknowledge

the limitations of scatter diagrams in some cases, we do believe they can facilitate understanding of the results of probabilistic analyses and the extent of uncertainty for decision-makers. The use of grey-scaling to illustrate density of the scatter is a device that can avoid some misinterpretation. In conclusion, this debate speaks, in part, to the training agenda for those sitting on such decision-making bodies, and to the importance of clear and understandable presentation of analyses by the academic community. The issue of how to appropriately interpret PSA outputs, such as cost-effectiveness acceptability curves, in the context of making a coverage decision, must also be addressed. Guidance on interpretation of outputs from PSAs would be welcomed.

Recommendations for further research

This section gives an indication of the future research agenda in the area of uncertainty, sensitivity analysis and CEA in health care.

Research questions relating to best practice in the conduct of sensitivity analysis:

- What are appropriate ranges for parameter values in univariate and multivariate sensitivity analyses?
- Deterministic sensitivity analyses are often characterised by the use of 'loose' language such as 'results are robust to the variation explored'. Linked to the first point, more work is required to define what is meant by such terms so that policy-makers interpret them correctly.
- In PSA, how does choice of distribution affect the results of CEAs?
- How should correlation between parameters best be considered in sensitivity analyses? How should this be made when data are lacking?

Research questions relating to best practice in the use of sensitivity analysis in policy decision-making:

- How does the level of uncertainty independently affect technology coverage decisions?
- Is it appropriate for decision-makers to trade level of uncertainty against level of cost-effectiveness? That is, to say 'yes' for technologies with relatively high ICERs, but low levels of uncertainty, and 'no' in the case of low ICERs but high levels of uncertainty?

Acknowledgements

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45. NICE. *Inhaled insulin for the treatment of diabetes* (*types 1 and 2*). URL: www.nice.org.uk/nicemedia/pdf/ Inhins3_FAD.pdf

46. NICE. *Methadone and buprenorphine for the management of opioid dependence*. URL: www.nice.org. uk/nicemedia/pdf/Drug_misuse-methadone_and_ buprenorphine_FAD.pdf

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disease on maintenance dialysis therapy. URL: www.nice. org.uk/nicemedia/pdf/FAD_Cinacalcet.pdf

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Appendix 1
Search terms

MEDLINE (searched on 11 February 2008)

Search 1

1. 'economic evaluation' OR economic analys* OR 'cost effectiveness' OR 'cost-effectiveness' OR 'cost-utility' OR 'cost utility' OR pharmacoeconom* OR 'health technology appraisal'
2. model* OR economic model* OR modelling OR markov model* OR 'stochastic model*' OR 'probabilistic model*' OR 'decision model*' OR 'decision tree*' OR patient level simulation model* OR cohort model* OR (decision AND model)
3. 'analys* of uncertainty' OR (analys* AND uncertainty) OR ((methodolog* OR sampling OR parameter* OR variability OR generali*ability OR decision) AND uncertainty) OR ((one-way OR two-way* OR univariate OR multivariate) AND sensitivity AND analys*) OR ((threshold OR extreme* OR scenari* OR simple) AND sensitivity AND analysis) OR 'probabilistic sensitivity analysis'
4. 1. AND 2. AND 3.

This search retrieved 876 papers.

Search 2

1. economic evaluation* OR economic analys* OR economic appraisal* OR health economic* OR cost effectiveness OR cost effectiveness analys* OR cost utility OR cost-utility OR cost-utility analys* OR cost analys* OR pharmacoeconom* OR health technology assessment OR pharmacoeconomic* AND submission OR health technology appraisal
2. analysis AND uncertainty OR ((methodological OR sampling OR parameter* OR variability OR generali*ability OR extrapolation OR decision OR analytical methods) AND uncertainty) OR ((one-way OR two-ways OR univariate OR multivariate OR multi-way OR simple) AND sensitivity AND analys*) OR threshold analys* OR analysis of extremes OR probabilistic sensitivity analysis OR monte carlo simulation*
3. checklist* OR check-list OR checkpoint* OR standard OR standardi*ation OR rule* OR criteria OR guidance OR guideline* OR problem* OR limitation OR principles OR methodolog* OR valid* OR good OR bad OR correct OR critically OR practically OR appraisal* OR evaluation* OR assessment*
4. 1. AND 2. AND 3.

This search retrieved 1401 papers.

Search 3

The search identified papers related to Briggs *et al.*,[11] which was identified in MEDLINE.

This search retrieved 126 papers.

Search 4

The search identified papers related to Briggs and Gray.[8]

This search retrieved 142 papers.

Search 5

The search identified papers related to Philips *et al.*[14]

This search retrieved 442 papers.

In total, after removing duplicates across searches, MEDLINE gave 1919 papers.

NHS Economic Evaluation Database (searched on 12 February 2008)

Search 1

1. methodology:ty
2. 'economic model' OR 'econometric model*' OR 'modelling' OR 'markov model*' OR 'stochastic model*' OR 'probabilistic model*' OR 'decision model' OR 'decision-analytic model*' OR 'decision tree*' OR 'patient-level simulation*' OR 'cohort model*'
3. (methodolog* OR structur* OR paramet* OR variabilit* OR heterogeneit*) AND uncertaint*
4. (one-way OR two-ways OR univariate OR multivariate OR multi-way* OR simple OR deterministic OR scenari* OR threshold* OR extreme*) AND sensitivity AND analys*
5. 'probabilistic sensitivity analys*' OR 'Monte Carlo'

6. #3 OR #4 OR #5
7. #1 AND #2 AND #6

This search retrieved 11 papers.

Search 2
1. methodology:ty
2. uncertainty
3. sensitivity AND analys*
4. one-way OR multi-way OR univariate OR multivariate OR simple OR probabilistic
5. (one-way OR multi-way OR univariate OR multivariate OR simple OR probabilistic) AND sensitivity
6. model* OR decision AND analytic AND model* OR markov AND model* OR decision AND tree* OR cohort AND model OR individual AND sampling AND model OR Monte AND Carlo AND simulat*
7. guideline* OR guidance OR checklist* OR standard* OR criteria OR good OR bad OR recommendations OR best OR audit OR principle* OR methodology*
8. 2. OR 3. OR 4.
9. 1. AND 8. AND 6. AND 7.

This search retrieved 68 papers.

Search 3
1. economic AND model*
2. modelling
3. decision AND analytic AND model*
4. decision AND tree
5. markov
6. sensitivity AND analys*
7. analysis AND of AND uncertainty
8. uncertainty
9. Monte AND carlo
10. methodology:ty
11. 1. OR 2. OR 3. OR 4. OR 5.
12. 6. OR 7. OR 8. OR 9.
13. 11. AND 12.
14. 13. AND 10.

This study retrieved 69 papers.

In total, after removing duplicates across searches, NHS EED gave 89 papers.

EMBASE (1980–2008, week 11) (searched on 24 February 2008)
Search 1

1. health economics/or economic evaluation/or 'cost benefit analysis'/or 'cost control'/or 'cost effectiveness analysis'/or 'cost minimization analysis'/or 'cost of illness'/or 'cost utility analysis'/
2. (markov model* or economic model or econometric model* or stochastic model* or statistical model* or mathematical model* or modelling or pharmacoeconomic* model or decision model* or decision-analytic model* or decision analytic model* or decision tree or individual sampling model* or patient-level simulation model* or monte carlo simulation). mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
3. (checklist* or rules or criteri* or guidance or guideline* or principle* or limitation* or principles or critical appraisal* or good practice).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
4. (sensitivity analysis or analys* of uncertainty or methodological uncertainty or sampling uncertainty or parameter* uncertainty or structural uncertainty or variability or generali*ability or deterministic sensitivity analysis or stochastic sensitivity analsyis or univariate analysis or multivariate analysis or scenario analysis or threshold analysis or probabilistic sensitivity analysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
5. 1 and 2 and 3 and 4 (189)

In total EMBASE gave 189 papers.

Appendix 2

Study selection process diagram
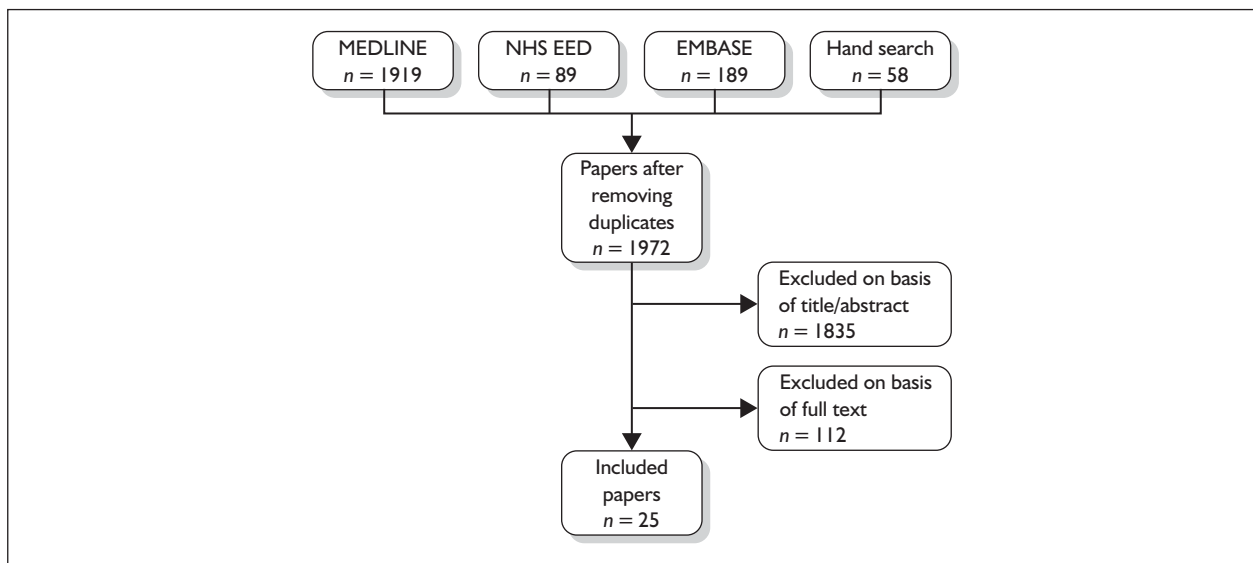
Appendix 3

