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D Craig, C McDaid, T Fonseca, C Stock,
S Duffy and N Woolacott

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Are adverse effects incorporated in economic models? An initial review of current practice

D Craig, C McDaid, T Fonseca, C Stock, S Duffy and N Woolacott*

CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York, UK

*Corresponding author

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The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

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

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 07/57/01. The protocol was agreed in May 2007. The assessment report began editorial review in August 2008 and was accepted for publication in May 2009. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Are adverse effects incorporated in economic models? An initial review of current practice

D Craig, C McDaid, T Fonseca, C Stock, S Duffy and N Woolacott*

CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York, UK

*Corresponding author

Objectives: To identify methodological research on the incorporation of adverse effects in economic models and to review current practice.

Data sources: Major electronic databases (Cochrane Methodology Register, Health Economic Evaluations Database, NHS Economic Evaluation Database, EconLit, EMBASE, Health Management Information Consortium, IDEAS, MEDLINE and Science Citation Index) were searched from inception to September 2007. Health technology assessment (HTA) reports commissioned by the National Institute for Health Research (NIHR) HTA programme and published between 2004 and 2007 were also reviewed.

Review methods: The reviews of methodological research on the inclusion of adverse effects in decision models and of current practice were carried out according to standard methods. Data were summarised in a narrative synthesis.

Results: Of the 719 potentially relevant references in the methodological research review, five met the inclusion criteria; however, they contained little information of direct relevance to the incorporation of adverse effects in models. Of the 194 HTA monographs published from 2004 to 2007, 80 were reviewed, covering a range of research and therapeutic areas. In total, 85% of the reports included adverse effects in the clinical effectiveness review and 54% of the decision models included adverse effects in the model; 49% included adverse effects in the clinical review and model. The link between adverse effects in the clinical review and model was generally weak; only 3/80 (< 4%) used the results of a meta-analysis from the systematic review of clinical effectiveness and none used only data from the review without further manipulation. Of the models including adverse effects, 67% used a clinical adverse effects parameter, 79% used a cost of adverse effects parameter, 86% used one of these and 60% used both. Most models (83%) used utilities, but only two (2.5%) used solely utilities to incorporate adverse effects and were explicit that the utility captured relevant adverse effects; 53% of those models that included utilities derived them from patients on treatment and could therefore be interpreted as capturing adverse effects. In total, 30% of the models that included adverse effects used withdrawals related to drug toxicity and therefore might be interpreted as using withdrawals to capture adverse effects, but this was explicitly stated in only three reports. Of the 37 models that did not include adverse effects, 18 provided justification for this omission, most commonly lack of data; 19 appeared to make no explicit consideration of adverse effects in the model.

Conclusions: There is an implicit assumption within modelling guidance that adverse effects are very important but there is a lack of clarity regarding how they should be dealt with and considered in modelling. In many cases a lack of clear reporting in the HTAs made it extremely difficult to ascertain what had actually been carried out in consideration of adverse effects. The main recommendation is for much clearer and explicit reporting of adverse effects, or their exclusion, in decision models and for explicit recognition in future guidelines that 'all relevant outcomes' should include some consideration of adverse events.

Contents

Due to the extensive nature of the appendices, Appendix 5 is available only in electronic format. The PDF file of the full report is available at www.hta.ac.uk/1676. It will also be available on *HTA on CD* (see the inside front cover for full details).

Glossary and list of abbreviations

Glossary

Adverse effect An undesirable and unintended effect of an intervention.

Adverse event Any noxious, pathological or unintended change in anatomical, physical or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of a clinical study whether or not considered treatment related. It includes exacerbation of pre-existing conditions or events, intercurrent illnesses, accidents, drug interactions or the significant worsening of disease.

Cost-effectiveness analysis Type of economic evaluation in which the health outcomes are expressed in natural (non-monetary) units.

Decision analysis A quantitative approach that assesses the relative value of different decision options under conditions of uncertainty. It usually involves the construction of a decision-analytic model.

Decision model See Decision analysis.

Economic decision model A decision model constructed for cost-effectiveness analysis.

HTA (health technology assessment) Assessment of the benefit of health-care interventions, typically comprising a systematic review of clinical effectiveness and an assessment of the cost-effectiveness of the intervention.

Quality-adjusted life-year An index of survival that is weighted or adjusted by a utility value associated with patients' quality of life during the survival period.

Utility The measure of the value of a given outcome (health state) in terms of the desirability or preference that an individual or society has for that outcome (measured on a 0–1 scale).

List of abbreviations

AE	adverse effect
HRQoL	health-related quality of life
HTA	health technology assessment
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
QALY	quality-adjusted life-year
RAA	research activity area
RCT	randomised controlled trial
TAR	Technology Assessment Report

Executive summary

Background

Health-care interventions have the potential for unwanted harm as well as the anticipated benefit. Decisions about adoption of treatment should consider both positive benefits and negative effects. Technology assessment, which comprises a systematic review of the clinical effectiveness evidence and an economic evaluation, is being used increasingly by decision-makers to help make treatment recommendations.

The overall aim of a technology assessment in health care is to aid the decision-maker in making a choice about the use of resources. There is a need to ensure that for all interventions being compared the relevant outcomes and resource use have been captured in the evaluation. All interventions will have multiple outcomes and outcomes will vary between interventions. In practice, outcomes are incorporated into models in a variety of ways: relative treatment effects, withdrawals, and costs as well as utilities. It is not clear that adverse effects are always considered as one of these outcomes despite their importance.

The initial step in developing the systematic incorporation of adverse effects in technology assessments should be to investigate existing methodological research and to review current practice in technology assessment to inform future developments.

Objectives

The two main objectives were: (1) to identify what, if any, methodological research exists on the incorporation of adverse effects in economic models and (2) to review current practice.

Methods

We conducted a review of methodological research related to the inclusion of adverse effects in decision models. Searches were conducted of relevant databases [Cochrane Methodology Register, Health Economic Evaluations Database (HEED), NHS Economic Evaluation Database (NHS EED), EconLit, EMBASE, Health Management Information Consortium, IDEAS (Internet Documents in Economics Access Service), MEDLINE and Science Citation Index] from inception to September 2007. In addition, relevant organisation websites were browsed for guidelines as potential sources of relevant research literature.

We conducted a review of health technology assessment reports. Reports were included if they were commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme and published between 2004 and 2007 and if they investigated the clinical and cost-effectiveness of a health technology using a systematic review and an economic model. Reports from 2004 onwards were selected because they would reflect current practice [2004 was the year that the National Institute for Health and Clinical Excellence (NICE) methods guide was issued] and, also, a previous study included reports up to and including 2003.

Results

Methodological research

The electronic searches identified 719 potentially relevant references. Five published articles met the inclusion criteria for the review; however, even these articles contained very little information or guidance of direct relevance to the incorporation of adverse effects in models. It is clear from the available guidance that *all* relevant outcomes should be included in the economic decision model, and there appears to be a general if not clearly stated consensus that this includes adverse effects.

Review of current practice

Of the 194 HTA monographs published from 2004 to 2007, 80 comprised both a systematic review and an economic model and were reviewed.

The majority of the reports (76%) were evaluations of treatments and therapeutic interventions, predominantly of pharmaceuticals. There were

20 reports of detection, screening and diagnosis (mainly evaluating diagnostic tests) and two in the area of prevention. Some reports spanned more than one research area, for example diagnosis and treatment. A wide range of therapeutic areas were investigated, most commonly cancer, cardiovascular diseases, musculoskeletal disorders, metabolic and endocrine disorders and mental health.

In total, 85% of the reports included adverse effects in the clinical effectiveness review and 54% of the decision models included adverse effects in the model. Just under half (49%) included adverse effects in both the clinical review and the model.

The link between the adverse effects in the clinical review and those in the model was generally weak. Although 18 of the models used adverse effect data from the clinical review and 14 reviews did include a meta-analysis of adverse effects, only 3/80 (< 4%) used the results of a meta-analysis from the systematic review of clinical effectiveness and none of these was able to use only the data from the review without some further manipulation being required.

There was no apparent relationship between inclusion of adverse effects in the model and therapeutic area, type of intervention or year of report, nor the type of model.

Of those models that did include adverse effects, 67% used a clinical adverse effects parameter (i.e. any effect parameter that is directly populated from the output of a clinical trial or the clinical effectiveness review), 79% used a cost of adverse effects parameter, 86% used one of these and 60% used both.

In some situations in which an explicit parameter had not been included it is possible that adverse effects may still have been implicitly considered, for example through the use of utilities. Most models (83%) used utilities but determining whether these utilities captured adverse effects was more difficult. Only two models (2.5%) used solely utilities to incorporate adverse effects and were explicit in their beliefs that the utility captured relevant adverse effects. A total of 35 reports (53% of those models that included utilities and 44% of all reports) derived utilities from patients on treatment and could therefore be interpreted as capturing adverse effects.

In total, 13 reports (30% of those models that included adverse effects and 16% of all reports) used withdrawals related to drug toxicity and therefore might be interpreted as using withdrawals to capture adverse effects, but this was explicitly stated in only three reports. However, the remaining 10 models also incorporated adverse effects explicitly through at least one other parameter.

Of the 37 models that were reviewed and classed as not having included adverse effects in the decision model, 18 provided some justification for this omission. Most commonly the justification was a lack of data, followed by the adverse effects having minimal impact on quality of life or cost.

Overall, 43 models included adverse effects and, as previously stated, 18 that did not include them gave a reason for their omission. Thus, 19/80 (24%) HTAs appeared to have made no explicit consideration of adverse effects in the model. No judgement was made on the need for, or appropriateness of, inclusion of adverse events in the models. It is possible that, when adverse events were not considered, their omission was appropriate and the only omission is some acknowledgement of this fact.

Conclusions

- The findings of the review of methodology papers show that, although there appears to be an implicit assumption within modelling guidance that adverse effects are very important, there appears to be a lack of clarity regarding how they should be dealt with and considered in modelling.
- The review found that, in line with the general guidance for decision modelling, all important outcomes appear to be included and most HTAs do include adverse effects in the decision model, although we have made no assessment on the appropriateness of the adverse events included or the validity of the methods used.
- The inclusion of adverse effects in the decision model did not appear to be dictated by the therapeutic area, type of intervention or type of model, nor how adverse effects were dealt with in the clinical review.
- In most cases the link between the adverse effects data used in the model and that presented in the systematic review was weak.
- In many cases a lack of clear reporting made it extremely difficult to ascertain what had actually been carried out in consideration of adverse effects. The transparency of the reports that were reviewed for this project varied greatly.

The main recommendation is for much clearer and explicit reporting of adverse effects, or their exclusion, in decision models. There should be explicit recognition in future guidelines that 'all relevant outcomes' should include some consideration of adverse events. As a minimum, separate sections on adverse effects should be included in the clinical effectiveness and modelling chapters of every technology assessment report. Whenever the inclusion of adverse effects is not relevant a justification should be explicitly provided by the authors. By doing this, the readers will be made aware that adverse effects were considered at some stage of the process.

Improved links between the outcomes of the model and the data inputs presented in the systematic review and model description may aid the reader's understanding and support the decision-maker. Even when a systematic review of adverse effect data is not feasible, summaries of such data should be presented in the clinical effectiveness review.

This review has not investigated how adequately adverse effects are captured. The methods used by analysts to determine the relevant outcomes to include in a decision model, and how they incorporate those relevant outcomes in the model, are unclear and require further research. Some quantification as to when generic preference scores might appropriately capture adverse effects is still required and, further, it may be appropriate to try to establish in what instances the possible insensitivities of a generic preference score could lead to misleading outcomes.

Chapter 1
Background

Adverse effects of health-care interventions

Health-care interventions have the potential for unwanted harm as well as the hoped-for benefit. These unwanted harms are known as adverse effects. Occurrences of harm recorded during a clinical study of a health-care intervention, and which may or may not be caused by the intervention, are referred to as adverse events. All drugs are associated with potential adverse effects, more specifically referred to as adverse drug reactions, some of which can be anticipated from the preclinical and clinical pharmacology and others which are unexpected and are identified only after considerable patient exposure in clinical practice. Some adverse effects in the context of one indication may actually represent another therapeutic indication for the drug. Procedural interventions are not necessarily free of unwanted adverse effects. A less-invasive surgical procedure may be beneficial in the short term but may be associated with an increased rate of reintervention in the long term, for example stapled haemorrhoidopexy.[1] Psychosocial interventions, although often assumed to be benign, can also have unwanted adverse effects but these may not be investigated.[2] Diagnostic tests can also have unwanted adverse effects, either directly, such as through adverse reactions to contrast media,[3] or through the negative consequences of false positives, which can result in unnecessary treatments, or iatrogenic effects, through raising concerns over health.[4] It is self-evident that the benefits of a treatment must not be outweighed by adverse effects, but how data are found and used to populate these two sides of the equation is complicated.

Research into adverse effects can be problematic in terms of their identification, quantification and valuation. In drug development, preclinical studies are conducted on homogeneous, inbred healthy animals and early investigations in humans are restricted to healthy individuals. Such studies are inadequate for the prediction of idiosyncratic adverse events that may occur in the context of the heterogeneous population of unique genetic and environmental factors. Randomised controlled trials (RCTs) designed primarily to investigate efficacy will, based on the early evidence, exclude patients at risk of adverse effects and therefore the data on adverse effects derived from such RCTs will never provide a complete picture of the adverse effect profile of a drug.[5] Additionally, the time horizon of many RCTs will not be long enough to capture rare but important adverse events. Similarly, RCTs of non-pharmacological interventions are likely to have selected populations, thereby limiting their generalisability. Larger observational studies, although not suffering from the failings of the RCTs, are limited by confounding factors, which prevent the drawing of unequivocal causal links between the intervention and an adverse event. Furthermore, even these large studies are limited by sample size when rare adverse effects are considered.

In addition to the difficulties in identifying adverse effects and deriving accurate estimates of their incidence, valuing them is also problematic. How does one weight the numerous minor adverse effects against the risk of a single serious event? How does the researcher value the reduction in risk of very rare events? These issues can also be problematic for other outcomes that are used to inform decision-making and they are part of the reason that many advocate the use of a single index score, which should, if appropriately measured, capture all relevant outcomes.

Adverse effects in health technology assessments

A recently published definition of health technology assessment (HTA) states that it is '… a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective health policies that are patient focused and seek to achieve best value. Despite its

policy goals HTA must be firmly rooted in research and the scientific method' (European network for Health Technology Assessment: www.eunethta.net/HTA/). Across countries the practice of HTA varies; often it comprises a systematic review of the clinical effectiveness evidence and an economic evaluation. This form of report is increasingly being used by decision-makers to help make treatment recommendations. For example, technology assessment reports that include a decision model are a key part of the decision-making process used by the National Institute for Health and Clinical Excellence (NICE) in England and Wales.[6] For the purpose of this project we have focused on technology assessments that have included both a systematic review and a decision model.

The ultimate objective of the assessment of health-care technologies is to assist decision-makers in the difficult task of choosing between two (or more) mutually exclusive alternatives by comparing benefits obtained against the resources consumed. In the absence of perfect information, decision models are a helpful tool to provide evidence so that societal health gains can be maximised from scarce resources. There is a need to ensure that for all interventions being compared the relevant outcomes and resource use have been captured in the evaluation. All interventions will have multiple outcomes and outcomes will vary between interventions. Importantly, these outcomes should be incorporated using some standard index; this may be best achieved through the use of a generic preference score [utility, health-related quality of life (HRQoL)] that will allow interventions with more than one outcome to be easily compared. The use of a single index allows the multidimensional changes in health to be translated into a single score. However, although this is the ideal method for incorporating the outcomes of an intervention into a decision model, in practice finding/calculating utilities that capture all of the relevant outcomes is difficult. Thus, a utility may capture one aspect of an intervention adequately, for example the efficacy, but may reflect poorly other outcomes, such as adverse effects. In practice, outcomes are incorporated into models in a variety of ways: relative treatment effects, withdrawals and costs, as well as utilities. Because of this diversity of methods, transparent reporting of decision models is essential.

Decisions about adoption of treatment should consider both negative and positive effects.[7–9] It has been recommended that systematic reviews of adverse effects should be considered as important as the review of efficacy. However, the vast majority of systematic reviews focus on efficacy or clinical effectiveness without adequately addressing adverse effects.[10] Similarly, it is not clear that economic evaluations always consider, and incorporate, the appropriate adverse effects. Decision models provide us with an explicit framework that we can use to help inform decision-making. However, the output of any model is heavily dependent on the model inputs and any results can be considered robust only if all relevant inputs have been included. For many interventions this should include some consideration of adverse effects.

If there is a failure of technology assessments to adequately incorporate adverse effects, this could limit the results obtained or recommendations made. The impact of including adverse events in the economic model could potentially change the findings; interventions found to be cost-effective may be shown to be not cost-effective, or less cost-effective than comparable treatments, when adverse effects are considered properly.

To redress this potential overemphasis on efficacy within technology assessment, the consideration of adverse effects data needs to be encouraged. The Centre for Reviews and Dissemination (CRD)[11] and the Cochrane Collaboration[12] have recently published initial guidance on incorporating adverse effects in systematic reviews. However, the need to include the results of such systematic reviews into economic models has not been addressed directly. Although the methodological guidance on good practice for decision-analytic modelling in health care issued by NICE in 2004 and updated in 2008[6] does not specifically address how adverse effects data are incorporated into the model the guidance does acknowledge the importance of their inclusion.

There is a possibility that the importance of adverse effects in decision models is undervalued. It is unclear how they are considered and incorporated in economic models; it is possible that they do not appropriately contribute to the evidence provided to decision-makers. The initial step in developing the methodology regarding the incorporation of adverse effects in technology assessments and to produce further guidance should be to review current practice to establish the current status.

