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

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Declared competing interests of authors: RS Taylor is an author on two of the HTA reports included in this review, is a member of PenTAG, which prepares technology assessment reports for NCCHTA on behalf of the National Institute for Health and Clinical Excellence (NICE), and is a NICE Appraisal Committee member. J Elston is an Academic Speciality Registrar in Public Health on placement at PenTAG.

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NIHR Health Technology Assessment Programme

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

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'.

The HTA Programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

Second, the HTA Programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

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Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

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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.

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Abstract

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

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Objective: To explore the use of surrogate outcomes in Health Technology Assessment (HTA) and provide a basis for guidance for their future use, validation and reporting. This report focuses on the role of surrogate outcomes in cost-effectiveness models (CEMs) within UK HTA Programme reports.

Data sources: Reports published in the UK HTA Programme monograph series in 2005 and 2006 formed the sampling frame for this study.

Review methods: Reports were selected on the basis that they addressed a treatment effectiveness/efficacy question, that they included a CEM and that the CEM was primarily based on a surrogate outcome. Reports addressing diagnostic, screening, aetiology, prognostic and methodological questions were excluded. Information was extracted from included reports by two reviewers using a standardised proforma. Surrogate outcomes were assessed according to two published validation frameworks [*Journal of the American Medical Association* (JAMA) criteria and Outcomes Measures in Rheumatology Clinical Trials (OMERACT) scoring schema]. A narrative synthesis of findings is presented in the form of tabular summaries and illustrative qualitative quotations.

Results: A total of 35 UK HTA reports published in 2005 and 2006 addressed an effectiveness/efficacy question and contained a CEM. Of these, four were found to have based their CEM on a surrogate outcome. All four reports sourced treatment-related changes in surrogate outcomes through a systematic review of the literature; however, there was some variability in the consistency and transparency by which these reports provided evidence of the validation for the surrogate–final outcome relationship. Only one of the reports undertook a systematic review to specifically seek the evidence base for the association between surrogate and final outcomes. Furthermore, this was the only report to provide level 1 surrogate–final outcome validation evidence, i.e. RCT data showing a strong association between the change in surrogate outcome (BPAR) and the change in final outcome (graft survival) at an individual patient level. This report met the JAMA criteria for acceptable evidence of a surrogate. Two reports provided level 2 evidence, i.e. observational study data showing the relationship between the surrogate and final outcome, and one report provided level 3 evidence, i.e. a review of disease natural history. None of the four reports achieved a sufficient score on the OMERACT schema to be judged to have acceptable evidence of a surrogate outcome by its authors.

Conclusions: In this survey of UK HTA reports about 10% of the CEMs therein were explicitly based on surrogate outcomes. The strength of evidence for the surrogate–final outcome relationship, transparency of quantification and exploration of uncertainty of this relationship were found to vary considerably. Recommendations are made for the use of surrogate outcomes in future HTA reports.

Contents

List of abbreviations

ADAS-cog	Alzheimer's Disease Assessment Scale, cognitive subscale
ADV	adefovir dipivoxil
ALT	alanine aminotranferase
BPAR	biopsy-confirmed acute rejection
CEA	cost-effectiveness analysis
CEM	cost-effectiveness model
CRD	Centre for Reviews and Dissemination, University of York
FDA	Food and Drug Administration
GFR	glomerular filtration rate
HAQ	Health Assessment Questionnaire
HR	hazard ratio
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICH	International Conference on Harmonisation
JAMA	*Journal of the American Medical Association*
NICE	National Institute for Health and Clinical Excellence
OMERACT	Outcomes Measures in Rheumatology Clinical Trials
PEG	pegylated interferon alpha-2a
PTE	proportion of treatment effect explained
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SF-36	Short Form 36 questionnaire
TAR	technology assessment report
US NIH	United States National Institutes of Health

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

Executive summary

Background and aim

Policy decisions on the adoption of health technologies should be based on evidence of effectiveness and cost-effectiveness from well-conducted randomised controlled trials (RCTs) that report final patient-relevant outcomes, i.e. death, morbid end points (such as myocardial infarction, stroke) or impaired health-related quality of life. Contrary to this there is increasing pressure on health-care policy-makers to reduce the time to health technology regulatory approval and reimbursement by the use of surrogate outcomes. Given that reliance on surrogate outcomes can ultimately lead to harmful patient outcomes, the use of such outcomes in Health Technology Assessment (HTA) remains controversial.

This study aimed to examine the use of surrogate outcomes in cost-effectiveness models (CEMs) in technology assessments by undertaking a systematic survey of UK HTA reports. For the purposes of this report we applied the following definition of a surrogate outcome – an end point that substitutes for and predicts a patient-relevant final outcome (i.e. mortality, important clinical events or health-related quality life).