NICE guidance decisions

Technology appraisal	Title	NICE guidance decision
TA103[40]	Psoriasis – efalizumab and etanercept	**1.1** Etanercept, within its licensed indications, administered at a dose not exceeding 25 mg twice weekly, is recommended for the treatment of adults with plaque psoriasis only when the following criteria are met: • The disease is severe as defined by a total Psoriasis Area Severity Index (PASI) of ten or more and a Dermatology Life Quality Index (DLQI) of more than ten. • The psoriasis has failed to respond to standard systemic therapies including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation); or the person is intolerant to, or has a contraindication to, these treatments. **1.2** Etanercept treatment should be discontinued in patients whose psoriasis has not responded adequately at 12 weeks and further treatment cycles are not recommended in these patients. An adequate response is defined as either: • a 75% reduction in the PASI score from when treatment started (PASI 75) or • a 50% reduction in the PASI score (PASI 50) and a five-point reduction in DLQI from when treatment started. Psoriasis FAD for consultation 23 09 05 (final) Page 1 of 32 CONFIDENTIAL **1.3** Efalizumab, within its licensed indications, is recommended for the treatment of adults with plaque psoriasis under the circumstances detailed in Section 1.1 only if their psoriasis has failed to respond to etanercept or they are shown to be intolerant of, or have contraindications to, treatment with etanercept. **1.4** Further treatment with efalizumab is not recommended in patients unless their psoriasis has responded adequately at 12 weeks as defined in Section 1.2. **1.5** It is recommended that the use of etanercept and efalizumab for psoriasis should be initiated and supervised only by specialist physicians experienced in the diagnosis and treatment of psoriasis. If a person has both psoriasis and psoriatic arthritis, their treatment should be managed by collaboration between a rheumatologist and a dermatologist.
TA105[41]	Colorectal cancer – laparoscopic surgery	**1.1** Laparoscopic (including laparoscopically assisted) resection is recommended as an alternative to open resection for individuals with colorectal cancer in whom both laparoscopic and open surgery are considered suitable. **1.2** Laparoscopic colorectal surgery should be performed only by surgeons who have completed appropriate training in the technique and who perform this procedure often enough to maintain competence. The exact criteria to be used should be determined by the relevant national professional bodies. Cancer networks and constituent Trusts should ensure that any local laparoscopic colorectal surgical practice meets these criteria as part of their clinical governance arrangements. **1.3** The decision about which of the procedures (open or laparoscopic) is undertaken should be made after informed discussion between the patient and the surgeon. In particular, they should consider: • the suitability of the lesion for laparoscopic resection • the risks and benefits of the two procedures • the experience of the surgeon in both procedures.

continued

Technology appraisal	Title	NICE guidance decision
TA106[42]	Hepatitis C – peginterferon alfa	**1.1** Combination therapy, comprising peginterferon alfa-2a and ribavirin or peginterferon alfa-2b and ribavirin, is recommended, within the licensed indications of these drugs, for the treatment of mild chronic hepatitis C.
		1.2 Monotherapy with peginterferon alfa-2a or peginterferon alfa-2b is recommended, within the licensed indications of these drugs, for the treatment of mild chronic hepatitis C for people who are unable to tolerate ribavirin, or for whom ribavirin is contraindicated.
		1.3 The decision on whether a person with mild chronic hepatitis C should be treated immediately or should wait until the disease has reached a moderate stage ('watchful waiting') should be made by the person after fully informed consultation with the responsible clinician. The decision to treat need not depend on a liver biopsy to determine the stage of the disease if treatment is initiated immediately. However, a biopsy may be recommended by the clinician for other reasons or if a strategy of watchful waiting is chosen.
		1.4 The duration of treatment should vary according to the licensed indications of the chosen drug, the genotype of the virus, the initial viral load, the response to treatment, and the treatment regimen chosen.
		1.5 Second or subsequent courses of treatment are not recommended for people who have been treated with a first course of either combination therapy or monotherapy with peginterferon alfa if they have not had an early response (as indicated by reduction in viral load at 12 weeks).
		1.6 There is insufficient evidence to recommend combination therapy or monotherapy with peginterferon alfa for people with mild chronic hepatitis C who are under the age of 18 years, or those who have had a liver transplant.
TA111[43]	Alzheimer's disease – donepezil, galantamine, rivastigmine (review) and memantine	This guidance relates to the approved licensed indications for the treatments under consideration − that is, mild to moderately severe Alzheimer's disease for donepezil, galantamine and rivastigmine, and moderate to severe Alzheimer's disease for memantine.
		The benefits of these drugs for patients with other forms of dementia (for example, vascular dementia or dementia with Lewy bodies) have not been assessed in this guidance.
		1.1 The three acetylcholinesterase inhibitors donepezil, galantamine and rivastigmine are recommended as options in the management of people with Alzheimer's disease of moderate severity only (that is, those with a Mini Mental State Examination [MMSE] score of between 10 and 20 points), and under the following conditions:
		• Only specialists in the care of people with dementia (that is, psychiatrists including those specialising in learning disability, neurologists, and physicians specialising in the care of the elderly) should initiate treatment. Carers' views on the patient's condition at baseline should be sought.
		• Patients who continue on the drug should be reviewed every 6 months by MMSE score and global, functional and behavioural assessment. Carers' views on the patient's condition at follow-up should be sought. The drug should only be continued while the patient's MMSE score remains at or above 10 points and their global, functional and behavioural condition remains at a level where the drug is considered to be having a worthwhile effect. Any review involving MMSE assessment should be undertaken by an appropriate specialist team, unless there are locally agreed protocols for shared care.
		1.2 When the decision has been made to prescribe an acetylcholinesterase inhibitor, it is recommended that therapy should be initiated with a drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). However, an alternative acetylcholinesterase inhibitor could be prescribed where it is considered appropriate having regard to adverse event profile, expectations around concordance, medical comorbidity, possibility of drug interactions, and dosing profiles.
		1.3 Memantine is not recommended as a treatment option for people with Alzheimer's disease except as part of well designed clinical studies.
		1.4 People with mild Alzheimer's disease who are currently receiving donepezil, galantamine or rivastigmine, and people with Alzheimer's disease currently receiving memantine, whether as routine therapy or as part of a clinical trial, may be continued on therapy (including after the conclusion of a clinical trial) until they, their carers and/or specialist consider it appropriate to stop.

Technology appraisal	Title	NICE guidance decision
TA112[44]	Breast cancer (early) – hormonal treatment	**1.1** The aromatase inhibitors anastrozole, exemestane and letrozole, within their licensed indications, are recommended as options for the adjuvant treatment of early oestrogen-receptor-positive invasive breast cancer in postmenopausal women.
		1.2 The choice of treatment should be made after discussion between the responsible clinician and the woman about the risks and benefits of each option. Factors to consider when making the choice include whether the woman has received tamoxifen before, the licensed indications and side-effect profiles of the individual drugs and, in particular, the assessed risk of recurrence.
TA113[45]	Diabetes – inhaled insulin	**1.1** Inhaled insulin is not recommended for the routine treatment of people with type 1 or type 2 diabetes mellitus.
		1.2 Inhaled insulin may be used as a treatment option for people with type 1 or type 2 diabetes mellitus who show evidence of poor glycaemic control despite other therapeutic interventions (including, where appropriate, diet, oral hypoglycaemic agents [OHAs] and subcutaneous insulin) and adequate educational support, **and** who are unable to initiate or intensify pre-prandial subcutaneous insulin therapy because of either:
		• a marked and persistent fear of injections that meet DSM-IV criteria for specific phobia 'blood injection injury type' diagnosed by a diabetes specialist or mental health professional
		• severe and persistent problems with injection sites (for example, as a consequence of lipohypertrophy) despite support with injection site rotation.
		1.3 In patients receiving inhaled insulin under the circumstances set out in section 1.2, treatment should only be continued beyond 6 months, and in the longer term, if there is evidence of a sustained improvement in glycated haemoglobin (HbA1c) that is judged to be clinically relevant to the individual patient's overall risk of developing long-term complications of diabetes.
		1.4 Initiation of inhaled insulin treatment and monitoring of response should be carried out at a specialist diabetes centre. The responsible clinician should discuss the risks and benefits of inhaled insulin with the patient so that an informed choice can be made regarding appropriate options for diabetes management, including psychological support and therapy for needle phobia if necessary.
		1.5 Data on the use of inhaled insulin according to this guidance should be collected as part of a coordinated prospective observational study. The data collected should include individual patient outcomes, adverse events and measurements of lung function.
TA114[46]	Drug misuse – methadone and buprenorphine	**1.1** Methadone and buprenorphine (oral formulations), using flexible dosing regimens, are recommended as options for maintenance therapy in the management of opioid dependence.
		1.2 The decision about which drug to use should be made on a case by case basis, taking into account a number of factors, including the person's history of opioid dependence, their commitment to a particular long-term management strategy, and an estimate of the risks and benefits of each treatment made by the responsible clinician in consultation with the person. If both drugs are equally suitable, methadone should be prescribed as the first choice.
		1.3 Methadone and buprenorphine should be administered daily, under supervision, for at least the first 3 months. Supervision should be relaxed only when the patient's compliance is assured. Both drugs should be given as part of a programme of supportive care.
TA115[47]	Drug misuse – naltrexone	**1.1** Naltrexone is recommended as a treatment option in detoxified formerly opioid-dependent people who are highly motivated to remain in an abstinence programme.
		1.2 Naltrexone should only be administered under adequate supervision to people who have been fully informed of the potential adverse effects of treatment. It should be given as part of a programme of supportive care.
		1.3 The effectiveness of naltrexone in preventing opioid misuse in people being treated should be reviewed regularly. Discontinuation of naltrexone treatment should be considered if there is evidence of such misuse.