Objectives

There were two main objectives to this research. They were:

1. To identify what, if any, methodological research exists on the incorporation of adverse effects in economic models.
2. To review published technology appraisals to establish the current practice of researchers. Our review did not fulfil the intentions laid out in the protocol in that it did not address the question, 'Are adverse effects incorporated adequately and appropriately in economic models?'. We decided that within this first stage project such subjective questions could not be addressed and thus we limited the review to the more objective questions of whether adverse effects were included and how they were included.

The aim of this research is to generate a sound body of information upon which to build recommendations for future research and/or best practice.

Chapter 2
Review of methodological research

Introduction

Before embarking on a review of practice in relation to the incorporation of adverse effects in economic models it was important to investigate the relevant methodological research available to researchers. We therefore conducted a review of such research. Because of the difficulties of searching and screening for publications relating to methodological research the publications and information identified by this review should be taken as a reasonable, but not necessarily exhaustive, sample of the existing information.

Methods of review of methodological research

Literature searching

Searches of all relevant databases were conducted to identify all relevant publications. Searches were initially undertaken in databases in which studies have been specifically designated as 'methodological'. Supplementary searches were then undertaken in larger more general health and economic databases.

Methodology databases searched:

- Cochrane Methodology Register (CMR)
- Health Economic Evaluations Database (HEED)
- NHS Economic Evaluation Database (NHS EED)

Other databases searched:

- EconLit
- EMBASE
- Health Management Information Consortium (HMIC)
- IDEAS (Internet Documents in Economics Access Service)
- MEDLINE
- MEDLINE In-Process
- Science Citation Index (SCI)

Searching for methodological studies in the 'methodology' databases was relatively straightforward. The CMR consists entirely of studies that report on methods used in the conduct of trials and reviews and both NHS EED and HEED have records that have been designated as methodological studies. These records can be retrieved by searching for the appropriate term in the record-type field.

The larger more general databases proved to be more difficult to search. None of the databases has assigned publication type terms to describe 'methodology' studies. It is also notoriously difficult to identify studies about 'adverse events' and 'economic models' as both have poor or non-existent subject indexing terms, are inadequately reported and consist of ill-defined terminology. Therefore a wide range of terms was used for each of these facets in order to capture all relevant records. Relevant records would have to contain reference to all three facets ('adverse events', 'economic modelling' and 'methodology'). It was recognised that some potentially relevant subject indexing terms were too broad and their inclusion would identify a large number of irrelevant records; such terms were removed from the search strategy. For similar reasons, certain free text terms (e.g. complication$, toxicity, safety, safe and methods, methodological, methodology, challenge$, guidance) were searched for in the title field only. Because one particularly useful study by Alex Sutton and Nicola Cooper[13] had been identified before searching, additional citation searches were undertaken in SCI for other potentially relevant studies by these authors.

In addition to these searches relevant organisation websites were browsed for relevant guidelines as a source of references to methodological research. These websites included those of NICE, the Canadian Agency for Drugs and Technologies in Health (CADTH), the Australian Department of Health and Ageing, and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). The Guidelines Around the World website list proved particularly useful (www.ispor.org/peguidelines/index.asp).

Details of the searching and screening methods are given in Appendix 1.

Selection and synthesis of included publications

It was anticipated that there would be very little available research relating to the incorporation of adverse effects into economic models and therefore our review included any published articles describing any methodological issues relevant to the incorporation of adverse effects into economic decision models. The inclusion criteria applied were:

1. the article had to discuss the methodology of economic decision modelling
2. the article had to discuss the incorporation of outcomes in an economic decision model with relevance to adverse effects.

National guidelines were not included in the review. Such guidelines should be based on methodological research but are not methodological research themselves.

Two reviewers independently screened the titles and abstracts of all articles identified by the searches. Any article of potential relevance was ordered and the full text of those articles was screened again for relevance by a third reviewer. Those articles that met the inclusion criteria were included in the review.

The data extracted included the objectives of the work described in the articles and any statements, results and conclusions relevant to the incorporation of adverse effects in models. The relevant information was examined for common themes and summarised by these themes.

Results of review of methodological research

The electronic searches identified 736 references. Of these, 44 were considered to be potentially relevant and were ordered for screening of the full paper. Full paper screening identified five published articles that met the inclusion criteria for the review (*Table 1*). The list of excluded articles is given in Appendix 6. It should be noted that even these 'included' articles contained very little information or guidance of direct relevance to the incorporation of adverse effects in models. The full data extraction is given in Appendix 4.

All five publications were appraisals of existing guidelines or practice and aimed to provide guidance for modellers. In two publications[14,15] the information relevant to adverse effects in models was derived from an appraisal of existing guidelines, whereas three publications[14,16,17] aimed to develop a checklist or specific guidance for modellers (Phillips *et al.*[14] did both); one publication[13] described a survey of the sources and quality of data used in economic models (HTAs between 1997 and 2003).

TABLE 1 *Publications identified for the review of guidance on adverse effects in models*

Publication	Title	Objectives
Philips 2004[14]	Review of guidelines for good practice in decision-analytic modelling in health technology assessment	To identify existing guidelines, develop a synthesised guideline plus accompanying checklist, and to provide guidance on key theoretical methodological and practical issues and consider the implications of this research for what might be expected of future decision-analytic models
Tappenden 2006[15]	Methodological issues in the economic analysis of cancer treatments	To appraise the existing guidelines for economic analysis of cancer treatments
Rovira 1995[16]	Economic analysis of health technologies and programmes: a Spanish proposal for methodological standardisation	To formulate an initial proposal of methodological standards and guidelines for economic evaluation
Cooper 2005[13]	Use of evidence in decision models: an appraisal of health technology assessments in the UK since 1997	To review the sources and quality of evidence used in the development of economic decision models in health technology assessments (HTAs)
Weinstein 2003[17]	Principles of good practice for decision analytic modelling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices – Modelling Studies	To describe the outcome of a task force convened to provide modellers with guidelines for conducting and reporting modelling studies

ISPOR, International Society for Pharmacoeconomics and Outcomes Research.

All five publications made some direct (if only passing) reference to adverse effects in models. Of the themes that could be taken as relevant to adverse effects in models the most common was the discussion of the inclusion of outcomes (*Table 2*). Three of the five articles addressed this directly and all three concurred that models should include *all* relevant outcomes. Two clarified that relevant outcomes meant those that differed between the interventions of interest; from this one can infer that when adverse effects differ in frequency or severity between treatments in a model, or at least if the resources used because of them differ, they should be included in the model.[14,16,17] All three explicitly stated that adverse effects should be considered as an outcome.[14,16,17]

The other themes were the choice of the model parameters (*Table 3*) and the source and quality of the (adverse effects) data (*Table 4*).

Adverse effects were rarely addressed when discussing the choice of parameter. Even though the publication by Philips *et al.*[14] has been included here, it merely states that 'the choice of outcomes in the model should be justified'. Tappenden *et al.*,[15] although advocating the inclusion of adverse effects, considered only those adverse effects that were expected to be avoided by the treatment of interest. They did not consider adverse effects incurred as a consequence of the treatment. Thus, overall, it may seem that adverse effects are not explicitly high on the list of priority outcomes

TABLE 2 *Statements relevant to adverse effects in models: the importance of including all relevant outcomes*

Study	Statement
Philips 2004[14]	All outcomes relevant to the condition should be included including adverse effects, with the exception of those that do not differ between the interventions or control being compared
Weinstein 2003[17]	Stated outcomes should not be omitted because of lack of data. Examples might be chronic health states corresponding to uncommon adverse events or disease sequelae that are not observed within clinical trials
Rovira 1995[16]	Stated that all effect on resources, the use of which varies between the options, should be considered in the analysis, e.g. those used to treat adverse effects

TABLE 3 *Statements relevant to adverse effects in models: choice of the model parameters*

Study	Statement
Philips 2004[14]	The choice of outcomes in the model should be justified
Tappenden 2006[15]	Stated that in the context of cancer adverse effects that are avoided by the use of treatment under assessment is an important outcome measure. However, the report goes on to say that this is not 'an ideal benefit measure for use in cost-effectiveness analysis' and suggests that use of health-related quality of life (HRQoL) is a better measure Stated that in cancer trials the use of preference-based methods to measure HRQoL is rare and so models almost always use indirect sources of evidence

TABLE 4 *Statements relevant to adverse effects in models: source and quality of data*

Study	Statement
Philips 2004[14]	It is recommended that a full systematic review should be conducted for key parameters but there is no clear definition of 'key parameters' The results of the model should be reported in the context of the full limitations of the available data
Cooper 2005[13]	The survey found that sources of data for adverse effects and complications were in many cases unclear and few used RCT or meta-analysis-derived data
Weinstein 2003[17]	Systematic reviews of the literature should be conducted on key model inputs. Evidence that such reviews have been done, or a justification for failing to do so ..., should accompany the model

to be considered in models. However, it is likely that adverse events may be considered as just one amongst many outcomes for a particular treatment and, as for any outcome, when they are important they will be a high priority.

Tappenden *et al.*[15] suggest that adverse effects are best included as part of HRQoL. This is because of the existence of multiple events/outcomes of varying severity and the need to capture and value these in an appropriate manner, i.e. through the use of a single index.

Three of the publications touched upon the source and quality of data (*Table 4*). Although two[14,17] of the five articles advocate conducting a full systematic review of key parameters, neither publication gives any guidance as to what is a key parameter. The study by Cooper *et al.*[13] would suggest that, in practice, in the majority of cases adverse effects are not considered a key parameter. In 10% of reports adverse effects had not been included in the model. When adverse effects and complications had been included, in 31% (at best) of the reports the source of the data was unclear. Data from meta-analysis of RCTs with direct comparison between interventions of interest and using final outcomes were used in 14% of cases, and data from a single directly relevant RCT were used in 17% of cases. A further 2% of reports used data from a single RCT using a surrogate outcome, 14% used data from case–control or cohort studies and 12% used expert opinion.

It is noteworthy that in the most recent review of guidance on economic decision modelling[14] a chapter on appropriate methods for the identification and quality assessment of secondary parameter estimates does not mention adverse effects.

Summary findings of review of methodological research

It is clear from the available guidance that all relevant outcomes should be included in the economic decision model and there appears to be a general if not clearly stated consensus that this includes adverse effects.

One might have expected adverse effects to feature in guidance on how to select parameters for the model. However, it is likely that adverse events may be considered as just another outcome for a particular treatment and, as such, when they are important they will be a high priority. The position taken by Tappenden *et al.*[15] that adverse effects are captured through HRQoL may be typical and it may well be that in most cases analysts attempt to capture adverse effects in this manner.

Guidance for decision modelling suggests that there should be a full systematic review for key parameters but there is no real indication that adverse effects should be considered as one of these key parameters. There is an implicit assumption that adverse effects are very important, but the lack of clear reference to adverse effects may well reflect uncertainty and lack of clarity regarding how they should be dealt with and considered in economic models.

Chapter 3
Review of existing practice

To establish researchers' current practice regarding the incorporation of adverse effects in decision models we reviewed published technology appraisals. This section provides an overview of the methods, results and discussion surrounding the review. This review did not include an appraisal of whether the appropriate adverse effects had been included in each report nor an appraisal of the way that adverse effects had been modelled; to do so would have required a thorough appraisal of each decision problem and as such would have been beyond the resources of this short report.

Methods

Literature searching

All HTA monographs dated from 2004 to 2007 were identified from the HTA website. A total of 186 records were identified.

Inclusion criteria

Studies were included in the review if they were HTA reports commissioned by the National Institute for Health Research (NIHR) HTA programme, were published between 2004 and 2007, and investigated the clinical and cost-effectiveness of a health technology using a systematic review and an economic model.

Study selection

Two reviewers independently screened all reports against the inclusion criteria. Any discrepancies were resolved by consensus or, when consensus could not be reached, a third reviewer was consulted.

Data extraction/coding

Data were extracted/coded by one researcher using a standardised data extraction form in EPPI-Reviewer and were checked by a second reviewer. Discrepancies were resolved by discussion and, if necessary, a third opinion was sought. Because of the technical nature of some of the data and poor reporting of modelling methodology, further data extraction by a health economist was necessary in some instances. The data extraction sheet is provided in Appendix 2.

Our classification of diseases and indications was taken from the Health Research Classification System of the UK Clinical Research Collaboration (www.hrcsonline.net/hrcs/files/HRCS). We merged the cardiovascular and stroke categories and omitted the 'general health relevance', which was considered to be superfluous and potentially confusing for readers.

For the purposes of this review an adverse effect was defined as an undesirable or unintended effect of the intervention. Information pertaining to a failure to prevent 'adverse events' such as death or stroke when prevention was the intended effect of the intervention was not extracted. To allow us to establish if the way in which adverse events were considered in the review impacted on how they were incorporated into the model we divided the reviews into two categories, 'broad' or 'narrow' focus. Any review that had a priori named specific adverse event(s) to be included was considered to have taken a narrow focus. Those which reported that any adverse events or an extensive list of adverse events were to be considered were categorised as having taken a broad focus. This distinction was made solely to allow us to look at whether a review considered by us to have taken a narrow focus regarding adverse events was more likely to be linked with a model that included those same adverse events.

The focus of this report was to establish if adverse effects of the interventions being evaluated had been considered. In most instances one can look at the review, identify included adverse effects and then look at the model and do the same thing. However, in HTAs of diagnostic technologies the clinical review often focuses on the actual technology whereas the decision model typically encompasses the effects of the technology and the effects of treatments or further testing implemented as a result of the test or screening. Although we are aware that the adverse effects of treatments following a positive test are relevant to the model and the decision problem being

evaluated, in the present review only adverse effects of the actual diagnostic technology of interest were considered.

To facilitate reporting, the utilities used in the models were classified on the basis of three broadly defined alternatives/approaches to value health benefits in terms of HRQoL used in the reports: first, utility values may be obtained by directly eliciting values from patients on treatment – either by means of direct elicitation or from a published study; second, utility values may be obtained by adopting utilities derived from published literature that has used either public or clinicians' elicitation; and third, utility values may be obtained through subjective judgment such as an interview with clinical experts or panels. The methodology within these three broad approaches is extremely variable and we have made no assessment as to the validity of the methods used. Rather, the classification is a simplification to allow us to estimate, albeit with some degree of uncertainty, the number of reports that may have implicitly captured adverse events by eliciting utilities from patients on treatment. This is not to say that other methods definitely will not have captured adverse events, but the level of reporting was not sufficient to easily allow this to be determined.

Analysis

The data were summarised in a narrative synthesis.

Results

General summary

Of the 186 HTA reports published between 2004 and 2007, 80 that included a systematic review and an economic model were included in the review. The 106 excluded reports are listed in Appendix 6. Full data extraction for included reports is given in Appendix 5.

Of the 80 HTA reports 47 (59%) were assessments conducted to inform NICE appraisals. Studies were categorised according to the Health Research Classification System, developed by the UK Clinical Research Collaboration (*Table 5*). Some reports encompassed more than one research area, for example both diagnosis and treatment. The majority of the reports (61/80, 76%) were evaluations of treatments and therapeutic interventions, predominantly of pharmaceuticals. There were 20 reports on detection, screening and diagnosis (mainly evaluating diagnostic tests) and two in the area of prevention.

A wide range of therapeutic areas was investigated (*Table 6*), most commonly cancer, cardiovascular diseases, musculoskeletal disorders, metabolic and endocrine disorders and mental health. In most topic areas the majority of reports related to a therapeutic intervention.

TABLE 5 *Research activity area*

Area of research	Number of reports[a]
Evaluation of treatments and therapeutic interventions (therapeutic):	***61 (76%)***
Cellular and gene therapies	2
Medical devices	4
Pharmaceuticals	47
Physical	1
Psychological and behavioural	3
Surgery	8
Detection screening and diagnosis (diagnostic):	***20 (25%)***
Discovery and preclinical testing of markers and technologies	1
Evaluation of markers and technologies	13
Population screening	6
Prevention of disease and conditions, and promotion of well-being (prevention):	***2 (3%)***
Nutrition and chemoprevention	2
Primary prevention interventions to modify behaviours or promote well-being	1

a The number of reports comes to more than 80 as reports could cover more than one area, e.g. diagnosis and treatment.

Characteristics of the decision-analytic models in the HTA reports

A variety of decision models analysed over a number of time frames were employed; details are presented in *Table 7*. The majority of the models [45/80 (56%)] were state transition models, with the remaining models almost all decision trees. A majority [53/80 (66%)] of the models were long-term models (more than 5 years), with 31/80 (38%) assessing technologies over a period of more than 20 years. Only a very small proportion (4/80, 5%) of the models were considered very short term (less than 1 year), with the remainder having time horizons between 1 and 5 years.

To explore how closely linked the systematic review and economic models were in these reports we examined whether one or more clinical effectiveness outcomes considered in the systematic review had been used to inform the economic model. The results are presented in *Table 8*.

In 75/80 (94%) of the reports, one or more clinical effectiveness outcomes considered in the systematic review were used to inform the cost-effectiveness model (*Table 8*). In the majority of instances the parameter was derived directly from the synthesis of studies in the review (51/80, 64%) or based on a subset of studies from the review (29%). In 13 (16%) instances it was derived from a source other than the systematic review and there were seven cases (9%) in which it was unclear from where the parameter value had been derived.

Adverse effects in the HTA reports

Of all of the reports, 68/80 (85%) included adverse effects as an outcome of interest in the clinical review and 43/80 (54%) included adverse effects in the economic model (*Table 9*). Overall, 39 (49%) included adverse effects in both the clinical review and the model, and 8 (10%) did neither. A total of 29 reports (36%) included adverse effects in only the review and four reports (5%) included adverse effects in only the model (see Appendix 3, *Tables 20* and *21*).[18–21] All four of these reports were of diagnostic interventions: two cardiovascular, one cancer and one metabolic.