Methods

Reports published in the UK HTA Programme monograph series in 2005 and 2006 formed the sampling frame for this study. Reports were selected on the basis that they addressed a treatment effectiveness/efficacy question, that they included a CEM and that the CEM was primarily based on a surrogate outcome. Reports addressing diagnostic, screening, aetiology, prognostic and methodological questions were excluded. Information was extracted from included reports by two reviewers using a standardised proforma. Surrogate outcomes were assessed according to two published validation frameworks [*Journal of the American Medical Association* (JAMA) criteria and Outcomes Measures in Rheumatology Clinical Trials (OMERACT) scoring schema]. A narrative synthesis of findings is presented in the form of tabular summaries and illustrative qualitative quotations. Recommendations are made for the use of surrogate outcomes in CEMs within future HTA reports.

Results

Of the 100 UK HTA reports published in 2005 and 2006, 35 addressed an effectiveness/efficacy question and contained a CEM. Of these, four (11%) reports were found to have based their CEM on a surrogate outcome: two reports in patients undergoing kidney transplant used an outcome of biopsy-confirmed acute rejection (BPAR) (final outcome – graft survival); one report of Alzheimer's disease used the cognitive function score (final outcome – need for full-time care); and one report of chronic hepatitis used seroconversion (final outcome – chronic hepatitis/liver cancer).

All four reports sourced treatment-related changes in surrogate outcomes through a systematic review of the literature; however, there was some variability in the consistency and transparency by which these reports provided evidence of the validation for the surrogate–final outcome relationship. Only one of the reports undertook a systematic review to specifically seek the evidence base for the association between surrogate and final outcomes. Furthermore, this was the only report to provide level 1 surrogate–final outcome validation evidence, i.e. RCT data showing a strong association between the change in surrogate outcome (BPAR) and the change in final outcome (graft survival) at an individual patient level. This report met the JAMA criteria for acceptable evidence of a surrogate. Two reports provided level 2 evidence, i.e. observational study data showing the relationship between the surrogate and final outcome, and one report provided level 3 evidence, i.e. a review of disease natural history. None of the four reports achieved a sufficient score on the OMERACT schema to be judged to have acceptable evidence of a surrogate outcome by its authors.

Proposed recommendations for selecting and/or using surrogate outcomes in HTA reports

The following recommendations for the use of surrogate outcomes (i.e. any end point that substitutes for and predicts a final patient-related outcome) are proposed. These recommendations are based on the findings of the review of the literature on the use of surrogate outcomes, the experience of the survey of the use of surrogates in UK HTA reports and feedback and discussion on the draft recommendations from InterTasc [UK HTA groups who undertake technology assessment reports commissioned by the National Institute for Health Research (NIHR) HTA Programme] and the technology assessment team at the National Institute for Health and Clinical Excellence (NICE). The rationale and source of each recommendation are shown in parentheses. These recommendations are intended to act as a list of considerations that policy-makers and HTA analysts should take into account when faced with the use of surrogate outcomes in CEMs in HTA reports. It is acknowledged that the practicalities and resource implications of implementing these recommendations have not been formally tested within this project.

1. Ideally, the assessment of clinical effectiveness and cost-effectiveness of a health technology should be based on final patient-related outcomes (i.e. mortality, important clinical events and health-related quality of life) (for rationale see Chapter 2, Risks of surrogate outcomes). To minimise the risk of bias, this evidence should be identified from a systematic review (and meta-analysis) of well-conducted RCTs.
2. When this is not possible and there is a requirement to use a surrogate outcome, the following should be undertaken:
   i. A review of the evidence for the validation of the surrogate–final outcome relationship (for rationale see Chapter 2, Validation of surrogate outcomes). To minimise the risk of bias such a review should be systematic.
   ii. The evidence on surrogate validation should be presented according to an explicit hierarchy such as the following: level 1: evidence demonstrating treatment effects on the surrogate correspond to effects on the patient-related outcome (from clinical trials); level 2: evidence demonstrating a consistent association between surrogate outcome and final patient-related outcome (from epidemiological/observational studies); level 3: evidence of biological plausibility of relationship between surrogate outcome and final patient-related outcome (from pathophysiological studies and/or understanding of the disease process) (for rationale see Chapter 2, Validation of surrogate outcomes). To achieve level 1 classification a surrogate must fulfil the level 1 and level 2 and level 3 criteria. To achieve level 2 classification a surrogate must fulfil the level 2 and level 3 criteria.
   iii. Consideration should be given to carrying out a CEM analysis based on a surrogate outcome when there is level 1 or 2 validation evidence (for rationale see Chapter 2, Risks of surrogate outcomes).
3. When a CEM analysis based on a surrogate outcome is undertaken:
   i. Provide a transparent explanation as to how the relationship between the surrogate and final outcomes is quantified within the CEM (for rationale see Chapter 4, Reports with CEMs based on a surrogate outcome).
   ii. Explicitly explore and discuss the uncertainty associated with use of the surrogate outcome in the CEM, especially through sensitivity analysis (for rationale see Chapter 4, Reports with CEMs based on a surrogate outcome). In accordance with recent HTA methodological developments, such uncertainty may be quantified using probabilistic sensitivity analysis.
   iii. Make specific research recommendations regarding the need for future research on the surrogate–final outcome relationship (for rationale see Chapter 4, Reports with CEMs based on a surrogate outcome). In accordance with recent HTA methodological developments, the impact of the surrogate outcome on decision uncertainty may be quantified by value of information analysis.
   iv. Include the term 'surrogate outcome' in the report executive summary/abstract to assist bibliographic identification (for rationale see Chapter 4, Reports with CEMs based on a surrogate outcome).