continued

53

Technology appraisal	Title	NICE guidance decision
TA117[48]	Hyperparathyroidism – cinacalcet	**1.1** Cinacalcet is not recommended for the routine treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy.
		1.2 Cinacalcet is recommended for the treatment of refractory secondary hyperparathyroidism in patients with end-stage renal disease (including those with calciphylaxis) only in those:
		• who have 'very uncontrolled' plasma levels of intact parathyroid hormone (defined as greater than 85 pmol/litre [800 pg/ml]) that are refractory to standard therapy, and a normal or high adjusted serum calcium level, **and**
		• in whom surgical parathyroidectomy is contraindicated, in that the risks of surgery are considered to outweigh the benefits.
		1.3 Response to treatment should be monitored regularly and treatment should be continued only if a reduction in the plasma levels of intact parathyroid hormone of 30% or more is seen within 4 months of treatment, including dose escalation as appropriate.
TA118[49]	Colorectal cancer (metastatic) – bevacizumab and cetuximab	**1.1** Bevacizumab in combination with 5-fluorouracil plus folinic acid, with or without irinotecan, is not recommended for the first-line treatment of metastatic colorectal cancer.
		1.2 Cetuximab in combination with irinotecan is not recommended for the second-line or subsequent treatment of metastatic colorectal cancer.
		1.3 People currently receiving bevacizumab or cetuximab should have the option to continue therapy until they and their consultants consider it appropriate to stop.
TA120[50]	Heart failure – cardiac resynchronisation	This guidance should be read in conjunction with 'Implantable cardioverter defibrillators for arrhythmias' (NICE technology appraisal guidance 95 – see appendix C). This guidance on cardiac resynchronisation therapy provides additional treatment options for some of the groups of people covered in the guidance on implantable cardioverter defibrillators (ICDs).
		1.1 Cardiac resynchronisation therapy with a pacing device (CRT-P) is recommended as a treatment option for people with heart failure who fulfil all the following criteria:
		• They are currently experiencing or have recently experienced New York Heart Association (NYHA) class III–IV symptoms.
		• They are in sinus rhythm:
		– **either** with a QRS duration of 150 ms or longer estimated by standard electrocardiogram (ECG)
		– **or** with a QRS duration of 120–149 ms estimated by ECG **and** mechanical dyssynchrony that is confirmed by echocardiography.
		• They have a left ventricular ejection fraction of 35% or less.
		• They are receiving optimal pharmacological therapy.
		1.2 Cardiac resynchronisation therapy with a defibrillator device (CRT-D) may be considered for people who fulfil the criteria for implantation of a CRT-P device in section 1.1 and who also separately fulfil the criteria for the use of an ICD device as recommended in NICE technology appraisal guidance 95.
TA121[51]	Glioma (newly diagnosed and high grade) – carmustine implants and temozolomide	Temozolomide and carmustine implants have been appraised individually for the treatment of newly diagnosed high-grade glioma. This guidance does not relate to the sequential use of these treatments.
		1.1 Temozolomide, within its licensed indications, is recommended as an option for the treatment of newly diagnosed glioblastoma multiforme (GBM) in patients with a World Health Organization (WHO) performance status of 0 or 1.
		1.2 Carmustine implants, within their licensed indications, are recommended as an option for the treatment of newly diagnosed high-grade glioma only for patients in whom 90% or more of the tumour has been resected.
		1.3 Treatment with carmustine implants should be provided only within specialist centres that in general conform to guidance in 'Improving outcomes for people with brain and other central nervous system tumours' (NICE cancer service guidance 2006), and should be supervised by specialist neurosurgeons who spend at least 50% of their clinical programmed activities in neuro-oncological surgery. The specialists should also have access to:

Technology appraisal	Title	NICE guidance decision
		• multidisciplinary teams to enable preoperative identification of patients in whom maximal resection is likely to be achievable
		• magnetic resonance imaging (MRI) to enable preoperative identification of patients in whom maximal resection is likely to be possible, and
		• image-directed technology, such as neuronavigation, for use intraoperatively to assist the achievement of maximal resection.
		1.4 Carmustine implants are not recommended for the treatment of newly diagnosed high-grade glioma for patients in whom less than 90% of the tumour has been resected.
TA128[52]	Haemorrhoid – stapled haemorroidopexy	This technology appraisal examined the currently available devices for stapled haemorrhoidopexy. The evidence considered refers to the HCS33 circular stapler (models PPH01 and PPH03: Ethicon-Endo-Surgery). At the time of the technology appraisal, there was no evidence to make recommendations for the Autosuture stapler with the STRAM kit adaptor. **1.1** Stapled haemorrhoidopexy, using a circular stapler specifically developed for haemorrhoidopexy, is recommended as an option for people in whom surgical intervention is considered appropriate for the treatment of prolapsed internal haemorrhoids.
TA130[53]	Rheumatoid arthritis – adalimumab, etanercept and infliximab	**1.1** The tumour necrosis factor alpha (TNF α) inhibitors adalimumab, etanercept and infliximab are recommended as options for the treatment of adults who have both of the following characteristics:
		• Active rheumatoid arthritis as measured by disease activity score (DAS28) greater than 5.1 confirmed on at least two occasions, 1 month apart.
		• Have undergone trials of two disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate (unless contraindicated). A trial of a DMARD is defined as being normally of 6 months, with 2 months at standard dose, unless significant toxicity has limited the dose or duration of treatment.
		1.2 TNF α inhibitors should normally be used in combination with methotrexate. Where a patient is intolerant of methotrexate or where methotrexate treatment is considered to be inappropriate, adalimumab and etanercept may be given as monotherapy.
		1.3 Treatment with TNF α inhibitors should be continued only if there is an adequate response at 6 months following initiation of therapy. An adequate response is defined as an improvement in DAS28 of 1.2 points or more.
		1.4 After initial response, treatment should be monitored no less frequently than 6-monthly intervals with assessment of DAS28. Treatment should be withdrawn if an adequate response (as defined in 1.3) is not maintained.
		1.5 If the patient has an inadequate initial response or experiences loss of response later during treatment with a TNF α inhibitor, prescription of an alternative TNF α inhibitor is not recommended.
		1.6 An alternative TNF α inhibitor may be considered for patients in whom treatment is withdrawn due to an adverse event before the initial 6 month assessment of efficacy, provided the risks and benefits have been fully discussed with the patient and documented.
		1.7 Escalation of dose of the TNF α inhibitors above their licensed starting dose is not recommended.
		1.8 Treatment should normally be initiated with the least expensive drug (taking into account administration costs, required dose and product price per dose). This may need to be varied in individual cases due to differences in the mode of administration and treatment schedules.
		1.9 Use of the TNF α inhibitors for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended.
		1.10 Initiation of TNF α inhibitors and follow-up of treatment response and adverse events should be undertaken only by a specialist.

Technology appraisal	Title	NICE guidance decision
TA132[54]	Hypercholesterolemia – ezetimibe	This guidance should be read in conjunction with NICE guidance on the initiation of statin therapy (NICE technology appraisal guidance 94). NICE has published clinical guidelines on the management of blood pressure and blood lipids in people with type 2 diabetes (Inherited clinical guideline H) and secondary prevention for patients following a myocardial infarction (NICE clinical guideline 48). The following clinical guidelines are under development: lipid modification; familial hypercholesterolaemia; type 2 diabetes (update). This guidance should be read in the context of the relevant clinical guideline, when available. **1.1** Ezetimibe monotherapy is recommended as an option for the treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia who would otherwise be initiated on statin therapy (as per NICE guidance TA 94 in adults with non-familial hypercholesterolaemia) but who are unable to do so because of contraindications to initial statin therapy. **1.2** Ezetimibe monotherapy is recommended as an option for the treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia who are intolerant to statin therapy (as defined in section 1.6). **1.3** Ezetimibe, co-administered with initial statin therapy, is recommended as an option for the treatment of adults with primary (heterozygous-familial or non-familial) hypercholesterolaemia who have been initiated on statin therapy (as per NICE guidance TA 94 in adults with non-familial hypercholesterolaemia) when: • serum total or low-density lipoprotein (LDL) cholesterol concentration is not appropriately controlled (as defined in section 1.5) either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy (as defined in section 1.6), and • consideration is being given to changing from initial statin therapy to an alternative statin. **1.4** When the decision has been made to treat with ezetimibe coadministered with a statin, ezetimibe should be prescribed on the basis of lowest acquisition cost. **1.5** For the purposes of this guidance, appropriate control of cholesterol concentrations should be based on individualised risk assessment in accordance with national guidance on the management of cardiovascular disease for the relevant populations. **1.6** For the purposes of this guidance, intolerance to initial statin therapy should be defined as the presence of clinically significant adverse effects from statin therapy that are considered to represent an unacceptable risk to the patient or that may result in compliance with therapy being compromised. Adverse effects include evidence of new-onset muscle pain (often associated with levels of muscle enzymes in the blood indicative of muscle damage), significant gastrointestinal disturbance or alterations of liver function tests.