TABLE 6 *Topic areas investigated*

		Research activity area			
Topic area	**Total**	**Therapeutic interventions**	**Prevention**	**Diagnostic**	**Other**
Blood	2	1	0	1	0
Cancer	18	14	0	4	0
Cardiovascular	14[a]	9	1	5	0
Congenital disorders	2	2	0	0	0
Ear	1	0	0	1	0
Eye	0	0	0	0	0
Infection	5	4	0	1	0
Inflammatory and immune system	1	1	0	0	0
Injuries and accidents	0	0	0	0	0
Mental health	7	7	0	0	0
Metabolic and endocrine	6	3	0	3	0
Musculoskeletal	8	8	0	0	0
Neurological	2	2	0	0	0
Oral or gastrointestinal	5	4	0	1	0
Renal and urogenital	5	2	0	3	0
Reproductive health and childbirth	1	1	0	0	0
Respiratory	0	0	0	0	0
Skin	4	4	0	1	0
Other	1[a]	1	1	0	0

a One report covered more than one research activity area.

TABLE 7 *Characteristics of the decision-analytic models in the HTA reports*

Characteristics	Total ($n = 80$)[a]
Type of model	
Decision tree	27
State transition model	45
Other	4
Unclear	4
Time horizon	
Up to 1 year	4
1–5 years	17
5–20 years	22
20 years plus	17[b]
Lifetime	18[b]
Unclear	9

a Three models used two time horizons.
b Four models specified lifetime and > 20 years.

Adverse effects in the clinical effectiveness review

Adverse effects were considered in 85% (68/80) of the clinical effectiveness reviews, either as an explicitly stated outcome of interest in the inclusion criteria or as data reported in the results (*Table 9*). In 12/68 (18%) systematic reviews including adverse event data, named adverse events for which data should be extracted had been explicitly identified at protocol stage. We classified these reviews as having adopted a narrow focus. The remaining 56 reports (82%) were classified as having adopted a broad focus, that is, there was a broad statement in the protocol of the review that adverse events were of interest or there was an extensive list of explicitly named adverse events. This separation was carried out to allow us to look at whether a review considered by us to have taken a narrow focus regarding adverse events was more likely to be linked with a model that included those same adverse events. In 14/68 (21%) of the systematic reviews the adverse event data were synthesised in a meta-analysis, therefore potentially providing a direct parameter for the cost-effectiveness model (*Table 9*).

Having a narrow focus regarding adverse effects and separate inclusion criteria may be indicative of a review in which an a priori importance was placed upon the synthesis of adverse effects data. The review found that the synthesis of adverse effects data in a meta-analysis was more common in reviews with a narrow focus than in those with a broad focus (83% versus 16%) but did not appear to be influenced by whether there were separate inclusion criteria for adverse effects in the review or the therapeutic area (*Table 10*; full list of topic areas in Appendix 3, *Table 22*). Of the 12 reviews taking a narrow focus, eight of the corresponding models included a clinical adverse event.

Cancer and cardiovascular heath were the most commonly investigated therapeutic areas but the proportion of reports that included adverse effects in the clinical effectiveness review was not higher than that in other therapeutic areas (*Table 11*).

TABLE 8 *Clinical effectiveness outcomes in the economic model*

Question	Number of reports
Has one or more of the outcomes considered in the clinical effectiveness review been used to inform the model?	
Yes	75 (94%)
No	4 (5%)
Unclear	1 (1%)
How was the parameter value used derived?[a]	
Directly from the synthesis of studies in the review	51 (64%)
Independently/alternative synthesis	13 (16%)
Synthesis conducted on a subset of studies	23 (29%)
Unclear	7 (9%)

a When there was more than one parameter there was more than one source and therefore the number of reports (percentage) for this question total more than 80 (>100%).

TABLE 9 *Adverse effects in the clinical effectiveness review/model*

Question	Number of reports
Did the specified outcomes include adverse events?	
Yes, broad focus[a]	56 (70%)
Yes, narrow focus[b]	12 (15%)
No	11 (14%)
Unclear	1 (1%)
Were there separate inclusion criteria in relation to obtaining adverse event data?	
Yes	13 (16%)
No	67 (84%)
Were the adverse event data synthesised in a meta-analysis?	
Yes	14 (18%)
No	66 (82%)
Are adverse effects included as a parameter in the model(s)?	
Yes	43 (54%)
No	37 (46%)

a Broad focus: adverse effects referred to in general terms or using a long comprehensive list.
b A few named adverse effects specified.

TABLE 10 *Adverse effect data synthesised in a meta-analysis by review characteristics*

	Meta-analysis?			
	Yes	**No**	**Unclear[a]**	**Total**
Focus				
Broad focus	9	46	0	56
Narrow focus	5	6	1	12
Separate inclusion criteria in relation to obtaining adverse effect data				
Yes	2	11	0	13
No	11	43	1	67
Health category (when five or more reports)				
Cancer	2	12	0	18
Cardiovascular	3	8	0	13
Infection	0	4	0	5
Mental health	2	4	1	7
Metabolic and endocrine	0	4	0	6
Musculoskeletal	2	6	0	8
Oral or gastrointestinal	2	2	0	5
Renal and urogenital	0	4	0	5

Rows do not sum to total because of numbers of reports without adverse effects in clinical review.
a One report[22] extracted as 'unclear' for meta-analysis because the systematic review was a 'review of reviews' and therefore there is uncertainty over how data were derived.

TABLE 11 *Number of reports that included adverse effects in the clinical effectiveness review by health category*

Health category	Yes	Yes, broad focus	Yes, narrow focus
Blood	2 (100%)	2	0
Cancer	14 (67%)	12	2
Cardiovascular	11 (79%)	8	3
Congenital disorders	2 (100%)	2	0
Ear	1 (100%)	1	0
Eye	0	0	0
Infection	4 (80%)	4	0
Inflammatory and immune system	1 (100%)	1	0
Injuries and accidents	0	0	0
Mental health	6 (86%)	3	3
Metabolic and endocrine	4 (67%)	3	1
Musculoskeletal	8 (100%)	8	0
Neurological	2 (100%)	2	0
Oral or gastrointestinal	5 (100%)	3	2
Renal and urogenital	4 (80%)	3	1
Reproductive health and childbirth	1 (100%)	1	0
Respiratory	0	0	0
Skin	4 (100%)	4	0
Other	0	0	0

Adverse effects in the economic model

Overall, 43/80 (54%) reviewed HTA reports reported the inclusion of adverse effects data as parameter(s) in the decision-analytical model.

As in the clinical section, cancer and cardiovascular heath were the most commonly investigated therapeutic areas (*Table 12*). In cardiovascular health and cancer reports there was no indication of a general tendency to include adverse effects more often in the systematic review than in the model or vice versa (cancer 67% and 61% respectively; cardiovascular health 79% and 86% respectively).

There are a number of ways within a decision-analytic framework in which adverse effects might be incorporated or captured. These include the model structure, clinical parameters (we have considered a clinical parameter to be any effect parameter that is directly populated from the output of a clinical trial or the clinical effectiveness review, e.g. probabilities of clinical events), utilities, costs and resources. How adverse effects are incorporated is heavily dependent on the intervention being evaluated, the impact that the adverse effect has and the scope of the decision problem.

Table 12 provides a breakdown by commissioner (NICE or other), research category, year of publication and therapeutic area of the number of reports in which the model explicitly included adverse events. The proportion of reports that included adverse events was higher among those conducted for the NICE appraisal programme than among other reports.

There was no difference in the mainstream types of model used between those models that did and those that did not include adverse effects or between the different research activity areas (*Table 13*). However, a greater proportion of reports that did include adverse effects in the model used either a 20 year plus or a lifetime horizon compared with a shorter time horizon: 51% compared with 24% (*Table 14*) (further details in Appendix 3, *Table 23*). The reason for this difference was not investigated but it may be because of the more comprehensive nature of long-term models.

Parameters by which adverse effects were included in the model

The main focus of this review was to establish those reviews that explicitly reported on the inclusion of adverse effects. Although we acknowledge that

TABLE 12 *Inclusion of adverse events as a parameter in the model by report characteristics*

	Adverse events included as a parameter in the model	Total
Commissioner		
NICE	29 (62%)	47
Other	14 (41%)	34
Research category		
Prevention	0	2
Diagnostic	8 (40%)	20
Therapeutic:	35 (57%)	61
Cancer	11 (61%)	18
Cardiovascular	12 (92%)	13
Year of publication		
2007 (up to 3 October)	10 (50%)	20
2006	16 (57%)	28
2005	9 (69%)	13
2004	8 (42%)	19
Total	43	82

NICE,, National Institute for Health and Clinical Excellence.

in many instances there is likely to be an implicit capturing of adverse effects, the analysis at this stage focused on explicit inclusion of a parameter that was stated to have captured the adverse effects relevant to the intervention being evaluated. The reporting of clinical and cost parameters of adverse effects appeared to be more explicit than the capturing of adverse events in the utilities or through the use of withdrawals. When the reporting of adverse effects in the model was not explicit, the model has been classed as not having incorporated adverse effects. The details of the 54% of decision models that explicitly included adverse effects parameters are summarised in Appendix 3, *Table 24*. Further details of these models and the parameters used to capture adverse effects are presented in the following sections.

TABLE 13 *Model structure*

	Are adverse effects included as a parameter in the model?					
	No (*n* = 37)		Yes (*n* = 43)		Total (*n* = 80)	
	n	%	n	%	n	%
Type of model						
Decision tree	14	38	13	30	27	34
State transition model	18	49	27	63	45	56
Other	2	5	2	5	4	5
Unclear	3	8	1	2	4	5
Research activity area						
Evaluation of treatments and therapeutic interventions	26	70	34	79	60	75
Detection, screening and diagnosis	11	30	8	19	19	24
Prevention of disease and conditions, and promotion of well-being	0	0	1	3	1	1

TABLE 14 *Totals for the time horizon of the model(s)*

		Time horizon					
		Up to 1 year	**1–5 years**	**5–20 years**	**20+ years**	**Lifetime**	**Unclear**
Adverse effects included in model?	Yes	2	7	11	12	14	3
	No	2	10	11	5	4	6
All models[a]		4	17	22	17	18	9

a Totals greater than 80 because some reports had more than one time horizon.

Clinical evidence or cost parameter for adverse effects

These parameters were the most explicit indicators that adverse effects had been included in the model. The reports that included these are listed in Appendix 3 (*Tables 25* and *26*) and summarised in *Table 15*.

A total of 67% of the decision models that included adverse effects incorporated them through the use of a clinical parameter. A total of 79% incorporated a cost parameter. Interestingly, three appear to include a clinical parameter (e.g. probability) and no cost/resource parameter (*Table 25*), suggesting that the clinical effect had no impact on resource use; and eight appear to incorporate cost parameters but no clinical parameter (*Table 28*), suggesting that, although the adverse effect had little clinical impact, it did affect the resource use, which has been accounted for in the cost.

In total, there were six models that captured adverse effects by neither a cost nor clinical probability but by using only utilities or withdrawals. Full details are presented in Appendix 3, *Table 27*.

Table 15 *Types of parameter used in models that did include adverse effects through the use of a clinical or cost parameter*

Parameter	***n*** **= 43**	**%**
Clinical AE parameter	29	67
Therapeutic	25	
Diagnostic	4	
Cost/resources of AEs	34	79
Therapeutic	28	
Diagnostic	6	
Clinical parameter or cost of AE	37	86
Clinical parameter and cost of AE	26	60

AE, adverse effect.

Utilities

In total, 66/80 (83%) of the reports incorporated a utility. These utilities did not necessarily capture adverse effects. Arguably a HRQoL measure may capture some relevant adverse effects and some authors explicitly reported that adverse effects might be reflected in utility scores (e.g. Woolacott *et al.*[23]). However, the reporting of the derivation of utilities was not always sufficiently explicit to confer certainty as to whether utilities captured relevant adverse effects.

We considered utilities within the three broadly defined categories outlined in the methods section: utility values may be obtained, first, by directly eliciting values from patients on treatment, either by means of direct elicitation or from a published study; second, by adopting utilities derived from published literature where they have used either public or clinicians' elicitation; and third, through subjective judgment such as an interview with clinical experts or panels (*Table 16*).

Among those reports that included HRQoL data in the model, the most common method of valuing health benefits (53%) was to derive them from patients on treatment, either directly as part of the analysis or through the use of a published study that had elicited them from the appropriate patient population. If one can infer that utilities derived from patients on treatment are likely to encompass adverse effects then one could surmise that almost 53% of models incorporated adverse effects through utilities. However, because of the lack of detailed reporting on the derivation of utilities it was not possible to be sure that in every case the utilities were derived in a manner that would capture the relevant adverse effects.

TABLE 16 *Types of utility used in models*

Utilities	*n*	%[a]
Based on judgement	19	29
From a secondary source or derived using clinicians'/public preferences	21	32
From patients on treatment (via primary or secondary source)	35	53
Total	66	

a Some reports use utilities derived by more than one method and so percentages do not total 100%

In an attempt to establish whether those models that did not appear to have included a clinical/cost parameter for adverse effects used utilities (decrements/disutilities) to capture adverse effects, further investigation was undertaken. Of the six reports that fell into this group, only two[18,24] were classified as having captured adverse effects solely through the use of utilities (*Table 27*).

Of these two studies, one report[24] appears to have derived utilities from patients on treatment and it is likely that some, if not all, of the relevant adverse effects may have been captured. The second report[18] is not so clear. Despite the fact that the report states explicitly that a disutility associated with the intervention is included in the model, this disutility appears to have been derived using the authors' or expert judgement. This method was employed because of a lack of available empirical evidence. Although every effort may have been made to account for adverse effects in the estimates, it is not clear that this method of deriving utilities is sufficiently robust to truly capture adverse effects. However, as we did not further investigate the appropriateness of the utilities it is not possible to draw any conclusions on their validity.

Withdrawals

A total of 16/80 (20%) of the reports had a model that incorporated withdrawals into the model structure. Three of these did not include adverse effects (Appendix 3, *Table 28*) but explicitly stated that withdrawals were incorporated to reflect compliance with monitoring or screening, therefore not adverse effects. The remaining 13 were all technology assessments of therapeutic interventions and in the most part the withdrawals appear to be due at least in part to toxicity; therefore, adverse effects may have been implicitly captured through the structure. Of these 13 models, four explicitly incorporated adverse effects through a cost/resource parameter and five explicitly incorporated both a cost and a clinical adverse effect parameter. The remaining four all included an explicit statement to say that adverse effects had been captured in the utility valuation[25] or through the use of withdrawals.[26–28] Therefore, all 13 were considered to have explicitly included adverse effects in the model.

Source of adverse effect data

To allow the link between the inclusion of adverse effects in the systematic review and the inclusion of adverse effects in the decision model to be evaluated the sources of the clinical parameters for adverse effects in the models are summarised in *Table 17*.

In total, 18 models (42%) used some adverse effect data from the accompanying review. Most others used other literature-based sources; very few relied solely on expert opinion.

A total of 14 reports had clinical reviews that reported a meta-analysis of adverse effect data (*Table 18*). Of these, eight (57%) included a clinical probability in the model, although only three of the models took their model input parameter for adverse effects from the accompanying review. However, even for these three models the link with the clinical review's meta-analysis of adverse effect data was not without some complication: in one[29] the differentiation between what was an efficacy outcome and what could be considered an adverse effect was blurred; in another[30] the data were derived from the systematic review but the method of meta-analysis was different for the model; and in the third[31] the results of the meta-analysis

TABLE 17 *Sources used to obtain the adverse effect parameter data used in the decision models*

Sources	*n* = 43	%
The accompanying systematic review	9	21
Both systematic review and other sources	9	21
Other sources, e.g. ad hoc selection or systematic searches	21	49
Expert opinion	2	5
Unclear	2	5

TABLE 18 *Source of adverse effect data in models for which accompanying review conducted a meta-analysis*

Source of adverse effect data in model	*n* = 14	%
The accompanying systematic review	3	21
Other sources, e.g. ad hoc selection or systematic searches (specify)	5	36
Both systematic review and other sources	1	7
Expert opinion	1	7
Unclear	0	0
Not applicable (because no adverse effect data considered or source not specified)	4	29

comprised only some of the model input for adverse effects.

The results also show that four models for which the accompanying review conducted a meta-analysis of adverse effects did not incorporate any adverse effects into the model. In one instance there was an explicit discussion around the lack of clinical difference in adverse effects and the lack of cost data. Full details are presented in Appendix 3, *Table 29*.

Reported rationale for not including adverse effects in the model

Of the 37 reports that did not include adverse effects in the decision model, 18 reported a rationale for this approach. These fell into five main categories (*Table 19*). Full details are provided in Appendix 3, *Table 30*.

Diagnostic/screening models

Of the 20 models classified as diagnostic/screening, eight explicitly incorporated adverse effects. No obvious differences between those diagnostic/screening models that did or did not include adverse effects were identified in terms of the type of diagnostic technology, the type of health category or how adverse effects were handled in the clinical effectiveness review (see Appendix 3, *Table 31*).

TABLE 19 *Summary of rationale for not including adverse effect parameters in the decision model*

	Justification/explanation	*n*
1	Lack of data on the relevant adverse effects, in the clinical review or generally	7
2	Adverse effects known to have only a minimal effect on HRQoL or costs/resources so no need to model	5
3	Difficult to distinguish between adverse effects and efficacy for this intervention, therefore implicit assumption that adverse effects would be captured in main efficacy parameters	1
4	No difference between the comparators for adverse effects, therefore no need to model	4
5	The intervention was found to be cost-effective without the inclusion of adverse effects, and the inclusion of adverse effects would only make it more so	1

HRQoL, health-related quality of life,

Chapter 4
Discussion

This research has systematically looked at the ways in which adverse events data are incorporated into decision modelling. It has mapped the variety of ways in which adverse effects have been evaluated and explicitly incorporated into decision-analytical models. We used systematic review methods to identify and include all relevant HTAs to produce an overview of current practice. No attempt has been made to determine the relevance or appropriateness of the adverse events. In some cases it is possible that adverse events were not relevant and have justifiably been excluded from the model.