Recommendations for future research

The following areas are suggested for further research:

- Given both the UK focus and the relatively small number of HTA reports with a CEM explicitly based on surrogate outcomes identified, the generalisability of the findings may be limited. This supports a more extensive survey of the use of surrogate outcomes in HTA across international jurisdictions. Consideration should be given to the role of surrogate outcomes in both the clinical effectiveness and the cost-effectiveness components of these reports. Furthermore, future empirical studies need to address those situations in which HTA reports may combine both surrogate and final outcomes and the validity of using surrogates across technology classes.
- The review of the literature in this report identified only two previous empirical studies designed to quantify the potential bias associated with the use of surrogate outcomes. Further empirical studies are needed to assess the potential biases of the use of surrogate outcomes in HTA and cost-effectiveness analyses, for example a comparison of the findings of cost-effectiveness analyses based on surrogate outcomes and cost-effectiveness analyses based on final outcomes.
- Testing of the new OMERACT surrogate scoring schema and the development of similar tools.
- Explore the transferability of the hierarchy of evidence framework for surrogate–final outcomes to the process of mapping disease-specific outcomes to health-related quality of life utility in CEM analyses.

Chapter 1

Aims and objectives

Aim

To explore the use of surrogate outcomes in Health Technology Assessment (HTA) and by doing so provide a basis for guidance for their future use, validation and reporting.

This report focuses on the role of surrogate outcomes in cost-effectiveness models (CEMs) within UK HTA Programme reports.

Objectives

Specifically, the objectives of the report are to:

- summarise current guidelines for the use of surrogate outcomes in HTA and CEMs
- survey the use of surrogate outcomes in CEMs in UK HTA Programme reports published in 2005 and 2006
- review current practice around the use (i.e. validation, quantification and reporting) of surrogate outcomes in CEMs in UK HTA Programme reports
- assess the validity of identified surrogates using existing frameworks
- provide recommendations on the use of surrogate outcomes in CEMs within future HTA reports.

Before addressing these objectives, Chapter 2 provides an overview of the use of surrogates in clinical trials, economic analysis and HTA based on a non-systematic literature review.

Chapter 2
Background

Rationale for the use of surrogate outcomes

One of the most important factors in determining the duration, size and cost of a clinical trial of a new or existing treatment is the choice of outcome. Ideally, decisions on the use of treatment should be based on well-conducted randomised controlled trials (RCTs) that assess clinically important 'final' patient-relevant outcomes, that is, outcomes of which the patient is aware and wants to avoid, for example death or morbid end points (e.g. myocardial infarction, stroke or impaired quality of life).[1,2]

However, conducting trials with final patient-relevant outcomes can require a very large sample size and/or periods of long follow-up for sufficient differences in outcome to be obtained to achieve statistical significance, particularly in the case of chronic diseases. Other end points can be used to substitute for, or act as a 'surrogate' for, the final outcome, the principal rationale being a more rapid accrual of data. Therefore, the use of surrogate outcomes may lead to shorter studies and faster times to licensing and dissemination of new treatments. In particular, when a patient's risk of serious morbidity or mortality is high and/or his or her illness is rare, use of surrogate outcomes may provide an attractive option when it comes to approval of new treatments for market access. Some common surrogate outcomes that have been used to gain regulatory approval are listed in *Table 1*.