Appendix 4
Data extraction form

Data extraction form
Author(s):
Title:
Publication info:
Reviewer:
1.1 Good practice: appropriate type of sensitivity analysis to address uncertainty
Parameter uncertainty:
Structural uncertainty:
Methodological uncertainty:
Other relevant statements:
1.2 Good practice: appropriate implementation of sensitivity analysis
Deterministic sensitivity analysis
One-way sensitivity analysis:
Multiway sensitivity analysis:
Scenario analysis:
Analysis of extremes:
Threshold analysis:
Probabilistic sensitivity analysis
2. Strengths and weaknesses of sensitivity analysis
Deterministic sensitivity analysis
One-way sensitivity analysis:
Multiway sensitivity analysis:
Scenario analysis:
Analysis of extremes:
Threshold analysis:
Probabilistic sensitivity analysis
Reviewer's comments:

Appendix 5

Supplementary tables for Chapter 3

TABLE 20 *Basis for selecting ranges in univariate sensitivity analysis (cells indicate technology assessment report numbers)*

Basis for selecting ranges	Parameter categories			
	Cost	**Utility**	**Patient**	**Other**
Estimates from the literature	105,[41] 111,[43] 118,[49] 128[52]	105,[41] 106,[42] 114,[46] 118,[49] 128[52]	106,[42] 118[49]	
Arbitrary percentage changes	106,[42] 113,[45] 117,[48] 118,[49] 121,[51] 128,[52] 132[54]	117,[48] 120,[50] 132[54]	105,[41] 113,[45] 117,[48] 120,[50] 130[53]	106[42]
Removal of effect	111[43]		105[41]	
Additional effect not included in base case			103[40]	
Variation in clinical practice	105[41]			
Quantiles of data[a]	117,[48] 120,[50] 121[51]	121[51]	120,[50] 121,[51] 132[54]	
Expert opinion	120[50]		112[44]	128[52]
Alternative methods of estimation[b]		128[52]	132[54]	
Unclear	103,[40] 106,[42] 111,[43] 112,[44] 114,[46] 117,[48] 120,[50] 121[51]	111,[43] 113,[45] 117,[48] 120,[50] 121[51]	103,[40] 105,[41] 111,[43] 117,[48] 120,[50] 128[52]	117[48]

a Including use of upper and lower quartile and extreme values.
b Using different sources or inclusion criteria for data synthesis.

TABLE 21 *Distributions used in probabilistic sensitivity analysis (cells indicate technology assessment report numbers)*

Distribution	Parameter categories			
	Cost	**Utility**	**Patient**	**Other**
Gamma	103,[40] 106,[42] 111,[43] 112[44]	111,[43] 128[52]	111[43]	111[43]
Normal	114,[46] 115,[47] 128,[52] 132[54]	103,[40] 132[54]	105,[41] 112,[44] 114,[46] 115,[47] 118,[49] 128[52]	111[43]
Bivariate normal			117,[48] 120[50]	
Multinormal		132[54]		
Triangular	105,[41] 132[54]		105,[41] 132[54]	
Lognormal	105,[41] 117,[48] 118,[49] 120,[50] 121[51]		105,[41] 117,[48] 120[50]	
Expnorminv			132[54]	
Beta		106,[42] 112,[44] 114,[46] 115,[47] 117,[48] 118,[49] 120,[50] 121[51]	105,[41] 106,[42] 117,[48] 118,[49] 120,[50] 121,[51] 132[54]	120,[50] 121[51]
Dirichlet			120[50]	
Uniform		117[48]	120[50]	
Poisson			120[50]	
Not stated	132[54]	132[54]		

TABLE 22 *Source of distribution for parameters (cells indicate technology assessment report numbers)*

Source of parameter distribution	Parameter categories			
	Cost	**Utility**	**Patient**	**Other**
Data		121[51]	112,[44] 117,[48] 118,[49] 120[50]	
Published values	103,[40] 105,[41] 106,[42] 111,[43] 117,[48] 120,[50] 121,[51] 128,[52] 132[54]	106,[42] 111,[43] 115,[47] 117,[48] 120,[50] 128,[52] 132[54]	105,[41] 106,[42] 111,[43] 114,[46] 115,[47] 117,[48] 120,[50] 121,[51] 128,[52] 132[54]	111[43]
Assumptions	111,[43] 114,[46] 115,[47] 118,[49] 121,[51] 132[54]	103,[40] 117,[48] 118[49]	105,[41] 117,[48] 118,[49] 120,[50] 121,[51] 132[54]	111,[43] 120,[50] 121[51]
Unclear	112,[44] 132[54]	112,[44] 132[54]	132[54]	

Appendix 6

Interview schedule for interviews with NICE Technology Appraisal Committee members

Venue:	Date/time of interview:
Interviewer:	Interviewee:
Designation:	Organisation:
Technology:	First appraisal date:

Interviewee role in appraisal:
A) Decision questions
What considerations led to you reaching the decision?
How important was the economic evidence in your own thinking?
In your opinion, how important was the economic evidence in the committee's thinking?
B) Economic evaluation questions
What is your interpretation of the results of the economic analysis?
Did you feel the committee reached a satisfactory consensus regarding the economic data?
Would you have liked to see more/less economic evidence?
Did you feel you (the team) understood the economic evidence presented?
Would you have liked further clarification?
What were the strengths of the analysis?
What were the strengths of its presentation?
What were the weaknesses of the analysis?
What were the weaknesses of its presentation?
In what other ways could evaluation of economic data be improved?
C) General questions
How did the appraisal differ from ones you've been involved in previously?
Do you feel economic evaluation has become more/less important to the appraisal process?
Are different committee members more or less concerned with health economics data?
How are other considerations (such as equity, patient choice, etc.) weighed against economic evidence/analysis?

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65

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By Lewis R, Whiting P, ter Riet G,
O'Meara S, Glanville J.

No. 15
Home treatment for mental health
problems: a systematic review.
By Burns T, Knapp M, Catty J,
Healey A, Henderson J, Watt H, *et al.*

No. 16
How to develop cost-conscious
guidelines.
By Eccles M, Mason J.

No. 17
The role of specialist nurses in multiple
sclerosis: a rapid and systematic review.
By De Broe S, Christopher F,
Waugh N.

No. 18
A rapid and systematic review
of the clinical effectiveness and
cost-effectiveness of orlistat in the
management of obesity.
By O'Meara S, Riemsma R,
Shirran L, Mather L, ter Riet G.

No. 19
The clinical effectiveness and cost-
effectiveness of pioglitazone for
type 2 diabetes mellitus: a rapid and
systematic review.
By Chilcott J, Wight J, Lloyd Jones
M, Tappenden P.

No. 20
Extended scope of nursing practice:
a multicentre randomised controlled
trial of appropriately trained nurses
and preregistration house officers in
preoperative assessment in elective
general surgery.
By Kinley H, Czoski-Murray C,
George S, McCabe C, Primrose J,
Reilly C, *et al.*

No. 21
Systematic reviews of the effectiveness of day care for people with severe mental disorders: (1) Acute day hospital versus admission; (2) Vocational rehabilitation; (3) Day hospital versus outpatient care.
By Marshall M, Crowther R, Almaraz- Serrano A, Creed F, Sledge W, Kluiter H, *et al*.

No. 22
The measurement and monitoring of surgical adverse events.
By Bruce J, Russell EM, Mollison J, Krukowski ZH.

No. 23
Action research: a systematic review and guidance for assessment.
By Waterman H, Tillen D, Dickson R, de Koning K.

No. 24
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of gemcitabine for the treatment of pancreatic cancer.
By Ward S, Morris E, Bansback N, Calvert N, Crellin A, Forman D, *et al*.

No. 25
A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer.
By Lloyd Jones M, Hummel S, Bansback N, Orr B, Seymour M.

No. 26
Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature.
By Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, *et al*.

No. 27
The cost-effectiveness of magnetic resonance imaging for investigation of the knee joint.
By Bryan S, Weatherburn G, Bungay H, Hatrick C, Salas C, Parry D, *et al*.

No. 28
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of topotecan for ovarian cancer.
By Forbes C, Shirran L, Bagnall A-M, Duffy S, ter Riet G.

No. 29
Superseded by a report published in a later volume.

No. 30
The role of radiography in primary care patients with low back pain of at least 6 weeks duration: a randomised (unblinded) controlled trial.
By Kendrick D, Fielding K, Bentley E, Miller P, Kerslake R, Pringle M.

No. 31
Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients.
By McColl E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N, *et al*.

No. 32
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer.
By Clegg A, Scott DA, Sidhu M, Hewitson P, Waugh N.

No. 33
Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives.
By Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G.

No. 34
Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) Meta-review; (2) Patient and nurse attitudes.
By David AS, Adams C.

No. 35
A systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression.
By Churchill R, Hunot V, Corney R, Knapp M, McGuire H, Tylee A, *et al*.

No. 36
Cost analysis of child health surveillance.
By Sanderson D, Wright D, Acton C, Duree D.

Volume 6, 2002

No. 1
A study of the methods used to select review criteria for clinical audit.
By Hearnshaw H, Harker R, Cheater F, Baker R, Grimshaw G.

No. 2
Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment.
By Hyde C, Wake B, Bryan S, Barton P, Fry-Smith A, Davenport C, *et al*.

No. 3
Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation.
By Wake B, Hyde C, Bryan S, Barton P, Song F, Fry-Smith A, *et al*.

No. 4
A systematic review of discharge arrangements for older people.
By Parker SG, Peet SM, McPherson A, Cannaby AM, Baker R, Wilson A, *et al*.

No. 5
The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children: a systematic review and economic evaluation.
By Peters J, Stevenson M, Beverley C, Lim J, Smith S.

No. 6
The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

No. 7
The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review.
By Berry E, Kelly S, Westwood ME, Davies LM, Gough MJ, Bamford JM, *et al*.

No. 8
Promoting physical activity in South Asian Muslim women through 'exercise on prescription'.
By Carroll B, Ali N, Azam N.

No. 9
Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation.
By Burls A, Clark W, Stewart T, Preston C, Bryan S, Jefferson T, *et al*.