Our review was subject to some limitations:

- Our review did not fulfil the intentions laid out in the protocol in that it did not address the question, 'Are adverse effects incorporated adequately and appropriately in economic models?'. In developing the data extraction forms it was decided that as a first-stage project such subjective complex questions could not be addressed. Thus, the review was limited to the more objective questions of whether adverse effects were included and how they were included.
- The review focused on NCCHTA-funded HTAs and therefore may not be generalisable to the broader HTA field. Furthermore, because of the large number of HTAs and limited resources, it was necessary to limit the sample of HTA reports included. The decision to include only reports from 2004 onwards was based on two factors: 2004 onwards would reflect current practice, particularly because 2004 was the year that the NICE methods guide was first issued; and the study by Cooper *et al.*[13] included reports up to and including 2003.
- The present work documents an overview of what has been carried out regarding the inclusion of adverse effects in models. It does not investigate how the inclusion or not of adverse effects in any given decision model, or the use of different modelling approaches, may have altered the conclusions of any given report.
- The present work did not investigate the relative merits of different approaches to the inclusion of adverse effects in decision models.
- Because of the limited scope of the project it was not possible to assess the appropriateness of the adverse events included.
- A number of simplifying assumptions were made to allow the information to be extracted and presented in a meaningful manner. These include the delineation of reviews into having a narrow or broad focus on adverse events.

Summary of findings from the review

The review covered a broad range of HTAs in terms of the therapeutic area, type of intervention and type of decision model employed. In total, 85% of the reports included adverse effects in the clinical effectiveness review and 54% of the decision models included adverse effects in the model. Just under half (49%) included adverse effects in both the clinical review and the model.

The link between the adverse effects in the clinical review and the model was generally weak. Although 18 of the models used adverse effects data from the clinical review and 14 reviews did include a meta-analysis of adverse effects, only 3/80 (< 4%) used the results of a meta-analysis from the systematic review of clinical effectiveness and none of these was able to use only the data from the review without some further manipulation being required.

There was no apparent relationship between inclusion of adverse effects in the model and therapeutic area, type of intervention or year of report, nor type of model. Models with a 20-year or longer time horizon did include adverse effects more often than those with shorter time horizons. This could be a reflection of the more comprehensive nature of long-term models, but was not investigated further.

Of those models that did include adverse effects, 67% used a clinical adverse effects parameter, 79%

used a cost of adverse effects parameter, 86% used one of these and 60% used both. It was beyond the remit of this review to determine whether these clinical and cost parameters were appropriate or adequate, or if all relevant adverse effects had been incorporated, or if the data used for their capture were reliable. These are all questions that require further research to be answered.

Most models (83%) used utilities but determining whether these utilities captured adverse effects was problematic. Only two models (2.5%) used solely utilities for adverse effects and were explicit in their beliefs that the utility captured relevant adverse effects. A total of 35 reports (81% of those models that included adverse effects and 44% of all reports) derived utilities from patients on treatment and might therefore be interpreted as capturing adverse effects. The issue of utility derivation is widely debated among health economists and it is not clear that there is consensus on who should value the health states, or which valuation technique should be used.[32] In an attempt to estimate the likelihood of adverse events being captured within the utility we used a simplifying assumption, namely that eliciting utilities from patients on treatment was the most likely method to have implicitly captured adverse effects. Further, only those models that had not explicitly captured adverse events through the use of cost or clinical data were investigated in any depth.

A total of 13 reports (30% of those models that included adverse effects and 16% of all reports) used withdrawals related to drug toxicity and therefore might be interpreted as using withdrawals to capture adverse effects, but this was explicitly stated in only three reports. However, the remaining 10 models also incorporated adverse effects explicitly through at least one other parameter.

Of the 37 models that our review classed as not having included adverse effects in the decision model, 18 gave a justification for this omission. Most commonly the justification was a lack of data, followed by the adverse effects having minimal impact on quality of life or cost.

Overall, 43 models included adverse effects and a further 18 gave a reason for not including adverse effects. Thus, 19/80 (24%) reports appeared to have no explicit consideration of adverse effects in the decision model.

Reporting of adverse effects

A key part of the present review was determining whether or not adverse effects had been included in the decision model. This proved to be more difficult than had been anticipated and raised important issues regarding the transparency of the reporting of models. In particular, the lack of explicit reporting with regards to which adverse effects had been considered in the model and how they had been captured and evaluated led to a number of difficulties. In many instances some interpretation and understanding of methodology was required to ascertain if and how adverse effects had been captured. For example, HTAs with poorly reported model structures failed to show when adverse effects had been captured through the withdrawal arm of a decision tree, or if one or more of the health states defined within the model structure included adverse events. Also common was a failure to mention adverse events anywhere in the text, presenting only a table of cost input parameters. Although it is legitimate to present adverse effects parameters in this way, and it is possible to unearth the relevant information from within the report, it is highly likely that many readers may miss this pertinent information and may well fail to understand how adverse effects were incorporated or, worse, may draw the erroneous conclusion that adverse effects were not included in the model.

It is widely accepted in the health economics community that more formal, transparent and replicable approaches to the identification and assessment of the quality of model inputs may reduce the 'black box' nature of decision models and lead to less scepticism regarding model outputs.[13] With specific reference to adverse effects, it is essential that reporting allows a reader to understand why adverse effects are important to the decision problem, how and where those adverse effects included were identified, and what methods were used to incorporate the relevant adverse effects into the model. When appropriate there must be clear justification for the non-inclusion of adverse events; legitimate decisions for not including adverse effects, such as adverse effects having a negligible impact on health outcomes, or no impact on costs and resources, should be explicitly reported.

The findings of the review of methodology papers (see Chapter 2, Summary findings of review of

methodological research) show that, although there appears to be an implicit assumption within modelling guidance that adverse effects are very important, there appears to be a lack of clarity and guidance on how they should be dealt with and considered in modelling. This is likely to be due in part to the diversity of the decision problems and the wide range of important/unimportant outcomes that this diversity creates. Within this range of outcomes adverse effects may be considered as just one more outcome. The most relevant outcomes, which may or may not include adverse effects, are specific to each treatment pathway evaluated.

The transparency of the reports that were reviewed for this project varied greatly. However, in many cases the reporting was insufficient for the audience for whom the reports are intended; determining which outcomes had been deemed most relevant and therefore included was problematic. We acknowledge the fact that the level of detail that can be reported is often restricted by word limits, but in the instance of HTA reports the limitations are not so restrictive as to limit the transparency of reporting.

Different ways to capture adverse effects

There are a number of areas within a decision-analytic framework in which adverse effects might be incorporated or captured. These include the model structure, clinical events, utilities, costs and resources. How adverse effects are incorporated is heavily dependent on the intervention being evaluated, the impact of the adverse effect and the scope of the decision problem.

The inclusion of adverse effects through a clinical event may seem the most obvious method. In practice, 67% of models used a clinical probability. However, use of a clinical probability is not a guarantee that all of the relevant adverse effects have been captured. Some reports included a single adverse effect or adverse effects of one intervention, with no consideration for the adverse effects of the comparator interventions. Detailed analysis of these issues was beyond the scope of the present review, but further research into this important issue is warranted. Clear explanations by authors of why certain clinical parameters are included rather than others should be an important aspect in the reporting of decision models. Only a very small proportion of models used data directly from the accompanying systematic review. It would appear that further efforts need to be made to include relevant adverse effects outcomes in the systematic reviews of HTAs. When a systematic review of adverse effects is not possible or feasible, the clinical effectiveness review could include a summary of the adverse effects profiles of the interventions of interest; this could then be used to structure and populate the model either directly or by helping the appropriate utilities to be used.

It is justifiable that some models include only a cost/resource parameter to capture adverse effects. For example, some adverse effects may have no significant or measurable impact on quality of life or health benefit, but may lead to an increase to inpatient length of stay. If this is true it may be appropriate for a cost estimate of that stay to be incorporated into the model. Our review found that 79% of models incorporated a cost parameter but only 10% incorporated cost parameters without explicit inclusion of a clinical parameter. This may be justifiable, but without justification it may make little sense to the reader.

In the evaluation of pharmaceutical interventions, adverse effects (i.e. toxicity) may be incorporated into the model structure through withdrawals. This allows individuals who experience the adverse effect to follow an alternative pathway, which has relevant costs and benefits associated with it. Of the 16 models that incorporated withdrawals, 13 were evaluating pharmaceutical drug interventions and appeared to include adverse effects in this manner. However, the nature of withdrawals and whether or not the reports' authors anticipated that they capture adverse effects was not explicitly reported in all of the HTAs.

A high proportion of the reports reviewed derived a utility outcome. This is not surprising given that this is recommended within the current NICE methods guide.[6] These guidelines reflect that it is important to be able to value outcomes, including adverse effects, in a consistent manner and that a single preference score is the most appropriate for policy decision-making purposes.[6] Although it is outside the scope of this report to debate the issues surrounding the use of generic valuation tools and whose values should be elicited, it is worth discussing the impact that these variations may have on the ability of the utility to capture adverse effects. It is likely that utilities elicited from patients on treatment may capture some, or all, of the adverse effects experienced by those patients. However, although a number of HTAs did appear

to derive utilities from patients on treatment, few made specific claims that adverse effects had been captured through this methodology.

The methods by which the utility valuations were obtained varied. The argument for the use of a generic preference-based measure is to allow comparisons between health-care programmes. Whether for the same condition or when they involve different medical conditions and treatments[32] there can be a need to address disparate outcomes in a consistent manner. This is the position that has been adopted by NICE.[6] However, an alternative is to use condition-specific descriptions that may be more sensitive to changes in the given condition and may better reflect the concerns of the patient.[33] This was not an issue that was explicitly addressed in this review, although the majority of reports, as would be expected given the NICE guidance, used, or mapped to, a generic measure. There is some evidence of generic measures being insensitive for certain conditions, such as respiratory disease, but there are a number of potential issues that need to be addressed when mapping non-preference-based measures onto preference-based measures and using values from the literature.[32]

Given the variation in ways of describing health, the valuation techniques and respondents (patients, general public, clinical experts), the values that are likely to be found in the literature may vary greatly. This complexity highlights the need for explicit reporting, which in turn would enable the reader to make better judgements about whether it is realistic to expect some adverse effects of interventions, long term or short term, to be captured within the utility. How best to ensure that any adverse effects of interventions are captured within the utility needs further investigation and it is likely that more rigorous methods will need to be adhered to.

The link between the systematic review and decision model

The scope of the decision problem being addressed by the systematic review component and the decision model may differ. Often, the systematic review may focus only on the effectiveness (both positive and negative) of the intervention being evaluated. The scope of the decision modelling question may be much broader, aiming to evaluate the total net benefit of an intervention including any downstream effects that might be observed. This leads to a divergence in both the question being posed and the data required to provide an answer.

The results of the review show that a high number of models (95%) considered one, or more, of the effectiveness outcomes that were evaluated in the systematic review and in the majority of instances the data from the review were used in some capacity. However, the links between the review and the modelling components are not as strong for adverse effects. A high proportion (85%) of the reviews evaluated adverse effects, some from a broad focus and some from a narrow focus. However, just over half of the models incorporated those same outcomes into the model, with fewer again utilising the data obtained by the review. This is not necessarily a negative finding; in some cases it may reflect the slightly different focus of the two components of the reports.

The source of the adverse effects parameter was rarely the results of the systematic review. Our review did not investigate in detail the other sources of adverse effects data, although it is clear that non-systematically derived literature-based data were the most commonly used. In their study, Cooper *et al*.[13] found that, at best, 14% of adverse effects outcome data were sourced from the best quality sources, i.e. a meta-analysis of randomised controlled trials.

Issues with evaluations of diagnostic/screening interventions

Economic evaluations of diagnostic tests are intrinsically more difficult than assessments of therapeutic interventions, mainly because of the uncertainty surrounding the relationship between the diagnostic test and the health outcomes finally achieved.[34] Decision modelling of diagnostic technologies typically encompasses the outcomes from future treatments and management as well as the impact of the actual test. It is not uncommon for such models to include adverse effects of treatments without including those of the test of interest. This may be because the impact of the adverse effects of the test are minimal compared with those of the future treatments. This may be entirely appropriate, but it needs to be stated explicitly. In general, diagnostic reports appear to separate into two groups: those that link the test to an intermediate outcome, for example cost per case detected, and those that link the test to a final outcome, for example cost per quality-adjusted life-year. As the aim of an HTA report is

to inform national policy, one might expect a wider perspective that included final outcomes in the form of utilities. However, this may not always be possible because of data limitations. Additionally, models that explicitly include adverse effects may tend to be those in economic evaluations of the more invasive diagnostic/screening technologies. Intuitively one can imagine that a test such as a coronary angiogram, which involves the injection of a dye into the blood, may be more likely to have adverse events associated with it than a test that involves a dipstick. Information on these issues was not data extracted, although it was observed that in some of those reports in which the test seemed more invasive there appeared to be some discussion around the impact of false positives on quality of life.

False-positive results from diagnostic technologies can have adverse effects. An HTA report published in 2000[35] found little evidence to support the impact of false positives on quality of life, although it is clear that both false positives and false negatives have the potential to impact on the outcomes of the decision model and to affect both the costs and benefits. The report found that decision analysis is likely to be valuable in demonstrating how false results (positive/negative) may be incorporated in screening decisions. Explicitly incorporating values associated with false results may show how they affect decisions about the appropriateness of screening. However, the report found limited empirical evidence to support its findings.

Chapter 5
Conclusions

- The findings of the review of methodology papers show that, although there appears to be an implicit assumption within modelling guidance that adverse effects are very important, there appears to be a lack of clarity regarding how they should be dealt with and considered in modelling. This may be because of the complexity of the issues that need to be dealt with. Further work is required to establish, if possible, what can be considered 'best practice' for a variety of situations for the inclusion of adverse effects.
- Our review found that, in line with the general guidance for decision modelling, all important outcomes appear to be included and most HTAs do include adverse effects in the decision model, although we have made no assessment of the validity of the methods used.
- The inclusion of adverse effects in the decision model did not appear to be dictated by the therapeutic area, type of intervention or type of model, nor how adverse effects were dealt with in the clinical review.
- In most cases the link between the adverse effects data used in the model and the data presented in the systematic review was weak.
- In many cases a lack of clear reporting made it extremely difficult to ascertain what had actually been carried out in consideration of adverse effects. The transparency of the reports that were reviewed for this project varied greatly. Every attempt was made to ensure that the data extraction was accurate. However, given the length and complexity of the reports we cannot rule out the possibility of errors. The reporting appeared to be insufficient for the audience for whom HTA reports are intended. This issue needs to be addressed and efforts made to ensure that these reports are accessible to all readers.

Recommendations for practice

- The main recommendation is for much clearer and explicit reporting of adverse effects in decision models. As a minimum, separate sections on adverse effects should be included in the clinical effectiveness and modelling chapters of every technology assessment report.
- Efforts should be made to ensure that all components of technology assessments explicitly consider those outcomes, including adverse effects, that are relevant to the decision problem. Similarly, there should be explicit recognition in future guidelines that 'all relevant outcomes' should include some consideration of adverse events.
- Whenever the inclusion of adverse effects is not relevant a justification should be explicitly provided by the authors. By doing this, the readers will be made aware that adverse effects were considered at some stage of the process.
- Improved links between the outcomes of the model and the data inputs presented in the systematic review and model description may aid the reader's understanding and support the decision-maker.
- Even when a systematic review of adverse effects data is not feasible, summaries of adverse effects data that can be used to address the decision problem should be presented in the clinical effectiveness review.

Recommendations for research

This report has presented an overview of the current situation regarding the consideration of adverse events in HTA models. It is clear that there are a number of limitations to, and issues outside the scope of, this project that still need to be addressed through further research. Our suggestions for further research include:

- A detailed review and critique of the methods used to identify and incorporate adverse effects in economic models.
- A detailed assessment of how to judge the relevance and appropriateness of the adverse events included. This may involve an in-depth analysis of a subset of reports involving interaction with the report authors.

- Although it is unlikely that any single standard methodological approach could be appropriate for all decision problems, some investigation into whether some methods are more appropriate for certain types of decision problems or clinical areas may be warranted.
- Further investigation into the methodology of mapping disease-specific outcome measures to generic outcome measures.

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Contribution of authors

Ms Dawn Craig assisted in the preparation of the protocol and contributed to the identification, extraction and interpretation of data and the preparation of the final report. Mr Steven Duffy conducted the literature searches and contributed relevant sections to the final report. Mr Tiago Fonseca contributed to the extraction and interpretation of data and the preparation of the final report. Dr Catriona McDaid contributed to the identification, extraction and interpretation of data and the preparation of the final report. Mr Christian Stock contributed to the identification, extraction and interpretation of data and the preparation of the final report. Dr Nerys Woolacott prepared the protocol and provided input at all stages of the project.

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Appendix 1

Searches and results for methodology papers

Literature searches

Cochrane Methodology Register (Cochrane Library) 2007 Issue 3

Searched 19 September 2007.
46 records were retrieved (44 methods studies and two methods reviews).

#1 adverse* or side or risk or risks or safe* or undesirable or unintended or toxicity or toxic or complication* or adr or adrs or tolerability or treatment next emergent or unwanted or unexpected or unintentional or harm or harms or harmful or drug near/2 surveillance or postmarketing near/2 surveillance or "post marketing" near/2 surveillance or ades or ade
#2 economic near/2 model* or econometric near/2 model* or markov or mathematical near/2 model* or cost* near/2 model* or pharmacoeconomic* near/2 model* or stochastic near/2 model* or statistical near/2 model* or theoretical model* or decision near/2 analysis or decision near/2 tree or decision near/2 triage or decision near/2 data or decision near/2 analytic* or decision near/2 model* or crystal near/2 ball
#3 (#1 and #2)

NHS EED (CRD internal databases) 1994 to August 2007

Searched 19 September 2007.
86 records were retrieved.

s 14/xno
s adverse$or side or risk or risks or safe$or undesirable or unintended or toxicity or toxic or complication$or adr or adrs or tolerability or treatment(w)emergent or unwanted or unexpected or unintentional or harm or harms or harmful or drug(w)surveillance or postmarketing(w) surveillance or post(w)marketing(w)surveillance or ades or ade
s s1 and s2

HEED (Wiley online) 1994 to August 2007

Searched 19 September 2007.
189 records were retrieved.

TE=methodological
AX=adverse* or side or risk or risks or safe* or undesirable or unintended or toxicity or toxic or complication* or adr or adrs or tolerability or (treatment emergent) or unwanted or unexpected or unintentional or harm or harms or harmful or (drug surveillance) or (postmarketing surveillance) or (post marketing surveillance) or (post-marketing surveillance) or ades or ade
CS=1 and 2

MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (OVID gateway) 1950 to September Week 2 2007

Searched 24 September 2007.
147 records were retrieved in MEDLINE and two in MEDLINE In-Process & Other Non-Indexed Citations.

1. Product Surveillance, Postmarketing/
2. Adverse Drug Reaction Reporting Systems/
3. exp Drug Hypersensitivity/
4. exp Drug Toxicity/
5. Iatrogenic Disease/
6. exp Abnormalities, Drug Induced/
7. exp Postoperative Complications/
8. exp Intraoperative Complications/
9. (adverse adj2 (interaction$or effect$or response$or reaction$or event$or outcome$)).ti,ab.
10. side effect$.ti,ab.
11. ((undesirable or unintended or unwanted or unexpected or unintentional or harm or harms or harmful) adj (effect$or reaction$or event$or outcome$)).ti,ab.
12. (adr or adrs or ades or ade).ti,ab.
13. treatment emergent.ti,ab.
14. drug safety.ti,ab.
15. drug surveillance.ti,ab.
16. drug toxicity.ti,ab.
17. tolerability.ti,ab.

18. (iatrogenic or iatrogenesis).ti,ab.
19. ((postmarketing or post marketing) adj2 surveillance).ti,ab.
20. complication$.ti.
21. toxicity.ti.
22. safety.ti.
23. safe.ti.
24. (harm or harms or harmful).ti.
25. or/1–24
26. exp Decision Support Techniques/
27. exp models, economic/
28. Markov chains/
29. ((economic or econometric or pharmacoeconomic or cost$) adj2 model$).ti,ab.
30. ((mathematical or stochastic or statistical or theoretical) adj2 model$).ti,ab.
31. (decision adj2 (analy$or tree or triage or data or model$)).ti,ab.
32. (crystal adj2 ball).ti,ab.
33. markov.ti,ab.
34. or/26–33
35. 25 and 34
36. Methods/
37. Research/mt, st
38. exp Research Design/mt, st
39. exp "Costs and Cost Analysis"/mt, st
40. (methodological adj (study or studies or research or issues)).ti,ab.
41. (methodology adj (study or studies or research or issues)).ti,ab.
42. methods.ti.
43. methodological.ti.
44. methodology.ti.
45. challenge$.ti.
46. guidance.ti.
47. or/36–46
48. 35 and 47

EMBASE (OVID gateway) 1980 to 2007 Week 38

Searched 24 September 2007.
223 records were retrieved.

1. exp postmarketing surveillance/
2. Adverse Drug Reaction/
3. exp Drug Hypersensitivity/
4. exp Drug Toxicity/
5. Iatrogenic Disease/
6. Postoperative Complication/
7. Peroperative Complication/
8. (adverse adj2 (interaction$or effect$or response$or reaction$or event$or outcome$)).ti,ab.
9. side effect$.ti,ab.
10. ((undesirable or unintended or unwanted or unexpected or unintentional or harm or harms or harmful) adj (effect$or reaction$or event$or outcome$)).ti,ab.
11. (adr or adrs or ades or ade).ti,ab.
12. treatment emergent.ti,ab.
13. drug safety.ti,ab.
14. drug surveillance.ti,ab.
15. drug toxicity.ti,ab.
16. tolerability.ti,ab.
17. (iatrogenic or iatrogenesis).ti,ab.
18. ((postmarketing or post marketing) adj2 surveillance).ti,ab.
19. complication$.ti.
20. toxicity.ti.
21. safety.ti.
22. safe.ti.
23. (harm or harms or harmful).ti.
24. or/1–23
25. decision support system/
26. statistical model/or stochastic model/or mathematical model/
27. Probability/
28. ((economic or econometric or pharmacoeconomic or cost$) adj2 model$).ti,ab.
29. ((mathematical or stochastic or statistical or theoretical) adj2 model$).ti,ab.
30. (decision adj2 (analy$or tree or triage or data or model$)).ti,ab.
31. (crystal adj2 ball).ti,ab.
32. markov.ti,ab.
33. or/25–32
34. 24 and 33
35. methodology/
36. (methodological adj (study or studies or research or issues)).ti,ab.
37. (methodology adj (study or studies or research or issues)).ti,ab.
38. methods.ti.
39. methodological.ti.
40. methodology.ti.
41. challenge$.ti.
42. guidance.ti.
43. or/35–42
44. 34 and 43

HMIC (OVID gateway) September 2007

Searched 24 September 2007.
85 records were retrieved.

1. (adverse$or side or risk or risks or safe$or undesirable or unintended or toxicity or toxic or complication$or adr or adrs or tolerability or treatment emergent or unwanted or unexpected or unintentional or harm or

harms or harmful or drug surveillance or postmarketing surveillance or post marketing surveillance or post-marketing surveillance or ades or ade).mp.
2. ((economic adj2 model$) or (econometric adj2 model$) or markov or (mathematical adj2 model$) or (cost$adj2 model$) or (pharmacoeconomic$adj2 model$) or (stochastic adj2 model$) or (statistical adj2 model$) or (theoretical adj2 model$) or (decision adj2 analy$) or (decision adj2 tree) or (decision adj2 triage) or (decision adj2 data) or (decision adj2 model$) or (crystal adj2 ball)).mp.
3. 1 and 2
4. exp RESEARCH METHODOLOGY/or exp RESEARCH METHODS/
5. (methodological or methodology).mp.
6. methods.ti.
7. or/4–6
8. 3 and 7

EconLIT (OVID SilverPlatter) 1969–2007/8

Searched 24 September 2007.
13 records were retrieved.

#1 adverse* or side or risk or risks or safe* or undesirable or unintended or toxicity or toxic or complication* or adr or adrs or tolerability or (treatment emergent) or unwanted or unexpected or unintentional or harm or harms or harmful or (drug surveillance) or (postmarketing surveillance) or (post marketing surveillance) or (post-marketing surveillance) or ades or ade
#2 model* in DE
#3 markov* in DE
#4 ((economic or econometric or pharmacoeconomic or cost*) near2 model*) in ti,ab
#5 ((mathematical or stochastic or statistical or theoretical) near2 model*) in ti,ab
#6 (decision near2 (analy* or tree or triage or data or model*)) in ti,ab
#7 (crystal near2 ball) in ti,ab
#8 markov* in ti,ab
#9 #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 #1 and #9
#11 method* in DE
#12 (methodological adj (study or studies or research or issues)) in ti,ab
#13 (methodology adj (study or studies or research or issues)) in ti,ab
#14 methods in ti
#15 methodological in ti
#16 methodology in ti
#17 challenge* in ti
#18 guidance in ti
#19 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
#20 #10 and #19
#21 (HEALTH PRODUCTION in DE) or (ANALYSIS-OF-HEALTH-CARE-MARKETS in DE) or (HEALTH-GOVERNMENT-POLICY in DE) or (HEALTH-GENERAL in DE) or (HEALTH-OTHER in DE)
#22 #20 and #21

IDEAS (RePeC website)

Searched 8 October 2007.
0 records were retrieved.

Each line searched separately:

adverse event
adverse events
side effect AND economic model
side effects AND economic model
side effect AND economic models
side effects AND economic models

Appendix 2

Data extraction form

Section A: Bibliographic information

A.1 Author
First author, year, {#EndNote number}
A.1.1 Author

A.2 Year of publication
A.2.1 2007
A.2.2 2006
A.2.3 2005
A.2.4 2004
A.2.5 2003
A.2.6 2002
A.2.7 2001
A.2.8 2000
A.2.9 1999
A.2.10 1998
A.2.11 1997

A.3 Endnote number
A.3.1 Endnote number

A.4 Update of an earlier HTA?
A.4.1 Yes (specify)
A.4.2 No

A.5 Eligibility
A.5.1 Include
A.5.2 Exclude (specify):
if (1) no economic model, (2) a model that has not been developed or modified/updated by the authors, (3) an updated version of the report has been published already

A.6 Research type
A.6.1 NICE TAR
A.6.2 Secondary research
A.6.3 Primary research
A.6.4 HTA report

Section B: Research classification

B.1 Description of decision problem (as stated in report)
B.1.1 Decision problem

B.2 Research activity area (RAA)
B.2.1 Evaluation of treatments and therapeutic interventions
B.2.2 Prevention of disease and conditions, and promotion of well-being
B.2.3 Detection, screening and diagnosis
B.2.4 Other

B.3 Specify RAA 'Evaluation of treatments and therapeutic interventions'
B.3.1 Not applicable
B.3.2 Pharmaceuticals
B.3.3 Cellular and gene therapies
B.3.4 Medical devices
B.3.5 Surgery
B.3.6 Radiotherapy
B.3.7 Psychological and behavioural
B.3.8 Physical
B.3.9 Complementary
B.3.10 Resources and infrastructure (evaluation of treatments)

B.4 Specify RAA 'Prevention of disease and conditions, and promotion of well-being'
B.4.1 Not applicable
B.4.2 Primary prevention interventions to modify behaviours or promote well-being
B.4.3 Interventions to alter physical and biological environmental risks
B.4.4 Nutrition and chemoprevention
B.4.5 Vaccines
B.4.6 Resources and infrastructure (prevention)

B.5 Specify RAA 'Detection, screening and diagnosis'
B.5.1 Not applicable
B.5.2 Discovery and preclinical testing of markers and technologies
B.5.3 Evaluation of markers and technologies
B.5.4 Influences and impact
B.5.5 Population screening
B.5.6 Resources and infrastructure (detection)

B.6 Specify RAA 'Other'
B.6.1 Not applicable
B.6.2 Development of treatments and therapeutic interventions
B.6.3 Management of diseases and conditions
B.6.4 Health and social care services research

B.7 Health category
B.7.1 Blood

B.7.2 Cancer
B.7.3 Cardiovascular
B.7.4 Congenital disorders
B.7.5 Ear
B.7.6 Eye
B.7.7 Infection
B.7.8 Inflammatory and immune system
B.7.9 Injuries and accidents
B.7.10 Mental health
B.7.11 Metabolic and endocrine
B.7.12 Musculoskeletal
B.7.13 Neurological
B.7.14 Oral or gastrointestinal
B.7.15 Renal and urogenital
B.7.16 Reproductive health and childbirth
B.7.17 Respiratory
B.7.18 Skin
B.7.19 Stroke
B.7.20 Generic health relevance
B.7.21 Other

Section C: Adverse effects in the clinical effectiveness review

C.1 Do the specified outcomes include AEs?
C.1.1 Yes, broad focus (specify)
C.1.2 Yes, narrow focus (specify)
C.1.3 No
C.1.4 Unclear

C.2 Were there separate inclusion criteria in relation to obtaining AE data (e.g. additional study designs included)
C.2.1 Yes (specify)
C.2.2 No (comment)
C.2.3 Unclear

C.3 Were the AE data synthesised in a meta-analysis?
C.3.1 Yes
C.3.2 No
C.3.3 Unclear
C.3.4 Not applicable (because no AE data)

Section D: Adverse effects in the economic model

D.1 Is more than one economic model presented or does an economic model consist of two or more parts (e.g. short-term and long-term model)?
D.1.1 Yes (specify)
D.1.2 No

D.2 What type(s) of economic model(s) was/were used?
D.2.1 Decision tree
D.2.2 State transition model, incl. Markov models
D.2.3 Other (specify)
D.2.4 Unclear (specify)

D.3 If a state transition model was used, was a cohort- or patient-level simulation employed?
D.3.1 Not applicable
D.3.2 Cohort
D.3.3 Patient level
D.3.4 Both
D.3.5 Unclear (specify)

D.4 What is the time horizon of the model(s)?
D.4.1 Lifetime
D.4.2 Long term as stated by the authors (specify)
D.4.3 Short term as stated by the authors (specify)
D.4.4 Number of years (specify)
D.4.5 Other (specify)
D.4.6 Unclear (specify)

D.5 Has one or more of the outcomes considered in the clinical effectiveness review been used to inform the model(s)?
D.5.1 Yes (specify)
D.5.2 No
D.5.3 Unclear (specify)

D.6 How was/were the parameter value(s) used derived? [Add comment if difficult to answer]
D.6.1 Directly from the synthesis of studies in the review
D.6.2 Synthesis conducted on a subset of studies (specify)
D.6.3 Independently/alternative synthesis (specify)
D.6.4 Unclear (specify)

D.7 Are AEs included as a parameter in the model(s)?
D.7.1 Yes (specify)
D.7.2 No
D.7.3 Unclear (specify)

D.8 Do(es) the model(s) consider any of the AEs included in the clinical effectiveness review?
D.8.1 Yes (specify)
D.8.2 No (specify)
D.8.3 Unclear
D.8.4 Not applicable (if no AEs were included in the clinical effectiveness review)

D.9 Is the source of the AE data specified?
D.9.1 Yes
D.9.2 No
D.9.3 Partial

D.9.4 Not applicable (because no AE data considered)

D.10 What sources were used to obtain the AE data?
D.10.1 The accompanying systematic review
D.10.2 Other sources, e.g. ad hoc selection or systematic searches (specify)
D.10.3 Both systematic review and other sources
D.10.4 Expert opinion
D.10.5 Unclear
D.10.6 Not applicable (because no AE data considered or source not specified)

D.11 Is the absence of AE data explained?
D.11.1 Not applicable
D.11.2 Yes (specify)
D.11.3 No

D.12 Did the model use a clinical AE parameter?
D.12.1 Yes
D.12.2 No

D.13 Did the model use utilities?
D.13.1 Yes
D.13.2 No

D.14 If the model used utilities, were these based on judgement?
D.14.1 Yes
D.14.2 No
D.14.3 Not applicable

D.15 If the model used utilities, were these obtained from a secondary source or derived using clinicians'/public preferences?
D.15.1 Yes
D.15.2 No
D.15.3 Not applicable

D.16 If the model used utilities, were preferences derived from patients on treatment?
D.16.1 Yes
D.16.2 No
D.16.3 Not applicable

D.17 Did the model incorporate the cost/resources of AEs?
D.17.1 Yes
D.17.2 No

D.18 Did the model incorporate withdrawals?
D.18.1 Yes
D.18.2 No

Section E: Comment (optional)

E.1 Comment by reviewer:
E.1.1 Comment

Appendix 3
Results tables

TABLE 20 *Did reports include adverse effects?*

	Do the specified SR outcomes include AEs?	Are AEs included as a parameter in the model(s)?	In both SR and model	Not at all	In SR but not model	In model but not SR
Abubakar 2007[36]	No	No		✗		
Adi 2007[37]	Yes, broad focus	No			✗	
Avenell 2004[38]	Yes, broad focus	No			✗	
Bamford 2007[39]	Yes, broad focus	No			✗	
Black 2007[40]	Yes, narrow focus	No			✗	
Brazzelli, 2006[41]	Yes, broad focus	No			✗	
Bridle 2004[42]	Yes, broad focus	No			✗	
Brown 2006[43]	Yes, narrow focus	Yes	✗			
Bryant 2004[44]	Yes, broad focus	No			✗	
Buxton 2006[45]	Yes, broad focus	Yes	✗			
Castelnuovo 2005[46]	Yes, narrow focus	Yes	✗			
Chen 2006[47]	Yes, broad focus	Yes	✗			
Clar 2005[48]	Yes, broad focus	No			✗	
Clark 2004[28]	Yes, broad focus	Yes	✗			
Clegg 2005[49]	Yes, broad focus	Yes	✗			
Collins 2007[50]	Yes, broad focus	Yes	✗			
Collins 2007[51]	Yes, broad focus	Yes	✗			
Connock 2006[52]	Yes, broad focus	Yes	✗			
Connock 2006[53]	Yes, broad focus	Yes	✗			
Connock 2007[54]	Yes, narrow focus	No			✗	
Connock 2006[55]	Yes, broad focus	No			✗	
Dalziel 2004[56]	Yes, broad focus	No			✗	
Davies 2006[31]	Yes, broad focus	Yes	✗			
Dretzke 2004[18]	No	Yes				✗
Dundar 2007[57]	Yes, broad focus	Yes	✗			
Fayter 2007[58]	No	No		✗		
Garrison 2007[59]	Yes, broad focus	No			✗	
Garside 2007[60]	Yes, broad focus	Yes	✗			
Garside 2006[19]	No	Yes				✗
Garside 2005[61]	Yes, broad focus	No			✗	
Garside 2004[62]	Yes, broad focus	Yes	✗			
Goodacre 2006[21]	No	Yes				✗
Green 2005[63]	Yes, broad focus	Yes	✗			
Greenhalgh 2005[22]	Yes, narrow focus	Yes	✗			

continued

TABLE 20 *Did reports include adverse effects? (continued)*

	Do the specified SR outcomes include AEs?	Are AEs included as a parameter in the model(s)?	In both SR and model	Not at all	In SR but not model	In model but not SR
Hartwell 2005[29]	Yes, broad focus	Yes	✗			
Hill 2004[64]	Yes, narrow focus	Yes	✗			
Hind 2007[65]	Yes, broad focus	Yes	✗			
Jones 2004[66]	Yes, narrow focus	Yes	✗			
Kaltenthaler 2006[67]	Unclear	No		✗		
Kaltenthaler 2004[68]	Yes, broad focus	Yes	✗			
Kanis 2007[69]	Yes, broad focus	No			✗	
Karnon 2004[70]	No	No		✗		
King 2006[27]	Yes, narrow focus	Yes	✗			
Knight 2004[71]	Yes, broad focus	No			✗	
Loveman2006[72]	Yes, broad focus	No			✗	
Main 2006[30]	Yes, broad focus	Yes	✗			
Main 2004[73]	Yes, broad focus	Yes	✗			
Martin 2006[74]	No	No		✗		
McCormack 2005[75]	Yes, narrow focus	Yes	✗			
McLeod 2007[76]	Yes, broad focus	Yes	✗			
Mowatt 2004[77]	Yes, broad focus	Yes	✗			
Murray 2006[78]	Yes, narrow focus	Yes	✗			
Nelson 2006[79]	Yes, broad focus	No			✗	
Pandor 2004[80]	Yes, broad focus	No			✗	
Pandor 2006[81]	Yes, broad focus	Yes	✗			
Robinson 2005[82]	Yes, broad focus	Yes	✗			
Rodgers 2006[83]	Yes, broad focus	No			✗	
Ross 2004[84]	Yes, broad focus	No			✗	
Shepherd 2004[85]	Yes, broad focus	No			✗	
Shepherd 2007[24]	Yes, broad focus	Yes	✗			
Shepherd 2006[86]	Yes, broad focus	No			✗	
Speight 2006[87]	No	No		✗		
Stevenson 2007[88]	Yes, broad focus	No			✗	
Stevenson 2005[89]	Yes, broad focus	Yes	✗			
Takeda 2007[90]	Yes, broad focus	Yes	✗			
Tappenden 2007[91]	Yes, broad focus	Yes	✗			
Thomas 2006[92]	Yes, broad focus	No			✗	
Ward 2007[93]	Yes, broad focus	No			✗	
Wardlaw 2006[20]	No	Yes				✗
Wardlaw 2004[94]	No	No		✗		
Warren 2004[95]	Yes, broad focus	No			✗	
Whiting 2006[96]	Yes, broad focus	No			✗	
Wilby 2005[97]	Yes, broad focus	No			✗	
Willis 2005[98]	No	No		✗		