No. 10
A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models.
By Richards RG, Sampson FC, Beard SM, Tappenden P.

No. 11
Screening for gestational diabetes: a systematic review and economic evaluation.
By Scott DA, Loveman E, McIntyre L, Waugh N.

No. 12
The clinical effectiveness and cost-effectiveness of surgery for people with morbid obesity: a systematic review and economic evaluation.
By Clegg AJ, Colquitt J, Sidhu MK, Royle P, Loveman E, Walker A.

No. 13
The clinical effectiveness of trastuzumab for breast cancer: a systematic review.
By Lewis R, Bagnall A-M, Forbes C, Shirran E, Duffy S, Kleijnen J, *et al*.

No. 14
The clinical effectiveness and cost-effectiveness of vinorelbine for breast cancer: a systematic review and economic evaluation.
By Lewis R, Bagnall A-M, King S, Woolacott N, Forbes C, Shirran L, *et al*.

67

No. 15
A systematic review of the effectiveness and cost-effectiveness of metal-on-metal hip resurfacing arthroplasty for treatment of hip disease.
By Vale L, Wyness L, McCormack K, McKenzie L, Brazzelli M, Stearns SC.

No. 16
The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation.
By Woolacott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, *et al*.

No. 17
A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept.
By Cummins C, Connock M, Fry-Smith A, Burls A.

No. 18
Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation.
By Bryant J, Cave C, Mihaylova B, Chase D, McIntyre L, Gerard K, *et al*.

No. 19
Clinical effectiveness and cost-effectiveness of growth hormone in adults in relation to impact on quality of life: a systematic review and economic evaluation.
By Bryant J, Loveman E, Chase D, Mihaylova B, Cave C, Gerard K, *et al*.

No. 20
Clinical medication review by a pharmacist of patients on repeat prescriptions in general practice: a randomised controlled trial.
By Zermansky AG, Petty DR, Raynor DK, Lowe CJ, Freementle N, Vail A.

No. 21
The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation.
By Jobanputra P, Barton P, Bryan S, Burls A.

No. 22
A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety.
By Kaltenthaler E, Shackley P, Stevens K, Beverley C, Parry G, Chilcott J.

No. 23
A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer.
By Forbes C, Wilby J, Richardson G, Sculpher M, Mather L, Reimsma R.

No. 24
A systematic review of the effectiveness of interventions based on a stages-of-change approach to promote individual behaviour change.
By Riemsma RP, Pattenden J, Bridle C, Sowden AJ, Mather L, Watt IS, *et al*.

No. 25
A systematic review update of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists.
By Robinson M, Ginnelly L, Sculpher M, Jones L, Riemsma R, Palmer S, *et al*.

No. 26
A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS.
By Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, *et al*.

No. 27
A randomised controlled crossover trial of nurse practitioner versus doctor-led outpatient care in a bronchiectasis clinic.
By Caine N, Sharples LD, Hollingworth W, French J, Keogan M, Exley A, *et al*.

No. 28
Clinical effectiveness and cost – consequences of selective serotonin reuptake inhibitors in the treatment of sex offenders.
By Adi Y, Ashcroft D, Browne K, Beech A, Fry-Smith A, Hyde C.

No. 29
Treatment of established osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M.

No. 30
Which anaesthetic agents are cost-effective in day surgery? Literature review, national survey of practice and randomised controlled trial.
By Elliott RA Payne K, Moore JK, Davies LM, Harper NJN, St Leger AS, *et al*.

No. 31
Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice.
By Stein K, Dalziel K, Walker A, McIntyre L, Jenkins B, Horne J, *et al*.

No. 32
The measurement of satisfaction with healthcare: implications for practice from a systematic review of the literature.
By Crow R, Gage H, Hampson S, Hart J, Kimber A, Storey L, *et al*.

No. 33
The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review.
By Garside R, Round A, Dalziel K, Stein K, Royle R.

No. 34
A comparative study of hypertonic saline, daily and alternate-day rhDNase in children with cystic fibrosis.
By Suri R, Wallis C, Bush A, Thompson S, Normand C, Flather M, *et al*.

No. 35
A systematic review of the costs and effectiveness of different models of paediatric home care.
By Parker G, Bhakta P, Lovett CA, Paisley S, Olsen R, Turner D, *et al*.

Volume 7, 2003

No. 1
How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study.
By Egger M, Jüni P, Bartlett C, Holenstein F, Sterne J.

No. 2
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of home versus hospital or satellite unit haemodialysis for people with end-stage renal failure.
By Mowatt G, Vale L, Perez J, Wyness L, Fraser C, MacLeod A, *et al*.

No. 3
Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease.
By Clark W, Raftery J, Barton P, Song F, Fry-Smith A, Burls A.

No. 4
A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus negative.
By Chilcott J, Lloyd Jones M, Wight J, Forman K, Wray J, Beverley C, *et al*.

No. 5
Systematic review and evaluation of the use of tumour markers in paediatric oncology: Ewing's sarcoma and neuroblastoma.
By Riley RD, Burchill SA, Abrams KR, Heney D, Lambert PC, Jones DR, *et al*.

No. 6
The cost-effectiveness of screening for *Helicobacter pylori* to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model.
By Roderick P, Davies R, Raftery J, Crabbe D, Pearce R, Bhandari P, *et al*.

No. 7

The clinical effectiveness and cost-effectiveness of routine dental checks: a systematic review and economic evaluation.

By Davenport C, Elley K, Salas C, Taylor-Weetman CL, Fry-Smith A, Bryan S, *et al*.

No. 8

A multicentre randomised controlled trial assessing the costs and benefits of using structured information and analysis of women's preferences in the management of menorrhagia.

By Kennedy ADM, Sculpher MJ, Coulter A, Dwyer N, Rees M, Horsley S, *et al*.

No. 9

Clinical effectiveness and cost–utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation.

By Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C.

No. 10

Evaluation of molecular tests for prenatal diagnosis of chromosome abnormalities.

By Grimshaw GM, Szczepura A, Hultén M, MacDonald F, Nevin NC, Sutton F, *et al*.

No. 11

First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS).

By Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM.

No. 12

The effectiveness and cost-effectiveness of ultrasound locating devices for central venous access: a systematic review and economic evaluation.

By Calvert N, Hind D, McWilliams RG, Thomas SM, Beverley C, Davidson A.

No. 13

A systematic review of atypical antipsychotics in schizophrenia.

By Bagnall A-M, Jones L, Lewis R, Ginnelly L, Glanville J, Torgerson D, *et al*.

No. 14

Prostate Testing for Cancer and Treatment (ProtecT) feasibility study.

By Donovan J, Hamdy F, Neal D, Peters T, Oliver S, Brindle L, *et al*.

No. 15

Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation.

By Boland A, Dundar Y, Bagust A, Haycox A, Hill R, Mujica Mota R, *et al*.

No. 16

Screening for fragile X syndrome: a literature review and modelling.

By Song FJ, Barton P, Sleightholme V, Yao GL, Fry-Smith A.

No. 17

Systematic review of endoscopic sinus surgery for nasal polyps.

By Dalziel K, Stein K, Round A, Garside R, Royle P.

No. 18

Towards efficient guidelines: how to monitor guideline use in primary care.

By Hutchinson A, McIntosh A, Cox S, Gilbert C.

No. 19

Effectiveness and cost-effectiveness of acute hospital-based spinal cord injuries services: systematic review.

By Bagnall A-M, Jones L, Richardson G, Duffy S, Riemsma R.

No. 20

Prioritisation of health technology assessment. The PATHS model: methods and case studies.

By Townsend J, Buxton M, Harper G.

No. 21

Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence.

By Cody J, Wyness L, Wallace S, Glazener C, Kilonzo M, Stearns S, *et al*.

No. 22

The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation.

By Loveman E, Cave C, Green C, Royle P, Dunn N, Waugh N.

No. 23

The role of modelling in prioritising and planning clinical trials.

By Chilcott J, Brennan A, Booth A, Karnon J, Tappenden P.

No. 24

Cost–benefit evaluation of routine influenza immunisation in people 65–74 years of age.

By Allsup S, Gosney M, Haycox A, Regan M.

No. 25

The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors.

By Wight J, Chilcott J, Holmes M, Brewer N.

No. 26

Can randomised trials rely on existing electronic data? A feasibility study to explore the value of routine data in health technology assessment.

By Williams JG, Cheung WY, Cohen DR, Hutchings HA, Longo MF, Russell IT.

No. 27

Evaluating non-randomised intervention studies.

By Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, *et al*.

No. 28

A randomised controlled trial to assess the impact of a package comprising a patient-orientated, evidence-based self-help guidebook and patient-centred consultations on disease management and satisfaction in inflammatory bowel disease.

By Kennedy A, Nelson E, Reeves D, Richardson G, Roberts C, Robinson A, *et al*.

No. 29

The effectiveness of diagnostic tests for the assessment of shoulder pain due to soft tissue disorders: a systematic review.

By Dinnes J, Loveman E, McIntyre L, Waugh N.

No. 30

The value of digital imaging in diabetic retinopathy.

By Sharp PF, Olson J, Strachan F, Hipwell J, Ludbrook A, O'Donnell M, *et al*.

No. 31

Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy.

By Law M, Wald N, Morris J.

No. 32

Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation.

By Ward S, Kaltenthaler E, Cowan J, Brewer N.

No. 33

Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review.

By Hummel S, Paisley S, Morgan A, Currie E, Brewer N.

No. 34

Literature searching for clinical and cost-effectiveness studies used in health technology assessment reports carried out for the National Institute for Clinical Excellence appraisal system.

By Royle P, Waugh N.

69

No. 19
A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder.
By Bridle C, Palmer S, Bagnall A-M, Darba J, Duffy S, Sculpher M, *et al*.

No. 20
Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis.
By Karnon J, Peters J, Platt J, Chilcott J, McGoogan E, Brewer N.

No. 21
Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement.
By Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC, *et al*.

No. 22
Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus.
By Dretzke J, Cummins C, Sandercock J, Fry-Smith A, Barrett T, Burls A.

No. 23
Clinical effectiveness and cost-effectiveness of prehospital intravenous fluids in trauma patients.
By Dretzke J, Sandercock J, Bayliss S, Burls A.

No. 24
Newer hypnotic drugs for the short-term management of insomnia: a systematic review and economic evaluation.
By Dündar Y, Boland A, Strobl J, Dodd S, Haycox A, Bagust A, *et al*.

No. 25
Development and validation of methods for assessing the quality of diagnostic accuracy studies.
By Whiting P, Rutjes AWS, Dinnes J, Reitsma JB, Bossuyt PMM, Kleijnen J.

No. 26
EVALUATE hysterectomy trial: a multicentre randomised trial comparing abdominal, vaginal and laparoscopic methods of hysterectomy.
By Garry R, Fountain J, Brown J, Manca A, Mason S, Sculpher M, *et al*.

No. 27
Methods for expected value of information analysis in complex health economic models: developments on the health economics of interferon-β and glatiramer acetate for multiple sclerosis.
By Tappenden P, Chilcott JB, Eggington S, Oakley J, McCabe C.

No. 28
Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis.
By Dalziel K, Round A, Stein K, Garside R, Price A.

No. 29
VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers.
By Iglesias C, Nelson EA, Cullum NA, Torgerson DJ, on behalf of the VenUS Team.

No. 30
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction.
By Mowatt G, Vale L, Brazzelli M, Hernandez R, Murray A, Scott N, *et al*.

No. 31
A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme.
By Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S.

No. 32
The Social Support and Family Health Study: a randomised controlled trial and economic evaluation of two alternative forms of postnatal support for mothers living in disadvantaged inner-city areas.
By Wiggins M, Oakley A, Roberts I, Turner H, Rajan L, Austerberry H, *et al*.

No. 33
Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review.
By Green JM, Hewison J, Bekker HL, Bryant, Cuckle HS.

No. 34
Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status.
By Critchley HOD, Warner P, Lee AJ, Brechin S, Guise J, Graham B.

No. 35
Coronary artery stents: a rapid systematic review and economic evaluation.
By Hill R, Bagust A, Bakhai A, Dickson R, Dündar Y, Haycox A, *et al*.

No. 36
Review of guidelines for good practice in decision-analytic modelling in health technology assessment.
By Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al*.

No. 37
Rituximab (MabThera®) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation.
By Knight C, Hind D, Brewer N, Abbott V.

No. 38
Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation.
By Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M, *et al*.

No. 39
Pegylated interferon α-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J.

No. 40
Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation.
By Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M, *et al*.

No. 41
Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups.
By Beswick AD, Rees K, Griebsch I, Taylor FC, Burke M, West RR, *et al*.

No. 42
Involving South Asian patients in clinical trials.
By Hussain-Gambles M, Leese B, Atkin K, Brown J, Mason S, Tovey P.

No. 43
Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes.
By Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N.

No. 44
Identification and assessment of ongoing trials in health technology assessment reviews.
By Song FJ, Fry-Smith A, Davenport C, Bayliss S, Adi Y, Wilson JS, *et al*.

No. 45
Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine
By Warren E, Weatherley-Jones E, Chilcott J, Beverley C.

71

No. 46
Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis.
By McCarthy CJ, Mills PM, Pullen R, Richardson G, Hawkins N, Roberts CR, *et al*.

No. 47
Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation.
By Green C, Colquitt JL, Kirby J, Davidson P, Payne E.

No. 48
Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis.
By Vickers AJ, Rees RW, Zollman CE, McCarney R, Smith CM, Ellis N, *et al*.

No. 49
Generalisability in economic evaluation studies in healthcare: a review and case studies.
By Sculpher MJ, Pang FS, Manca A, Drummond MF, Golder S, Urdahl H, *et al*.

No. 50
Virtual outreach: a randomised controlled trial and economic evaluation of joint teleconferenced medical consultations.
By Wallace P, Barber J, Clayton W, Currell R, Fleming K, Garner P, *et al*.

Volume 9, 2005

No. 1
Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne.
By Ozolins M, Eady EA, Avery A, Cunliffe WJ, O'Neill C, Simpson NB, *et al*.

No. 2
Do the findings of case series studies vary significantly according to methodological characteristics?
By Dalziel K, Round A, Stein K, Garside R, Castelnuovo E, Payne L.

No. 3
Improving the referral process for familial breast cancer genetic counselling: findings of three randomised controlled trials of two interventions.
By Wilson BJ, Torrance N, Mollison J, Wordsworth S, Gray JR, Haites NE, *et al*.

No. 4
Randomised evaluation of alternative electrosurgical modalities to treat bladder outflow obstruction in men with benign prostatic hyperplasia.
By Fowler C, McAllister W, Plail R, Karim O, Yang Q.

No. 5
A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with inoperable oesophageal cancer.
By Shenfine J, McNamee P, Steen N, Bond J, Griffin SM.

No. 6
Impact of computer-aided detection prompts on the sensitivity and specificity of screening mammography.
By Taylor P, Champness J, Given-Wilson R, Johnston K, Potts H.

No. 7
Issues in data monitoring and interim analysis of trials.
By Grant AM, Altman DG, Babiker AB, Campbell MK, Clemens FJ, Darbyshire JH, *et al*.

No. 8
Lay public's understanding of equipoise and randomisation in randomised controlled trials.
By Robinson EJ, Kerr CEP, Stevens AJ, Lilford RJ, Braunholtz DA, Edwards SJ, *et al*.

No. 9
Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies.
By Greenhalgh J, Knight C, Hind D, Beverley C, Walters S.

No. 10
Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology.
By Smith SC, Lamping DL, Banerjee S, Harwood R, Foley B, Smith P, *et al*.

No. 11
Clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) (Xigris®) for the treatment of severe sepsis in adults: a systematic review and economic evaluation.
By Green C, Dinnes J, Takeda A, Shepherd J, Hartwell D, Cave C, *et al*.

No. 12
A methodological review of how heterogeneity has been examined in systematic reviews of diagnostic test accuracy.
By Dinnes J, Deeks J, Kirby J, Roderick P.

No. 13
Cervical screening programmes: can automation help? Evidence from systematic reviews, an economic analysis and a simulation modelling exercise applied to the UK.
By Willis BH, Barton P, Pearmain P, Bryan S, Hyde C.

No. 14
Laparoscopic surgery for inguinal hernia repair: systematic review of effectiveness and economic evaluation.
By McCormack K, Wake B, Perez J, Fraser C, Cook J, McIntosh E, *et al*.

No. 15
Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation.
By Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDaid C, *et al*.

No. 16
A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine.
By Peveler R, Kendrick T, Buxton M, Longworth L, Baldwin D, Moore M, *et al*.

No. 17
Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation.
By Hartwell D, Colquitt J, Loveman E, Clegg AJ, Brodin H, Waugh N, *et al*.

No. 18
A randomised controlled comparison of alternative strategies in stroke care.
By Kalra L, Evans A, Perez I, Knapp M, Swift C, Donaldson N.

No. 19
The investigation and analysis of critical incidents and adverse events in healthcare.
By Woloshynowych M, Rogers S, Taylor-Adams S, Vincent C.

No. 20
Potential use of routine databases in health technology assessment.
By Raftery J, Roderick P, Stevens A.

No. 21
Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study.
By Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J, *et al*.

No. 22
A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis.
By Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J.

No. 23

A systematic review to examine the impact of psycho-educational interventions on health outcomes and costs in adults and children with difficult asthma.

By Smith JR, Mugford M, Holland R, Candy B, Noble MJ, Harrison BDW, *et al*.

No. 24

An evaluation of the costs, effectiveness and quality of renal replacement therapy provision in renal satellite units in England and Wales.

By Roderick P, Nicholson T, Armitage A, Mehta R, Mullee M, Gerard K, *et al*.

No. 25

Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation.

By Wilson J, Connock M, Song F, Yao G, Fry-Smith A, Raftery J, *et al*.

No. 26

Indirect comparisons of competing interventions.

By Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, *et al*.

No. 27

Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling.

By Robinson M, Palmer S, Sculpher M, Philips Z, Ginnelly L, Bowens A, *et al*.

No. 28

Outcomes of electrically stimulated gracilis neosphincter surgery.

By Tillin T, Chambers M, Feldman R.

No. 29

The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation.

By Garside R, Stein K, Castelnuovo E, Pitt M, Ashcroft D, Dimmock P, *et al*.

No. 30

Systematic review on urine albumin testing for early detection of diabetic complications.

By Newman DJ, Mattock MB, Dawnay ABS, Kerry S, McGuire A, Yaqoob M, *et al*.

No. 31

Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis.

By Cochrane T, Davey RC, Matthes Edwards SM.

No. 32

Longer term clinical and economic benefits of offering acupuncture care to patients with chronic low back pain.

By Thomas KJ, MacPherson H, Ratcliffe J, Thorpe L, Brazier J, Campbell M, *et al*.

No. 33

Cost-effectiveness and safety of epidural steroids in the management of sciatica.

By Price C, Arden N, Coglan L, Rogers P.

No. 34

The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis.

By Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL.

No. 35

Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials.

By King M, Nazareth I, Lampe F, Bower P, Chandler M, Morou M, *et al*.

No. 36

The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review.

By Bryant J, Brodin H, Loveman E, Payne E, Clegg A.

No. 37

A trial of problem-solving by community mental health nurses for anxiety, depression and life difficulties among general practice patients. The CPN-GP study.

By Kendrick T, Simons L, Mynors-Wallis L, Gray A, Lathlean J, Pickering R, *et al*.