TABLE 20 *Did reports include adverse effects? (continued)*

	Do the specified SR outcomes include AEs?	Are AEs included as a parameter in the model(s)?	In both SR and model	Not at all	In SR but not model	In model but not SR
Wilson 2005[99]	Yes, broad focus	Yes	✗			
Wilson 2007[100]	Yes, narrow focus	Yes	✗			
Woolacott 2006[26]	Yes, broad focus	Yes	✗			
Woolacott 2006[23]	Yes, broad focus	No			✗	
Wu 2006[101]	Yes, broad focus	Yes	✗			
Yao 2006[25]	Yes, narrow focus	Yes	✗			
Total = 80	68 (85%)	43 (53.75%)	39 (48.75%)	8 (10%)	29 (36.25%)	4 (5%)

AEs, adverse effects; SR, systematic review.

TABLE 21 *Reports that included adverse effects in the model but not the clinical review*

Dretzke 2004[18]	Detection, screening and diagnosis	Metabolic and endocrine	To determine the role of autoantibody tests for autoimmune disease (specifically coeliac disease and thyroid disease) in children with newly diagnosed type I diabetes mellitus
Garside 2006[19]	Detection, screening and diagnosis	Cancer	To assess the impact of endoscopic surveillance in preventing morbidity and mortality from adenocarcinoma in patients with Barrett's oesophagus
Goodacre 2006[21]	Detection, screening and diagnosis	Cardiovascular	To estimate the diagnostic accuracy of non-invasive tests for proximal deep vein thrombosis (DVT) and isolated calf DVT in patients with clinically suspected DVT or at high risk of DVT and identify factors associated with variation in diagnostic performance. It also aimed to identify practical diagnostic algorithms for DVT and to estimate the diagnostic accuracy, clinical effectiveness and cost-effectiveness of each
Wardlaw, 2006[20]	Detection, screening and diagnosis	Cardiovascular	To determine whether less invasive imaging tests (ultrasound, magnetic resonance angiography, computed tomographic angiography and contrast-enhanced magnetic resonance angiography), alone or combined, could replace intra-arterial angiography, what effect this would have on strokes and deaths, endarterectomies performed and costs, and whether less invasive tests were cost-effective

TABLE 22 *Meta-analysis of adverse effects data undertaken by health category*

	Yes	No	Unclear	Total
Blood	2	0	0	2
Cancer	2	12	0	18
Cardiovascular	3	8	0	13
Congenital disorders	0	2	0	2
Ear	0	1	0	1
Eye	0	0	0	0
Infection	0	4	0	5
Inflammatory and immune system	0	1	0	1
Injuries and accidents	0	0	0	0
Mental health	2	4	1	7
Metabolic and endocrine	0	4	0	6
Musculoskeletal	2	6	0	8
Neurological	0	2	0	2
Oral or gastrointestinal	2	2	0	5
Reproductive health and childbirth	0	1	0	1
Respiratory	0	0	0	0
Skin	1	3	0	4
Stroke	0	0	0	1
Generic health relevance	0	1	0	1
Other	0	0	0	1
Renal and urogenital	0	4	0	4
Total	14	55	1	82

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TABLE 23 *Time horizons for decision models in reviewed HTA reports*

Author	Are AEs included as a parameter in the model(s)?	What is the time horizon of the model(s)?	Up to 1 year	1–5 years	5–20 years	20+ years	Lifetime	Unclear
Abubakar 2007[36]	No	1 year		✗				
Adi 2007[37]	No	1 year		✗				
Avenell 2004[38]	No	6 years			✗			
Bamford 2007[39]	No	1 year		✗				
Black 2007[40]	No	20 years				✗		
Brazzelli 2006[41]	No	5 years			✗			
Bridle 2004[42]	No	3 weeks	✗					
Brown 2006[43]	Yes	Short-term (not specified)		✗				
Bryant 2004[44]	No	5 years			✗			
Buxton 2006[45]	Yes	20 years				✗		
Castelnuovo 2005[46]	Yes	10 years			✗			
Chen 2006[47]	Yes	Lifetime					✗	
Clar 2005[48]	No	50 years				✗		
Clark 2004[28]	Yes	Lifetime					✗	
Clegg 2005[49]	Yes	5 years			✗			
Collins 2007[51]	Yes	15 years			✗			
Collins 2007[50]	Yes	1 year		✗				
Connock 2006[52]	Yes	Lifetime					✗	
Connock 2006[55]	No	Lifetime					✗	
Connock 2007[54]	No	1 year		✗				
Connock 2006[53]	Yes	Up to 15 years			✗			
Dalziel 2004[56]	No	20 years				✗		
Davies 2006[31]	Yes	1 month and 1, 10, 30 years in sensitivity analyses	✗					
Dretzke 2004[18]	Yes	Lifetime					✗	
Dundar 2007[57]	Yes	Unclear						✗
Fayter 2007[58]	No	Lifetime					✗	

continued

TABLE 23 *Time horizons for decision models in reviewed HTA reports (continued)*

Author	Are AEs included as a parameter in the model(s)?	What is the time horizon of the model(s)?	Up to 1 year	1–5 years	5–20 years	20+ years	Lifetime	Unclear
Garrison 2007[59]	No	2 years		✗				
Garside 2005[61]	No	1 year for adult cohorts and 14 years for child cohorts		✗	✗			
Garside 2006[19]	Yes	20 years				✗		
Garside 2007[60]	Yes	Lifetime					✗	
Garside 2004[62]	Yes	10 years			✗			
Goodacre 2006[21]	Yes	Lifetime					✗	
Green 2005[63]	Yes	Lifetime					✗	
Greenhalgh 2005[22]	Yes	1 year		✗				
Hartwell 2005[29]	Yes	6 months	✗					
Hill 2004[64]	Yes	5 years			✗			
Hind 2007[65]	Yes	35 years				✗		
Jones 2004[66]	Yes	Lifetime					✗	
Kaltenthaler 2004[68]	Yes	1 year		✗				
Kaltenthaler 2006[67]	No	1.5 years		✗				
Kanis 2007[69]	No	10 years			✗			
Karnon 2004[70]	No	First screen age 24 years to last screen age 64 years						✗
King 2006[27]	Yes	1 year		✗				
Knight 2004[71]	No	15 years			✗			
Loveman 2006[72]	No	5 years			✗			
Main 2004[73]	Yes	40 years				✗		
Main 2006[30]	Yes	Unclear						✗
Martin 2006[74]	No	Unclear						✗
McCormack 2005[75]	Yes	5 years and 25 years			✗	✗		
McLeod 2007[76]	Yes	1 year and 2–20 years		✗	✗			
Mowatt 2004[77]	Yes	25 years				✗		
Murray 2006[78]	Yes	25 years				✗		
Nelson 2006[79]	No	Model not run						✗

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Author	Are AEs included as a parameter in the model(s)?	What is the time horizon of the model(s)?	Up to 1 year	1–5 years	5–20 years	20+ years	Lifetime	Unclear
Pandor 2004[80]	No	1 year		✗				
Pandor 2006[81]	Yes	50 years				✗		
Robinson 2005[82]	Yes	Lifetime (50 years)				✗	✗	
Rodgers 2006[83]	No	Short-term (not specified)		✗				
Ross 2004[84]	No	4 years		✗				
Shepherd 2004[85]	No	30 years				✗		
Shepherd 2006[86]	No	Lifetime					✗	
Shepherd 2007[24]	Yes	Lifetime (60 years)				✗	✗	
Speight 2006[87]	No	Lifetime (60 years)					✗	
Stevenson 2005[89]	Yes	10 years			✗			
Stevenson 2007[88]	No	10 years			✗			
Takeda 2007[90]	Yes	Lifetime					✗	
Tappenden 2007[91]	Yes	Lifetime					✗	
Thomas 2006[92]	No	18 weeks	✗					
Ward 2007[93]	No	Lifetime					✗	
Wardlaw 2004[94]	No	Unclear						✗
Wardlaw 2006[20]	Yes	20 years				✗		
Warren 2004[95]	No	Unclear						✗
Whiting 2006[96]	No	Unclear						✗
Wilby 2005[97]	No	15 years			✗			
Willis 2005[98]	No	Long term (not specified)			✗			
Wilson 2005[99]	Yes	10 years			✗			
Wilson 2007[100]	Yes	3 years		✗				
Woolacott 2006[23]	No	10 years			✗			
Woolacott 2006[26]	Yes	Lifetime (40 years)				✗	✗	
Wu 2006[101]	Yes	Unclear						✗
Yao 2006[25]	Yes	10 years			✗			

AEs, adverse effects.

TABLE 24 *Parameters for inclusion of adverse effects in models by HTA report*

Author	Are AEs included as a parameter in the model(s)?	Did the model use a clinical AE parameter?	Did the model use utilities?	If the model used utilities, were these based on judgement?	If the model used utilities, were these obtained from a secondary source or derived using clinicians'/public preferences?	If the model used utilities, were preferences derived from patients on treatment?	Did the model incorporate the cost/ resources of AEs?	Did the model incorporate withdrawals?
Abubakar 2007[36]	No	No	No	Not applicable	Not applicable	Not applicable	No	No
Adi 2007[37]	No	No	Yes	Yes	No	No	No	Yes
Avenell 2004[38]	No	No	Yes	Yes	No	No	No	No
Bamford 2007[39]	No	No	Yes	No	No	Yes	No	No
Black 2007[40]	No	No	No	Not applicable	Not applicable	Not applicable	No	No
Brazzelli 2006[41]	No	No	No	Not applicable	Not applicable	Not applicable	No	No
Bridle 2004[42]	No	No	No	Not applicable	Not applicable	Not applicable	No	No
Brown 2006[43]	Yes	Yes	No	Not applicable	Not applicable	Not applicable	Yes	No
Bryant 2004[44]	No	No	No	Not applicable	Not applicable	Not applicable	No	No
Buxton 2006[45]	Yes	Yes	Yes	No	No	Yes	Yes	No
Castelnuovo 2005[46]	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Chen 2006[47]	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Clar 2005[48]	No	No	Yes	Yes	No	No	No	No
Clark 2004[28]	Yes	No	Yes	No	No	Yes	No	Yes
Clegg 2005[49]	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Collins 2007[50]	Yes	No	Yes	Yes	No	No	Yes	No
Collins 2007[51]	Yes	Yes	Yes	No	No	Yes	Yes	No
Connock 2006[52]	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Connock 2006[53]	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Connock 2007[54]	No	No	Yes	Yes	No	No	No	No
Connock 2006[55]	No	No	Yes	Yes	No	No	No	No
Dalziel 2004[56]	No	No	Yes	No	No	Yes	No	No
Davies 2006[31]	Yes	Yes	Yes	No	Yes	No	Yes	No
Dretzke 2004[18]	Yes	No	Yes	Yes	No	No	No	No
Dundar 2007[57]	Yes	No	Yes	No	No	Yes	Yes	Yes
Fayter 2007[58]	No	No	Yes	Yes	No	Yes	No	Yes
Garrison 2007[59]	No	No	Yes	No	No	Yes	No	No

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Author	Are AEs included as a parameter in the model(s)?	Did the model use a clinical AE parameter?	Did the model use utilities?	If the model used utilities, were these based on judgement?	If the model used utilities, were these obtained from a secondary source or derived using clinicians'/public preferences?	If the model used utilities, were preferences derived from patients on treatment?	Did the model incorporate the cost/ resources of AEs?	Did the model incorporate withdrawals?
Garside 2007[60]	Yes	No	Yes	No	Yes	No	Yes	Yes
Garside 2006[19]	Yes	No	Yes	Yes	No	No	Yes	No
Garside 2005[61]	No	No	Yes	Yes	No	Yes	No	No
Garside2004[62]	Yes	Yes	Yes	No	No	Yes	Yes	No
Goodacre 2006[21]	Yes	Yes	Yes	No	Yes	No	Yes	No
Green 2005[63]	Yes	Yes	Yes	No	No	Yes	Yes	No
Greenhalgh 2005[22]	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Hartwell 2005[29]	Yes	Yes	Yes	No	No	Yes	No	No
Hill 2004[64]	Yes	Yes	Yes	No	Yes	No	Yes	No
Hind 2007[65]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Jones 2004[66]	Yes	Yes	Yes	No	Yes	No	Yes	No
Kaltenthaler 2006[67]	No	No	Yes	No	No	Yes	No	Yes
Kaltenthaler 2004[68]	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Kanis 2007[69]	No	No	Yes	Yes	No	No	No	No
Karnon 2004[70]	No	No	Yes	No	Yes	No	No	No
King 2006[27]	Yes	No	Yes	No	No	Yes	No	Yes
Knight 2004[71]	No	No	Yes	No	No	Yes	No	No
Loveman2006[72]	No	No	Yes	No	No	Yes	No	No
Main 2006[30]	Yes	Yes	Yes	No	Yes	No	Yes	No
Main 2004[73]	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Martin 2006[74]	No	No	No	Not applicable	Not applicable	Not applicable	No	No
McCormack 2005[75]	Yes	Yes	Yes	No	No	Yes	No	No
McLeod 2007[76]	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Mowatt 2004[77]	Yes	Yes	Yes	No	Yes	No	No	No
Murray 2006[78]	Yes	Yes	Yes	No	Yes	No	Yes	No
Nelson 2006[79]	No	No	No	Not applicable	Not applicable	Not applicable	No	No
Pandor 2004[80]	No	No	No	Not applicable	Not applicable	Not applicable	No	No

continued

TABLE 24 *Parameters for inclusion of adverse effects in models by HTA report (continued)*

Author	Are AEs included as a parameter in the model(s)?	Did the model use a clinical AE parameter?	Did the model use utilities?	If the model used utilities, were these based on judgement?	If the model used utilities, were these obtained from a secondary source or derived using clinicians'/public preferences?	If the model used utilities, were preferences derived from patients on treatment?	Did the model incorporate the cost/ resources of AEs?	Did the model incorporate withdrawals?
Pandor 2006[81]	Yes	No	Yes	No	No	Yes	Yes	Yes
Robinson 2005[82]	Yes	Yes	Yes	No	No	Yes	Yes	No
Rodgers 2006[83]	No	No	No	Not applicable	Not applicable	Not applicable	No	No
Ross 2004[84]	No	No	No	Not applicable	Not applicable	Not applicable	No	No
Shepherd 2004[85]	No	No	Yes	Yes	No	No	No	No
Shepherd 2007[24]	Yes	No	Yes	No	No	Yes	No	No
Shepherd 2006[86]	No	No	Yes	Yes	No	Yes	No	No
Speight 2006[87]	No	No	Yes	No	No	Yes	No	No
Stevenson 2007[88]	No	No	Yes	No	No	Yes	No	No
Stevenson 2005[89]	Yes	No	Yes	No	Yes	No	Yes	No
Takeda 2007[90]	Yes	Yes	Yes	No	Yes	No	Yes	No
Tappenden 2007[91]	Yes	Yes	Yes	No	Yes	No	Yes	No
Thomas 2006[92]	No	No	No	Not applicable	Not applicable	Not applicable	No	No
Ward 2007[93]	No	No	Yes	No	No	Yes	No	No
Wardlaw 2006[20]	Yes	Yes	Yes	Yes	No	No	Yes	No
Wardlaw 2004[94]	No	No	Yes	No	No	Yes	No	No
Warren 2004[95]	No	No	Yes	No	No	Yes	No	No
Whiting 2006[96]	No	No	Yes	No	Yes	No	No	No
Wilby 2005[97]	No	No	Yes	No	No	Yes	No	No
Willis 2005[98]	No	No	No	Not applicable	Not applicable	Not applicable	No	No
Wilson 2005[99]	Yes	No	Yes	Yes	No	No	Yes	Yes
Wilson 2007[100]	Yes	Yes	Yes	No	Yes	No	Yes	No
Woolacott 2006[26]	Yes	No	Yes	No	No	Yes	No	Yes
Woolacott 2006[23]	No	No	Yes	No	No	Yes	No	No
Wu 2006[101]	Yes	No	No	Not applicable	Not applicable	Not applicable	Yes	No
Yao 2006[25]	Yes	No	Yes	No	Yes	No	No	Yes

AE, adverse effect.

TABLE 25 *Models that used a clinical parameter to capture adverse effects*

Author	Did the model use a clinical AE parameter?	Did the model incorporate the cost/ resources of AEs?
Brown 2006[43]	Yes	Yes
Buxton 2006[45]	Yes	Yes
Castelnuovo 2005[46]	Yes	Yes
Chen 2006[47]	Yes	Yes
Clegg 2005[49]	Yes	Yes
Collins 2007[51]	Yes	Yes
Connock 2006[52]	Yes	Yes
Connock 2006[53]	Yes	Yes
Davies 2006[31]	Yes	Yes
Garside2004[62]	Yes	Yes
Goodacre 2006[21]	Yes	Yes
Green 2005[63]	Yes	Yes
Greenhalgh 2005[22]	Yes	Yes
Hartwell 2005[29]	Yes	No
Hill 2004[64]	Yes	Yes
Hind 2007[65]	Yes	Yes
Jones 2004[66]	Yes	Yes
Kaltenthaler 2004[68]	Yes	Yes
Main 2006[30]	Yes	Yes
Main 2004[73]	Yes	Yes
McCormack 2005[75]	Yes	No
McLeod 2007[76]	Yes	Yes
Mowatt 2004[77]	Yes	No
Murray 2006[78]	Yes	Yes
Robinson 2005[82]	Yes	Yes
Takeda 2007[90]	Yes	Yes
Tappenden 2007[91]	Yes	Yes
Wardlaw 2006[20]	Yes	Yes
Wilson 2007[100]	Yes	Yes

AE, adverse effect.

TABLE 26 *Reports with cost parameter for adverse effects in model*

Author	Did the model incorporate the cost/ resources of AEs?	Did the model use a clinical AE parameter?	Did the model use utilities?	Did the model incorporate withdrawals?
Woolacott 2006[26]	No	No	Yes	Yes
Dretzke 2004[18]	No	No	Yes	No
King 2006[27]	No	No	Yes	Yes
Mowatt 2004[77]	No	Yes	No	No
Shepherd 2007[24]	No	No	Yes	No
Yao 2006[25]	No	No	Yes	Yes
Clark 2004[28]	No	No	Yes	Yes
Hartwell 2005[29]	No	Yes	Yes	No
McCormack 2005[75]	No	Yes	Yes	No
Collins 2007[50]	Yes	No	Yes	No
Garside 2006[19]	Yes	No	Yes	No
Wilson 2005[99]	Yes	No	Yes	Yes
Wu 2006[101]	Yes	No	No	No
Clegg 2005[49]	Yes	Yes	Yes	No
Connock 2006[52]	Yes	Yes	Yes	No
Garside 2007[60]	Yes	No	Yes	Yes
Pandor 2006[81]	Yes	No	Yes	Yes
Stevenson 2005[89]	Yes	No	Yes	No
Brown 2006[43]	Yes	Yes	No	No
Buxton 2006[45]	Yes	Yes	Yes	No
Castelnuovo 2005[46]	Yes	Yes	Yes	No
Chen 2006[47]	Yes	Yes	Yes	Yes
Collins 2007[51]	Yes	Yes	Yes	No
Connock 2006[53]	Yes	Yes	Yes	Yes
Davies 2006[31]	Yes	Yes	Yes	No
Garside2004[62]	Yes	Yes	Yes	No
Goodacre 2006[21]	Yes	Yes	Yes	No
Green 2005[63]	Yes	Yes	Yes	No
Greenhalgh 2005[22]	Yes	Yes	Yes	Yes
Hill 2004[64]	Yes	Yes	Yes	No
Hind 2007[65]	Yes	Yes	Yes	Yes
Jones 2004[66]	Yes	Yes	Yes	No
Kaltenthaler 2004[68]	Yes	Yes	Yes	No
Main 2006[30]	Yes	Yes	Yes	No
Main 2004[73]	Yes	Yes	Yes	No
McLeod 2007[76]	Yes	Yes	Yes	Yes
Murray 2006[78]	Yes	Yes	Yes	No
Robinson 2005[82]	Yes	Yes	Yes	No
Takeda 2007[90]	Yes	Yes	Yes	No
Tappenden 2007[91]	Yes	Yes	Yes	No
Wardlaw 2006[20]	Yes	Yes	Yes	No
Wilson 2007[100]	Yes	Yes	Yes	No
Dundar 2007[57]	Yes	No	Yes	Yes

AE, adverse effect.

TABLE 27 *Models that included adverse effects but not via a clinical parameter*

Author	Did the model use a clinical AE parameter?	Did the model incorporate the cost/resources of AEs?	Did the model incorporate withdrawals?	Did the model use utilities?	If the model used utilities, were these based on judgement?	If the model used utilities, were these obtained from a secondary source or derived using clinicians'/public preferences?	If the model used utilities, were preferences derived from patients on treatment?
Clark 2004[28]	No	No	Yes	Yes	No	No	Yes
Dretzke 2004[18]	No	No	No	Yes	Yes	No	No
King 2006[27]	No	No	Yes	Yes	No	No	Yes
Shepherd 2007[24]	No	No	No	Yes	No	No	Yes
Woolacott 2006[26]	No	No	Yes	Yes	No	No	Yes
Yao 2006[25]	No	No	Yes	Yes	No	Yes	No

AE, adverse effect.

TABLE 28 *Models that included withdrawals in the structure*

Author	Did the model incorporate withdrawals?	Are AEs included as a parameter in the model(s)?	Did the model use a clinical AE parameter?	Did the model use utilities?	Did the model incorporate the cost/ resources of AEs?
Adi 2007[37]	Yes	No	No	Yes	No
Fayter 2007[58]	Yes	No	No	Yes	No
Kaltenthaler 2006[67]	Yes	No	No	Yes	No
Chen 2006[47]	Yes	Yes	Yes	Yes	Yes
Clark 2004[28]	Yes	Yes	No	Yes	No
Connock 2006[53]	Yes	Yes	Yes	Yes	Yes
Dundar 2007[57]	Yes	Yes	No	Yes	Yes
Garside 2007[60]	Yes	Yes	No	Yes	Yes
Greenhalgh 2005[22]	Yes	Yes	Yes	Yes	Yes
Hind 2007[65]	Yes	Yes	Yes	Yes	Yes
King 2006[27]	Yes	Yes	No	Yes	No
McLeod 2007[76]	Yes	Yes	Yes	Yes	Yes
Pandor 2006[81]	Yes	Yes	No	Yes	Yes
Wilson 2005[99]	Yes	Yes	No	Yes	Yes
Woolacott 2006[26]	Yes	Yes	No	Yes	No
Yao 2006[25]	Yes	Yes	No	Yes	No

AE, adverse effect.

TABLE 29 *Source of adverse effect model parameter data*

Author	What sources were used to obtain the adverse effect data?
Brown 2006[43]	Both systematic review and other sources Results from systematic review used for probability of no gastrointestinal (GI) adverse event; GI discomfort; uncomplicated (symptomatic or endoscopic) ulcer; and serious GI complication. Meta-analysis results could not be used for probabilities of events occurring as a result of these outcomes and these were obtained from individual trials/studies
Buxton 2006[45]	Other sources, e.g. ad hoc selection or systematic searches (specify) The data used seem to be additional data (not reported as part of clinical effectiveness) obtained from the authors of one of the studies included in the systematic review
Castelnuovo 2005[46]	Other sources, e.g. ad hoc selection or systematic searches (specify) Data were taken from studies also included in the systematic review
Chen 2006[47]	Other sources, e.g. ad hoc selection or systematic searches (specify)
Clark 2004[28]	Both systematic review and other sources
Clegg 2005[49]	Other sources, e.g. ad hoc selection or systematic searches (specify) Adverse effects of heart transplantation from other publications; those for left ventricular assist devices from hospital programme data
Collins 2007[51]	Unclear It is not clear from the report that the adverse events data are derived from the systematic review; however, no other source is cited for them

TABLE 29 *Source of adverse effect model parameter data (continued)*

Author	What sources were used to obtain the adverse effect data?
Collins 2007[50]	Other sources, e.g. ad hoc selection or systematic searches (specify) Costs of complications due to coronary angiography (CA) from Visser (reference number 129) – an economic evaluation (EE) included in review of EEs. Utilities based on clinical judgement and data from published source
Connock 2006[52]	Expert opinion
Connock 2006[53]	Both systematic review and other sources Data for some drugs taken from trials in the effectiveness review. For the older drugs estimates were made based on an assumption of an increase in toxicity and slight decrease in efficacy compared with previous drug in preferred order of treatment use
Davies 2006[31]	The accompanying systematic review
Dretzke 2004[18]	Other sources, e.g. ad hoc selection or systematic searches (specify) – assumptions used about disutility of biopsy and also gluten-free diet if diagnosed positive
Dundar 2007[57]	Other sources, e.g. ad hoc selection or systematic searches (specify) NHS reference costs for hospital treatment and manufacturer's submission
Garside 2006[19]	Both systematic review and other sources Review and assumptions
Garside 2007[60]	Both systematic review and other sources Costs of adverse effects of drugs from NHS reference sources
Garside 2004[62]	Both systematic review and other sources Data were taken from studies included in the systematic review
Goodacre 2006[21]	Other sources, e.g. ad hoc selection or systematic searches (specify) Data taken from reports on adverse effects of venography. These were not included in the clinical review
Green 2005[63]	The accompanying systematic review
Greenhalgh 2005[22]	Other sources, e.g. ad hoc selection or systematic searches (specify) Unclear from where values for clozapine adverse effects for schizophrenia model were derived. Utilities for depression model derived from a published study
Hartwell 2005[29]	The accompanying systematic review
Hill 2004[64]	Other sources, e.g. ad hoc selection or systematic searches (specify) See above (source of clinical effectiveness data)
Hind 2007[65]	The accompanying systematic review
Jones 2004[66]	Other sources, e.g. ad hoc selection or systematic searches (specify) Data from another meta-analysis were used
Kaltenthaler 2004[68]	Other sources, e.g. ad hoc selection or systematic searches (specify) Estimates for death after diagnostic endoscopic retrograde cholangiopancreatography (ERCP) and overall complications obtained from a paper not included in the clinical effectiveness review. None of the included studies in the clinical effectiveness review reported mortality associated with ERCP; six reported adverse effects associated with ERCP
King 2006[27]	The accompanying systematic review
Main 2004[73]	The accompanying systematic review
Main 2006[30]	The accompanying systematic review Probability of experiencing grade 3 or 4 adverse events using a Bayesian meta-analysis

continued

TABLE 29 *Source of adverse effect model parameter data (continued)*

Author	What sources were used to obtain the adverse effect data?
McCormack 2005[75]	Other sources, e.g. ad hoc selection or systematic searches (specify) Data from another trial were used
McLeod 2007[76]	Unclear Most data including costs were taken from a manufacturer's submission
Mowatt 2004[77]	Other sources, e.g. ad hoc selection or systematic searches (specify) Parameter values taken from earlier economic evaluation (Patterson *et al.*); however, the original source of the data is unclear
Murray 2006[78]	Both systematic review and other sources
Pandor 2006[81]	Other sources, e.g. ad hoc selection or systematic searches (specify) Costs of adverse events were taken from a model submitted by the industry/other publication
Robinson 2005[82]	The accompanying systematic review for the short-term model Other sources, e.g. ad hoc selection or systematic searches (specify), for the long-term model
Shepherd 2007[24]	Other sources, e.g. ad hoc selection or systematic searches (specify) – assumption regarding disutility
Stevenson 2005[89]	Other sources, e.g. ad hoc selection or systematic searches (specify) Data on breast cancer risk taken from a previous model of breast cancer. The parameter value for the risk of coronary heart disease (CHD) was an assumption. Costs taken from another publication. The same values were used for all treatments considered
Takeda 2007[90]	The accompanying systematic review Unclear – the source was unclear regarding the inclusion of adverse events in utilities
Tappenden 2007[91]	Other sources, e.g. ad hoc selection or systematic searches (specify) None of the sources used to obtain the data for costs of adverse events was included in the clinical effectiveness review
Wardlaw 2006[20]	Other sources, e.g. ad hoc selection or systematic searches (specify) Costs of adverse events were taken from a cost investigation reported by the authors. Data about incidence of adverse events were taken from an epidemiological study
Wilson 2005[99]	Other sources, e.g. ad hoc selection or systematic searches (specify) Data for costs of adverse effects taken from manufacturer's submission. Utilities and withdrawals do not explicitly capture adverse effects Not applicable (because no adverse effect data considered or source not specified)
Wilson 2007[100]	Other sources, e.g. ad hoc selection or systematic searches (specify) Models from manufacturers' submissions
Woolacott 2006[26]	The accompanying systematic review Source of withdrawal rate data from a trial in the systematic review. The same data used for both interventions considered
Wu 2006[101]	Expert opinion (using Delphi process)
Yao 2006[25]	Both systematic review and other sources In the basic adult model a lack of relevant data from the studies included in the systematic review meant that adverse effects were included in the model by assuming that a fixed percentage of patients were affected and these were input as penalties in terms of loss of quality of life and cost. Default values were set at 10% of patients: quality of life loss = –0.1 QALYs and cost loss = –£200 In the paediatric model withdrawal because of adverse effects was used. From the clinical review it could be seen that there was only a difference between a tacrolimus-based regimen (TAS) and a ciclosporin-based regimen (CAS) and therefore this was the only comparison in the model that incorporated adverse effects. Data were taken from the systematic review

TABLE 30 *Table of justifications for the omission of adverse effects from the decision model*

Author	Is the absence of AE data explained?	Do the specified outcomes include AEs?
Abubakar 2007[36]	No	No
Connock 2006[55]	No	Yes, broad focus
Connock 2007[54]	No	Yes, narrow focus
Garrison 2007[59]	No	Yes, broad focus
Garside 2005[61]	No	Yes, broad focus
Karnon 2004[70]	No	No
Martin 2006[74]	No	No
Pandor 2004[80]	No	Yes, broad focus
Rodgers 2006[83]	No	Yes, broad focus
Shepherd 2004[85]	No	Yes, broad focus
Shepherd 2006[86]	No	Yes, broad focus
Speight 2006[87]	No	No
Stevenson 2007[88]	No	Yes, broad focus
Thomas 2006[92]	No	Yes, broad focus
Wardlaw 2004[94]	No	No
Whiting 2006[96]	No	Yes, broad focus
Willis 2005[98]	No	No
Bryant 2004[44]	No	Yes, broad focus
Loveman 2006[72]	No. The authors acknowledge that patient withdrawals were not incorporated into the model. Authors may feel AEs included under HRQoL	Yes, broad focus
Ward 2007[93]	Yes. A rationale was given as to why costs and disutilities of adverse events were not modelled. Costs: It was stated that the drug under investigation is known to be well tolerated and to have a good safety profile as was shown by the evidence of the trials included in this review and by postmarketing surveillance data. Therefore, associated costs of managing adverse events were expected to be small and were not modelled. Disutilities: A 12-month study designed to determine the effects of pravastatin on HRQoL in older adults found that the drug was well tolerated and did not adversely affect HRQoL. It was stated that the drug is prescribed for life, so there may be a disutility associated with this, but it was assumed that this is small in comparison to the benefits received	Yes, broad focus
Black 2007[40]	Yes. As two formulations of insulin were being compared it was only adverse effects on lung function that might have differed between the treatments. However, as the clinical review found there to be no difference, lung function was not actually modelled	Yes, narrow focus
Clar 2005[48]	Yes. Complication rates were assumed to be the same between the alternative treatments and assumed to net out as there were no firm data available on the extent of variation in the complications rate between interventions	Yes, broad focus

continued

TABLE 30 *Table of justifications for the omission of adverse effects from the decision model (continued)*

Author	Is the absence of AE data explained?	Do the specified outcomes include AEs?
Wilby 2005[97]	Yes. Costs of adverse events were considered small	Yes, broad focus
Avenell 2004[38]	Yes. Economic model was of diet and exercise to prevent diabetes. There were no adverse effects of diet and exercise in the clinical review. Adverse effects of other interventions not relevant to model	Yes, broad focus
Ross 2004[84]	Yes. Hypercalcaemia model: The costs of treating side effects were not included because the frequency of side effects was negligible and there were no statistically significant differences in side effects between treatment arms in any of the four studies. Skeletal morbidity model: Costs of treating side effects were not included because of the rarity of serious side effects	Yes, broad focus
Nelson 2006[79]	Yes. Insufficient reliable data were available to populate the model and therefore the model was not run	Yes, broad focus
Dalziel 2004[56]	Yes. The authors acknowledge that AEs not included but point out that the intervention of interest was found to be cost-effective, and the inclusion of AEs in the model would only make it more so	Yes, broad focus
Brazzelli 2006[41]	Yes. The authors do comment that none of the included studies reported adverse events	Yes, broad focus
Knight 2004[71]	Yes. The authors state that in costing R-CHOP vs CHOP they attempted to include elements for which the costs differ significantly between the two treatments. Trial results indicated that there was no statistically significant difference in adverse events between the two groups. Therefore, adverse event costs were not included in the model	Yes, broad focus
Kanis 2007[69]	Yes. The authors state that the prevalence of adverse effects with bisphosphonates is not well documented and impact on quality of life expressed in utilities is unknown. Also the impact of adverse effects on compliance is unknown. Thus, although acknowledging that adverse effects could impact on cost-effectiveness, they are not included in the analysis	Yes, broad focus
Adi 2007[37]	Yes. The clinical review found no significant difference between naltrexone and placebo for any serious adverse event	Yes, broad focus
Bridle 2004[42]	Yes. The costs of adverse events were not formally considered in the model because of the lack of suitable cost data. The exclusion of the adverse events identified in the clinical review was considered to have little impact on the results of the model given the very short time horizon considered in the model	Yes, broad focus
Woolacott 2006[23]	Yes. There is some discussion as to why the costs of adverse events were not included in the model. The report states that the cost implications of serious adverse events are unclear because of the uncertainty around the incidence of such events. Regarding common adverse events, the assumption was made that common adverse events generally resolve when therapy is discontinued and discontinuation was explicitly considered in the model	Yes, broad focus

TABLE 30 *Table of justifications for the omission of adverse effects from the decision model (continued)*

Author	Is the absence of AE data explained?	Do the specified outcomes include AEs?
Kaltenthaler 2006[67]	Yes. Adverse effects not specifically mentioned. However, with this type of indication and intervention it may be difficult to distinguish between lack of efficacy and worsening of the condition (adverse effect)	Unclear
Warren 2004[95]	Yes. Most of the AEs reported in the clinical effectiveness review related to injection site pain	Yes, broad focus
Fayter 2007[58]	Yes. Some suggestion in final discussion that there are as yet no data	No
Bamford 2007[39]	Yes. The authors state that no adverse events data were reported in any of the included studies	Yes, broad focus

AE, adverse effect; HRQoL, health-related quality of life.