No. 38

The causes and effects of socio-demographic exclusions from clinical trials.

By Bartlett C, Doyal L, Ebrahim S, Davey P, Bachmann M, Egger M, *et al*.

No. 39

Is hydrotherapy cost-effective? A randomised controlled trial of combined hydrotherapy programmes compared with physiotherapy land techniques in children with juvenile idiopathic arthritis.

By Epps H, Ginnelly L, Utley M, Southwood T, Gallivan S, Sculpher M, *et al*.

No. 40

A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study.

By Hobbs FDR, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, *et al*.

No. 41

Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty and total hip arthroplasty.

By Keating JF, Grant A, Masson M, Scott NW, Forbes JF.

No. 42

Long-term outcome of cognitive behaviour therapy clinical trials in central Scotland.

By Durham RC, Chambers JA, Power KG, Sharp DM, Macdonald RR, Major KA, *et al*.

No. 43

The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.

By Castelnuovo E, Stein K, Pitt M, Garside R, Payne E.

No. 44

Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis.

By Knowles R, Griebsch I, Dezateux C, Brown J, Bull C, Wren C.

No. 45

The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation.

By Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P, *et al*.

No. 46

The effectiveness of the Heidelberg Retina Tomograph and laser diagnostic glaucoma scanning system (GDx) in detecting and monitoring glaucoma.

By Kwartz AJ, Henson DB, Harper RA, Spencer AF, McLeod D.

No. 47

Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation.

By Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, *et al*.

73

No. 48
Systematic review of effectiveness of different treatments for childhood retinoblastoma.
By McDaid C, Hartley S, Bagnall A-M, Ritchie G, Light K, Riemsma R.

No. 49
Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis.
By Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R, *et al*.

No. 50
The effectiveness and cost-effectiveness of parent training/education programmes for the treatment of conduct disorder, including oppositional defiant disorder, in children.
By Dretzke J, Frew E, Davenport C, Barlow J, Stewart-Brown S, Sandercock J, *et al*.

Volume 10, 2006

No. 1
The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease.
By Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, *et al*.

No. 2
FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke.
By Dennis M, Lewis S, Cranswick G, Forbes J.

No. 3
The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews.
By Black C, Bagust A, Boland A, Walker S, McLeod C, De Verteuil R, *et al*.

No. 4
A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery.
By Whiting P, Gupta R, Burch J, Mujica Mota RE, Wright K, Marson A, *et al*.

No. 5
Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies.
By Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson PR.

No. 6
Systematic review and evaluation of methods of assessing urinary incontinence.
By Martin JL, Williams KS, Abrams KR, Turner DA, Sutton AJ, Chapple C, *et al*.

No. 7
The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review.
By Connock M, Frew E, Evans B-W, Bryan S, Cummins C, Fry-Smith A, *et al*.

No. 8
Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling.
By Garside R, Pitt M, Somerville M, Stein K, Price A, Gilbert N.

No. 9
Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation.
By Main C, Bojke L, Griffin S, Norman G, Barbieri M, Mather L, *et al*.

No. 10
Evaluation of molecular techniques in prediction and diagnosis of cytomegalovirus disease in immunocompromised patients.
By Szczepura A, Westmoreland D, Vinogradova Y, Fox J, Clark M.

No. 11
Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study.
By Wu O, Robertson L, Twaddle S, Lowe GDO, Clark P, Greaves M, *et al*.

No. 12
A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers.
By Nelson EA, O'Meara S, Craig D, Iglesias C, Golder S, Dalton J, *et al*.

No. 13
Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial).
By Michaels JA, Campbell WB, Brazier JE, MacIntyre JB, Palfreyman SJ, Ratcliffe J, *et al*.

No. 14
The cost-effectiveness of screening for oral cancer in primary care.
By Speight PM, Palmer S, Moles DR, Downer MC, Smith DH, Henriksson M, *et al*.

No. 15
Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis.
By Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, *et al*.

No. 16
Systematic review of the effectiveness and cost-effectiveness of HealOzone® for the treatment of occlusal pit/fissure caries and root caries.
By Brazzelli M, McKenzie L, Fielding S, Fraser C, Clarkson J, Kilonzo M, *et al*.

No. 17
Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment.
By Lewis SW, Davies L, Jones PB, Barnes TRE, Murray RM, Kerwin R, *et al*.

No. 18
Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation.
By Rodgers M, Nixon J, Hempel S, Aho T, Kelly J, Neal D, *et al*.

No. 19
Cognitive behavioural therapy in addition to antispasmodic therapy for irritable bowel syndrome in primary care: randomised controlled trial.
By Kennedy TM, Chalder T, McCrone P, Darnley S, Knapp M, Jones RH, *et al*.

No. 20
A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1.
By Connock M, Juarez-Garcia A, Frew E, Mans A, Dretzke J, Fry-Smith A, *et al*.

No. 21
Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation.
By Wright M, Grieve R, Roberts J, Main J, Thomas HC, on behalf of the UK Mild Hepatitis C Trial Investigators.

No. 22
Pressure relieving support surfaces: a randomised evaluation.
By Nixon J, Nelson EA, Cranny G, Iglesias CP, Hawkins K, Cullum NA, *et al*.

No. 23
A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents.
By King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G, *et al*.

No. 24
The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review.
By Connock M, Burls A, Frew E, Fry-Smith A, Juarez-Garcia A, McCabe C, *et al*.

No. 25
Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model.
By Thomas KS, Keogh-Brown MR, Chalmers JR, Fordham RJ, Holland RC, Armstrong SJ, *et al*.

No. 26
A systematic literature review of the effectiveness of non-pharmacological interventions to prevent wandering in dementia and evaluation of the ethical implications and acceptability of their use.
By Robinson L, Hutchings D, Corner L, Beyer F, Dickinson H, Vanoli A, *et al*.

No. 27
A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modelling of cost-effectiveness and cost–utility for these groups in a UK context.
By Buxton M, Caine N, Chase D, Connelly D, Grace A, Jackson C, *et al*.

No. 28
Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation.
By Shepherd J, Jones J, Takeda A, Davidson P, Price A.

No. 29
An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial.
By Harvey S, Stevens K, Harrison D, Young D, Brampton W, McCabe C, *et al*.

No. 30
Accurate, practical and cost-effective assessment of carotid stenosis in the UK.
By Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, *et al*.

No. 31
Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation.
By Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, *et al*.

No. 32
The cost-effectiveness of testing for hepatitis C in former injecting drug users.
By Castelnuovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A, *et al*.

No. 33
Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation.
By Kaltenthaler E, Brazier J, De Nigris E, Tumur I, Ferriter M, Beverley C, *et al*.

No. 34
Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy.
By Williams C, Brunskill S, Altman D, Briggs A, Campbell H, Clarke M, *et al*.

No. 35
Psychological therapies including dialectical behaviour therapy for borderline personality disorder: a systematic review and preliminary economic evaluation.
By Brazier J, Tumur I, Holmes M, Ferriter M, Parry G, Dent-Brown K, *et al*.

No. 36
Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model.
By Whiting P, Westwood M, Bojke L, Palmer S, Richardson G, Cooper J, *et al*.

No. 37
Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme.
By O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A.

No. 38
A comparison of the cost-effectiveness of five strategies for the prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling.
By Brown TJ, Hooper L, Elliott RA, Payne K, Webb R, Roberts C, et al.

No. 39
The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review.
By Waugh N, Black C, Walker S, McIntyre L, Cummins E, Hillis G.

No. 40
What are the clinical outcome and cost-effectiveness of endoscopy undertaken by nurses when compared with doctors? A Multi-Institution Nurse Endoscopy Trial (MINuET).
By Williams J, Russell I, Durai D, Cheung W-Y, Farrin A, Bloor K, *et al*.

No. 41
The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation.
By Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P.

No. 42
A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness.
By Chen Y-F, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, *et al*.

No. 43
Telemedicine in dermatology: a randomised controlled trial.
By Bowns IR, Collins K, Walters SJ, McDonagh AJG.

No. 44
Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model.
By Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C.

No. 45
Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation.
By Murray A, Lourenco T, de Verteuil R, Hernandez R, Fraser C, McKinley A, *et al*.

No. 46
Etanercept and efalizumab for the treatment of psoriasis: a systematic review.
By Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Bravo Vergel Y, *et al*.

No. 47
Systematic reviews of clinical decision tools for acute abdominal pain.
By Liu JLY, Wyatt JC, Deeks JJ, Clamp S, Keen J, Verde P, *et al*.

No. 48
Evaluation of the ventricular assist device programme in the UK.
By Sharples L, Buxton M, Caine N, Cafferty F, Demiris N, Dyer M, *et al*.

75

No. 24
The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis.

By McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, Edwards D, *et al*.

No. 25
A randomised controlled trial and economic evaluation of direct versus indirect and individual versus group modes of speech and language therapy for children with primary language impairment.

By Boyle J, McCartney E, Forbes J, O'Hare A.

No. 26
Hormonal therapies for early breast cancer: systematic review and economic evaluation.

By Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L.

No. 27
Cardioprotection against the toxic effects of anthracyclines given to children with cancer: a systematic review.

By Bryant J, Picot J, Levitt G, Sullivan I, Baxter L, Clegg A.

No. 28
Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation.

By McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y, *et al*.

No. 29
Prenatal screening and treatment strategies to prevent group B streptococcal and other bacterial infections in early infancy: cost-effectiveness and expected value of information analyses.

By Colbourn T, Asseburg C, Bojke L, Philips Z, Claxton K, Ades AE, *et al*.

No. 30
Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review.

By Garrison KR, Donell S, Ryder J, Shemilt I, Mugford M, Harvey I, *et al*.

No. 31
A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial.

By Prescott RJ, Kunkler IH, Williams LJ, King CC, Jack W, van der Pol M, *et al*.