TABLE 31 *Table of diagnostic technologies: an exploration of inclusion of adverse effects in the model*

Author	Are AEs included as a parameter in the model(s)?	Specify RAA 'Detection, screening and diagnosis'	Health category	Do the specified outcomes include AEs?	Separate inclusion criteria in relation to obtaining AE data?	Were the AE data synthesised in a meta-analysis?	Year of publication
Abubakar 2007[36]	No	Evaluation of markers and technologies	Infection	No	No	NA	2007
Karnon 2004[70]	No	Evaluation of markers and technologies	Cancer	No	No	NA	2004
Martin 2006[74]	No	Evaluation of markers and technologies	Other	No	No	NA	2006
Nelson 2006[79]	No	Evaluation of markers and technologies	Skin	Yes, broad focus	No	No	2006
Pandor 2004[80]	No	Evaluation of markers and technologies	Metabolic and endocrine	Yes, broad focus	No	No	2004
Rodgers 2006[83]	No	Evaluation of markers and technologies	Renal and urogenital	Yes, broad focus	No	No	2006
Wardlaw 2004[94]	No	Evaluation of markers and technologies	Cardiovascular	No	No	NA	2004
Whiting 2006[96]	No	Evaluation of markers and technologies	Renal and urogenital	Yes, broad focus	No	No	2006
Bamford 2007[39]	No	Population screening	Ear	Yes, broad focus	No	No	2007
Fayter 2007[58]	No	Population screening	Metabolic and endocrine	No	No	NA	2007
Speight 2006[87]	No	Population screening	Cancer	No	No	NA	2006
Willis 2005[98]	No	Population screening	Cancer	No	No	NA	2005
Mowatt 2004[77]	Yes	Discovery and preclinical testing of markers and technologies	Cardiovascular	Yes, broad focus	No	No	2004
Collins 2007[50]	Yes	Evaluation of markers and technologies	Cardiovascular	Yes, broad focus	Yes	No	2007
Dretzke 2004[18]	Yes	Evaluation of markers and technologies	Metabolic and endocrine	No	No	NA	2004
Goodacre 2006[21]	Yes	Evaluation of markers and technologies	Cardiovascular	No	No	NA	2006
Kaltenthaler 2004[68]	Yes	Evaluation of markers and technologies	Oral or gastrointestinal	Yes, broad focus	No	No	2004
Wardlaw 2006[20]	Yes	Evaluation of markers and technologies	Cardiovascular	No	No	NA	2006
Garside 2006[19]	Yes	Population screening	Cancer	No	No	NA	2006
Wu 2006[101]	Yes	Population screening	Blood	Yes, broad focus	No	Yes	2006

AE, adverse effect; NA, not applicable; RAA, research activity area.

Appendix 4

Data extraction methodology papers

Philips 2004[14] – Review of guidelines for good practice in decision-analytic modelling in health technology assessment

HTA monograph

Objectives
To identify existing guidelines, develop a synthesised guideline plus accompanying checklist, and provide guidance on key theoretical methodological and practical issues and consider the implications of this research for what might be expected of future decision-analytic models.

Conclusions
The checklist that was developed preformed well in terms of identifying those aspects of the model that should be of particular concern to the reader. The checklist can not, however, provide answers to the appropriateness of the model structure and structural assumptions.

Findings and conclusions relevant to adverse effects
- The choice of outcomes in the model should be justified. All outcomes relevant to the condition should be included, including adverse effects, with the exception of those that do not differ between the interventions or control being compared. Ideally, a full systematic review should be conducted for key parameters but no clear definition of key parameters.
- The results of the model should be reported in the context of the full limitations of the available data.
- It is important that justification is given for the data used (both the parameters and their specific values).
- Noteworthy that the chapter on appropriate methods for the identification and quality assessment of secondary parameter estimates does not mention adverse effects.

Tappenden 2006[15] – Methodological issues in the economic analysis of cancer treatments
Objective
To appraise the existing guidelines for the economic analysis of cancer treatments.

Findings and conclusions relevant to adverse effects
- States that in the context of cancer adverse effects that are avoided by the use of treatment under assessment is an important outcome measure. However, the report goes on to say that this is not 'an ideal benefit measure for use in cost-effectiveness analysis' and suggests that use of HRQoL is a better measure.
- States that in cancer trials the use of preference-based methods to measure HRQoL is rare, and so models almost always use indirect sources of evidence (we can check this with our review). This publication did not mention adverse effects of the intervention.

Rovira 1995[16] – Economic analysis of health technologies and programmes: a Spanish proposal for methodological standardisation
Objective
To formulate an initial proposal of methodological standards and guidelines for economic evaluation.

Findings and conclusions relevant to adverse effects
- States that all effects on resources, the use of which varies between the options, should be considered in the analysis, e.g. those used to treat adverse effects.

Cooper 2005[13] – Use of evidence in decision models: an appraisal of health technology assessments in the UK since 1997
Objective
To review the sources and quality of evidence used in the development of economic decision models in HTAs.

Findings and conclusions relevant to adverse effects
- The authors identified the level of evidence used to support the data used in the model and found that although the data on clinical effectiveness were mostly derived from the accompanying review there was much more variability in the data sources for other parameters. These latter data were often rated

5 or 6 in the hierarchy of evidence, i.e. they were derived from patient preference or expert opinion.
- Also of relevance was the finding that 'the mechanism for identifying sources of evidence for other model parameters was rarely reported and appeared to be ad hoc'.
- For adverse effects and complications, in 10% of reports it was not applicable, presumably because they had not used adverse effects in the model. At best, in 31% of reports the source of the data was unclear. Data from meta-analysis of RCTs with direct comparison between interventions of interest and using final outcomes were used in 14% of cases, and data from a single directly relevant RCT were used in 17% of cases. A total of 2% of reports used data from a single RCT using a surrogate outcome, 14% used data from case–control or cohort studies and 12% used expert opinion.

Weinstein 2003[17] – Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices – Modeling Studies

Objective

To describe the outcome of a task force convened to provide modellers with guidelines for conducting and reporting modelling studies.

Findings and conclusions relevant to adverse effects

- 'States should not be omitted because of lack of data. Examples might be chronic health states corresponding to uncommon adverse events or disease sequelae that are not observed within clinical trials.'
- Systematic reviews of the literature should be conducted on key model inputs. Evidence that such reviews have been carried out, or a justification for failing to do so based on the adequacy and generalisability of readily obtained data, should accompany the model.

Appendix 6

Excluded papers and reports

Excluded papers (methodology literature searches)

1. Adang EMM, Ament A, Dirksen CD. Medical technology assessment and the role of economic evaluation in health care. *J Eval Clin Pract* 1996;**2**:287–94.

2. American Diabetes Association Consensus Panel. Guidelines for computer modeling of diabetes and its complications. *Diabetes Care* 2004;**27**:2262–5.

3. Ananth CV, Kleinbaum DG. Regression models for ordinal responses: a review of methods and applications. *Int J Epidemiol* 1997;**26**:1323–33.

4. Beresniak A, Taboulet F. The evaluation of medication-related side effects by medico-economic modelling techniques [French]. *Therapie* 1997;**52**:59–63.

5. Black DM, Palermo L, Grima DT. Developing better economic models of osteoporosis: considerations for the calculation of the relative risk of fracture. *Value Health* 2006;**9**:54–8.

6. Brewer T, Colditz GA. Postmarketing surveillance and adverse drug reactions: current perspectives and future needs. *JAMA* 1999;**281**:824–9.

7. Bryan S, Williams I, McIver S. Seeing the NICE side of cost-effectiveness analysis: a qualitative investigation of the use of CEA in NICE technology appraisals. *Health Econ* 2007;**16**:179–93.

8. Coyle D, Buxton MJ, O'Brien BJ. Measures of importance for economic analysis based on decision modeling. *J Clin Epidemiol* 2003;**56**:989–97.

9. Dalziel K, Round A, Stein K, Garside R, Castelnuovo E, Payne L. Do the findings of case series studies vary significantly according to methodological characteristics? *Health Technol Assess* 2005;9(2):1–146.

10. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000;**356**:1255–9.

11. Edwards JE, McQuay HJ, Moore RA, Collins SL. Reporting of adverse effects in clinical trials should be improved: lessons from acute postoperative pain. *J Pain Symptom Manage* 1999;**18**:427–37.

12. Elvik R. Cost-benefit analysis of road safety measures: applicability and controversies. *Accid Anal Prev* 2001;**33**:9–17.

13. Ernst E, Pittler MH. Assessment of therapeutic safety in systematic reviews: literature review. *BMJ* 2001;**323**:546.

14. Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *Int J Technol Assess Health Care* 2005;**21**:240–5.

15. Golder S, Loke Y, McIntosh HM. Room for improvement? A survey of the methods used in systematic reviews of adverse effects. *BMC Med Res Methodol* 2006;**6**:3.

16. Grieve R, Hutton J, Green C. Selecting methods for the prediction of future events in cost-effectiveness models: a decision-framework and example from the cardiovascular field. *Health Policy* 2003;**64**:311–24.

17. Hahn S, Williamson PR, Hutton JL, Garner P, Flynn EV. Assessing the potential for bias in meta-analysis due to selective reporting of subgroup analyses within studies. *Stat Med* 2000;**19**:3325–36.

18. Hutton JL, Williamson PR. Bias in meta-analysis due to outcome variable selection within studies. *Appl Stat* 2000;**49**:359–70.

19. Ioannidis JP, Evans SJ, Gøtzsche PC, O'Neill RT, Altman DG, Schulz K, *et al*. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004;**141**:781–8.

20. Ioannidis JP, Lau J. Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. *JAMA* 2001;**285**:437–43.

21. Ioannidis JP, Lau J. Improving safety reporting from randomised trials. *Drug Saf* 2002;**25**:77–84.

22. Johannesson M. On the discounting of gained life-years in cost-effectiveness analysis. *Int J Technol Assess Health Care* 1992;**8**:359–64.

23. Lancar R, Kramar A, Haie-Meder C. Non-parametric methods for analysing recurrent complications of varying severity. *Stat Med* 1995;**14**:2701–12.

24. Land M, Vogel C, Gefeller O. Partitioning methods for multifactorial risk attribution. *Stat Methods Med Res* 2001;**10**:217–30.

25. Li wan Po A, Herxheimer A, Poolsup N, Aziz Z. How do Cochrane reviewers address adverse effects of drug therapy? [Abstract]. In *8th Cochrane Colloquium. Evidence for action: challenges for the Cochrane Collaboration in the 21st century.* Cape Town: South Africa; 2000. Available from: www.cochrane.org/colloquia/abstracts/capetown/capetowno39.html

26. Lipsitz SR. Methods for estimating the parameters of a linear model for ordered categorical data. *Biometrics* 1992;**48**:271–81.

27. MacNab YC, Kmetic A, Gustafson P, Sheps S. An innovative application of Bayesian disease mapping methods to patient safety research: a Canadian adverse medical event study. *Stat Med* 2006;**25**:3960–80.

28. McIntosh HM, Woolacott NF, Bagnall AM. Assessing harmful effects in systematic reviews. *BMC Med Res Methodol* 2004;**4**:19.

29. Montgomery SA, Kasper S. Side effects, dropouts from treatment and cost consequences. *Int Clin Psychopharmacol* 1998;**13**:S1–S5.

30. Papanikolaou PN, Churchill R, Wahlbeck K, Ioannidis JP. Safety reporting in randomized trials of mental health interventions. *Am J Psychiatry* 2004;**161**:1692–7.

31. Papanikolaou PN, Ioannidis JP. Availability of large-scale evidence on specific harms from systematic reviews of randomized trials. *Am J Med* 2004;**117**:582–9.

32. Ross SD. Drug-related adverse events: a readers' guide to assessing literature reviews and meta-analyses. *Arch Intern Med* 2001;**161**:1041–6.

33. Schulzer M, Mancini GB. Unqualified success and unmitigated failure: number-needed-to-treat-related concepts for assessing treatment efficacy in the presence of treatment-induced adverse events. *Int J Epidemiol* 1996;**25**:704–12.

34. Sculpher MJ, Pang FS, Manca A, Drummond MF, Golder S, Urdahl H, *et al.* Generalisability in economic evaluation studies in healthcare: a review and case studies. *Health Technol Assess* 2004;**8**(49):1–192.

35. Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. *JAMA* 1996;**276**:1339–41.

36. Stason WB. Cost-effectiveness analysis in health care: opportunities and challenges to international comparisons. In Lasser U, Roccella EJ, Rosenfeld JB, Wenzel A, editors. *Costs and benefits in health care and prevention: an international approach to priorities in medicine*. Berlin: Springer-Verlag; 1990. pp. 20–6.

37. Stricker BH, Psaty BM. Detection, verification, and quantification of adverse drug reactions. *BMJ* 2004;**329**:44–7.

38. Sutton AJ, Cooper NJ, Lambert PC, Jones DR, Abrams KR, Sweeting MJ. Meta-analysis of rare and adverse event data. *Exp Rev Pharmacoecon Outcomes Res* 2002;**2**:367–79.

39. Vandenbroucke JP. When are observational studies as credible as randomised trials?" *Lancet* 2004;**363**:1728–31.

Excluded HTA reports (of those published 2004–7 inclusive but not including both a systematic review and an economic model)

1. Bartlett C, Doyal L, Ebrahim S, Davey P, Bachmann M, Egger M, *et al.* The causes and effects of socio-demographic exclusions from clinical trials. *Health Technol Assess* 2005;**9**(38):1–152.

2. Barton P, Jobanputra P, Wilson J, Bryan S, Burls A. The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis. *Health Technol Assess* 2004;**8**(11):1–91.

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Professor Robert E Hawkins, CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor Richard Hobbs, Head of Department of Primary Care & General Practice, University of Birmingham

Professor Alan Horwich, Dean and Section Chairman, The Institute of Cancer Research, London

Professor Allen Hutchinson, Director of Public Health and Deputy Dean of ScHARR, University of Sheffield

Professor Peter Jones, Professor of Psychiatry, University of Cambridge, Cambridge

Professor Stan Kaye, Cancer Research UK Professor of Medical Oncology, Royal Marsden Hospital and Institute of Cancer Research, Surrey

Dr Duncan Keeley, General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping, Research Degrees Programme Director and Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy, Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay, Professor of Psychiatry for the Elderly, University of Leicester

Professor Julian Little, Professor of Human Genome Epidemiology, University of Ottawa

Professor Alistaire McGuire, Professor of Health Economics, London School of Economics

Professor Rajan Madhok, Medical Director and Director of Public Health, Directorate of Clinical Strategy & Public Health, North & East Yorkshire & Northern Lincolnshire Health Authority, York

Professor Alexander Markham, Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Dr Peter Moore, Freelance Science Writer, Ashtead

Dr Andrew Mortimore, Public Health Director, Southampton City Primary Care Trust

Dr Sue Moss, Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Professor Miranda Mugford, Professor of Health Economics and Group Co-ordinator, University of East Anglia

Professor Jim Neilson, Head of School of Reproductive & Developmental Medicine and Professor of Obstetrics and Gynaecology, University of Liverpool

Mrs Julietta Patnick, National Co-ordinator, NHS Cancer Screening Programmes, Sheffield

Professor Robert Peveler, Professor of Liaison Psychiatry, Royal South Hants Hospital, Southampton

Professor Chris Price, Director of Clinical Research, Bayer Diagnostics Europe, Stoke Poges

Professor William Rosenberg, Professor of Hepatology and Consultant Physician, University of Southampton

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Dr Susan Schonfield, Consultant in Public Health, Hillingdon Primary Care Trust, Middlesex

Dr Eamonn Sheridan, Consultant in Clinical Genetics, St James's University Hospital, Leeds

Dr Margaret Somerville, Director of Public Health Learning, Peninsula Medical School, University of Plymouth

Professor Sarah Stewart-Brown, Professor of Public Health, Division of Health in the Community, University of Warwick, Coventry

Professor Ala Szczepura, Professor of Health Service Research, Centre for Health Services Studies, University of Warwick, Coventry

Mrs Joan Webster, Consumer Member, Southern Derbyshire Community Health Council

Professor Martin Whittle, Clinical Co-director, National Co-ordinating Centre for Women's and Children's Health, Lymington

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The printed version also excludes some of the the appendices.

View/download the appendices

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The HTA programme and the authors would like to know your views about this report.

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We look forward to hearing from you.

NETSCC, Health Technology Assessment
Alpha House
University of Southampton Science Park
Southampton SO16 7NS, UK
Email: hta@hta.ac.uk
www.hta.ac.uk

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