No. 32
Current practice, accuracy, effectiveness and cost-effectiveness of the school entry hearing screen.

By Bamford J, Fortnum H, Bristow K, Smith J, Vamvakas G, Davies L, *et al*.

No. 33
The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: a systematic review and economic evaluation.

By Black C, Cummins E, Royle P, Philip S, Waugh N.

No. 34
Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis.

By Thompson Coon J, Rogers G, Hewson P, Wright D, Anderson R, Cramp M, *et al*.

No. 35
The Birmingham Rehabilitation Uptake Maximisation Study (BRUM). Homebased compared with hospital-based cardiac rehabilitation in a multi-ethnic population: cost-effectiveness and patient adherence.

By Jolly K, Taylor R, Lip GYH, Greenfield S, Raftery J, Mant J, *et al*.

No. 36
A systematic review of the clinical, public health and cost-effectiveness of rapid diagnostic tests for the detection and identification of bacterial intestinal pathogens in faeces and food.

By Abubakar I, Irvine L, Aldus CF, Wyatt GM, Fordham R, Schelenz S, *et al*.

No. 37
A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial.

By Marson AG, Appleton R, Baker GA, Chadwick DW, Doughty J, Eaton B, *et al*.

No. 38
Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anti-coagulation therapy: a systematic review and economic modelling.

By Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D, *et al*.

No. 39
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder.

By Soares-Weiser K, Bravo Vergel Y, Beynon S, Dunn G, Barbieri M, Duffy S, *et al*.

No. 40
Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation.

By Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A.

No. 41
The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation.

By Burr JM, Mowatt G, Hernández R, Siddiqui MAR, Cook J, Lourenco T, *et al*.

No. 42
Acceptability, benefit and costs of early screening for hearing disability: a study of potential screening tests and models.

By Davis A, Smith P, Ferguson M, Stephens D, Gianopoulos I.

No. 43
Contamination in trials of educational interventions.

By Keogh-Brown MR, Bachmann MO, Shepstone L, Hewitt C, Howe A, Ramsay CR, *et al*.

No. 44
Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers.

By Facey K, Bradbury I, Laking G, Payne E.

No. 45
The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation.

By Garside R, Pitt M, Anderson R, Rogers G, Dyer M, Mealing S, *et al*.

No. 46
Drug-eluting stents: a systematic review and economic evaluation.

By Hill RA, Boland A, Dickson R, Dündar Y, Haycox A, McLeod C, *et al*.

No. 47
The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model.

By Fox M, Mealing S, Anderson R, Dean J, Stein K, Price A, *et al*.

No. 48
Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study.

By Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knight R, *et al*.

No. 20

Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in children under the age of 12 years.

By Main C, Shepherd J, Anderson R, Rogers G, Thompson-Coon J, Liu Z, *et al*.

No. 21

Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation.

By Ara R, Tumur I, Pandor A, Duenas A, Williams R, Wilkinson A, *et al*.

No. 22

Topical or oral ibuprofen for chronic knee pain in older people. The TOIB study.

By Underwood M, Ashby D, Carnes D, Castelnuovo E, Cross P, Harding G, *et al*.

No. 23

A prospective randomised comparison of minor surgery in primary and secondary care. The MiSTIC trial.

By George S, Pockney P, Primrose J, Smith H, Little P, Kinley H, *et al*.

No. 24

A review and critical appraisal of measures of therapist–patient interactions in mental health settings.

By Cahill J, Barkham M, Hardy G, Gilbody S, Richards D, Bower P, *et al*.

No. 25

The clinical effectiveness and cost-effectiveness of screening programmes for amblyopia and strabismus in children up to the age of 4–5 years: a systematic review and economic evaluation.

By Carlton J, Karnon J, Czoski-Murray C, Smith KJ, Marr J.

No. 26

A systematic review of the clinical effectiveness and cost-effectiveness and economic modelling of minimal incision total hip replacement approaches in the management of arthritic disease of the hip.

By de Verteuil R, Imamura M, Zhu S, Glazener C, Fraser C, Munro N, *et al*.

No. 27

A preliminary model-based assessment of the cost–utility of a screening programme for early age-related macular degeneration.

By Karnon J, Czoski-Murray C, Smith K, Brand C, Chakravarthy U, Davis S, *et al*.

No. 28

Intravenous magnesium sulphate and sotalol for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and economic evaluation.

By Shepherd J, Jones J, Frampton GK, Tanajewski L, Turner D, Price A.

No. 29

Absorbent products for urinary/faecal incontinence: a comparative evaluation of key product categories.

By Fader M, Cottenden A, Getliffe K, Gage H, Clarke-O'Neill S, Jamieson K, *et al*.

No. 30

A systematic review of repetitive functional task practice with modelling of resource use, costs and effectiveness.

By French B, Leathley M, Sutton C, McAdam J, Thomas L, Forster A, *et al*.

No. 31

The effectiveness and cost-effectivness of minimal access surgery amongst people with gastro-oesophageal reflux disease – a UK collaborative study. The REFLUX trial.

By Grant A, Wileman S, Ramsay C, Bojke L, Epstein D, Sculpher M, *et al*.

No. 32

Time to full publication of studies of anti-cancer medicines for breast cancer and the potential for publication bias: a short systematic review.

By Takeda A, Loveman E, Harris P, Hartwell D, Welch K.

No. 33

Performance of screening tests for child physical abuse in accident and emergency departments.

By Woodman J, Pitt M, Wentz R, Taylor B, Hodes D, Gilbert RE.

No. 34

Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation.

By Rodgers M, McKenna C, Palmer S, Chambers D, Van Hout S, Golder S, *et al*.

No. 35

Systematic review and economic modelling of effectiveness and cost utility of surgical treatments for men with benign prostatic enlargement.

By Lourenco T, Armstrong N, N'Dow J, Nabi G, Deverill M, Pickard R, *et al*.

No. 36

Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: a systematic review and economic evaluation.

By Wang D, Cummins C, Bayliss S, Sandercock J, Burls A.

Volume 13, 2009

No. 1

Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia: a systematic review and economic evaluation.

By McLeod C, Fleeman N, Kirkham J, Bagust A, Boland A, Chu P, *et al*.

No. 2

Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis.

By Simpson EL, Stevenson MD, Rawdin A, Papaioannou D.

No. 3

Surgical procedures and non-surgical devices for the management of non-apnoeic snoring: a systematic review of clinical effects and associated treatment costs.

By Main C, Liu Z, Welch K, Weiner G, Quentin Jones S, Stein K.

No. 4

Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea–hypopnoea syndrome: a systematic review and economic analysis.

By McDaid C, Griffin S, Weatherly H, Durée K, van der Burgt M, van Hout S, Akers J, *et al*.

No. 5

Use of classical and novel biomarkers as prognostic risk factors for localised prostate cancer: a systematic review.

By Sutcliffe P, Hummel S, Simpson E, Young T, Rees A, Wilkinson A, *et al*.

No. 6

The harmful health effects of recreational ecstasy: a systematic review of observational evidence.

By Rogers G, Elston J, Garside R, Roome C, Taylor R, Younger P, *et al*.

No. 7

Systematic review of the clinical effectiveness and cost-effectiveness of oesophageal Doppler monitoring in critically ill and high-risk surgical patients.

By Mowatt G, Houston G, Hernández R, de Verteuil R, Fraser C, Cuthbertson B, *et al*.

No. 8

The use of surrogate outcomes in model-based cost-effectiveness analyses: a survey of UK Health Technology Assessment reports.

By Taylor RS, Elston J.

No. 9

Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) – a randomised controlled trial.

By Potter J, Mistri A, Brodie F, Chernova J, Wilson E, Jagger C, *et al*.

No. 10
Routine antenatal anti-D prophylaxis for RhD-negative women: a systematic review and economic evaluation.
By Pilgrim H, Lloyd-Jones M, Rees A.

No. 11
Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation.
By Tappenden P, Jackson R, Cooper K, Rees A, Simpson E, Read R, *et al*.

No. 12
Improving the evaluation of therapeutic interventions in multiple sclerosis: the role of new psychometric methods.
By Hobart J, Cano S.

No. 13
Treatment of severe ankle sprain: a pragmatic randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of three types of mechanical ankle support with tubular bandage. The CAST trial.
By Cooke MW, Marsh JL, Clark M, Nakash R, Jarvis RM, Hutton JL, *et al*., on behalf of the CAST trial group.

No. 14
Non-occupational postexposure prophylaxis for HIV: a systematic review.
By Bryant J, Baxter L, Hird S.

No. 15
Blood glucose self-monitoring in type 2 diabetes: a randomised controlled trial.
By Farmer AJ, Wade AN, French DP, Simon J, Yudkin P, Gray A, *et al*.

No. 16
How far does screening women for domestic (partner) violence in different health-care settings meet criteria for a screening programme? Systematic reviews of nine UK National Screening Committee criteria.
By Feder G, Ramsay J, Dunne D, Rose M, Arsene C, Norman R, *et al*.

No. 17
Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation.
By Simpson, EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J.

No. 18
The role of magnetic resonance imaging in the identification of suspected acoustic neuroma: a systematic review of clinical and cost-effectiveness and natural history.
By Fortnum H, O'Neill C, Taylor R, Lenthall R, Nikolopoulos T, Lightfoot G, *et al*.

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Development of a decision support tool for primary care management of patients with abnormal liver function tests without clinically apparent liver disease: a record-linkage population cohort study and decision analysis (ALFIE).
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By Hay AD, Redmond NM, Costelloe C, Montgomery AA, Fletcher M, Hollinghurst S, *et al*.

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A randomised controlled trial to compare minimally invasive glucose monitoring devices with conventional monitoring in the management of insulin-treated diabetes mellitus (MITRE).
By Newman SP, Cooke D, Casbard A, Walker S, Meredith S, Nunn A, *et al*.

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