Surrogate outcome – definition

Terms such as 'surrogate outcome or end point', 'biomarker' or 'biological marker' are often used interchangeably. This heterogeneity in terminology has led to some confusion over the identification of what may be considered a surrogate outcome and the role of surrogate outcomes.

There are important differences between these terms, particularly in terms of what constitutes a surrogate outcome. The distinctions made by the Biomarkers Definitions Working Group of the United States National Institutes of Health (US NIH)[4] are helpful in this respect and are summarised in *Table 2*.

Two key tenets of a surrogate outcome are that it represents an end point that is intended to substitute for and be predictive of a final patient-relevant clinical outcome.

TABLE 1 *Some examples of common surrogate outcomes used to gain regulatory approval*

Disease	Surrogate outcome	Final patient-relevant outcome
HIV infection	CD4 count	AIDS or death
Cancer	Tumour size reduction	Mortality
Colon cancer	Carcinoembryonic antigen	Disease progression
Prostate cancer	Prostate-specific antigen	Disease progression
Cardiovascular disease	Blood pressure, cholesterol level	Haemorrhagic stroke, myocardial infarction
Glaucoma	Intraocular pressure	Vision loss
Osteoporosis	Bone density	Bone fracture

AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus.
Adapted from Burzykowski *et al.*[3]

TABLE 2 *Definitions of the US NIH Biomarkers Definitions Working Group*

Term	Definition
Biological marker (biomarker)	A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological response to a therapeutic intervention
Clinical (final) outcome	A characteristic or variable that reflects how a patient feels, functions or survives
Surrogate outcome	A biomarker that is intended to substitute for a clinical (final) outcome. A surrogate end point is expected to predict clinical benefit

Risks of surrogate outcomes

The early use of surrogate outcomes has led to some dramatic breakthroughs in treatments. This is perhaps best illustrated by the dramatic surge of the AIDS epidemic and the impressive therapeutic results obtained with highly active antiretroviral therapy based on the use of CD4 cell counts and viral load, which substituted for time to clinical events and overall survival.[5]

However, despite their potential appeal, and success in some areas, the use of surrogate outcomes in trials has been controversial. Their use, at least in some applications, has led to erroneous or even harmful conclusions.[6,7] One of the most well-known cases involved the approval of three cardiovascular drugs, encainide, flecainide and moricizine, by the United States Food and Drug Administration (FDA). The drugs were approved as they were shown to effectively suppress arrhythmias. It was believed that, because ventricular arrhythmia is associated with an almost fourfold increase in the rate of cardiac complication-related death, the drugs would reduce mortality. After the drugs had been approved and introduced into clinical practice the Cardiac Arrhythmia Suppression Trials (CAST I and II) were conducted to evaluate how the three drugs would affect the survival of patients who had a myocardial infarction and ventricular arrhythmia. Both trials showed that, although the drugs did suppress the rate of arrhythmia, the number of deaths among patients treated with the drugs was more than twice that observed in patients receiving placebo.[8]

In addition to arrhythmia suppression, Fleming and DeMets[6] catalogue several other examples of so-called 'false-positive' conclusions as the result of the early approval of drugs on the basis of surrogate outcomes. They also provide a number of potential explanations for these failures (as illustrated in *Figure 1*).

More recently, Ridker and Torres[9] reviewed the various characteristics of 324 consecutive cardiovascular trials published in three major general medical journals [*Journal of the American Medical Association* (JAMA), the *Lancet* and the *New England Journal of Medicine*] between January 2000 and July 2005. The authors found that trials reporting a surrogate outcome as a primary outcome were more likely to report a positive treatment effect [77 out of 115 trials (67%)] than those trials that reported a final patient-related primary outcome [113 out of 209 trials (54%), $p = 0.02$].

The reviews of Fleming and DeMets[6] and Ridker and Torres[9] suggest that the use of surrogate outcomes in HTA may lead to two levels of error: (1) a conclusion that a new treatment has a greater health benefit than risk when the opposite is true (false positive); (2) an overestimate of the true level of benefit of a new treatment (bias). Furthermore, at least theoretically, the use of a surrogate outcome could lead to a false negative or underestimate of treatment effect. When possible, policy-makers and HTA analysts would seek to avoid such errors.

Validation of surrogate outcomes

The balance of potential advantages and risks in using surrogate outcomes within clinical trials highlights the need for criteria by which the validity of surrogate measures can be judged. The following broad hierarchy has been proposed as part of the International Conference on Harmonisation guidelines for the conduct of clinical trials for the registration of drugs (ICH-9).[10]

> In practice, the strength of the evidence for surrogacy depends upon (i) the biological plausibility of the relationship, (ii) the demonstration in epidemiological studies of the prognostic value of the surrogate for the

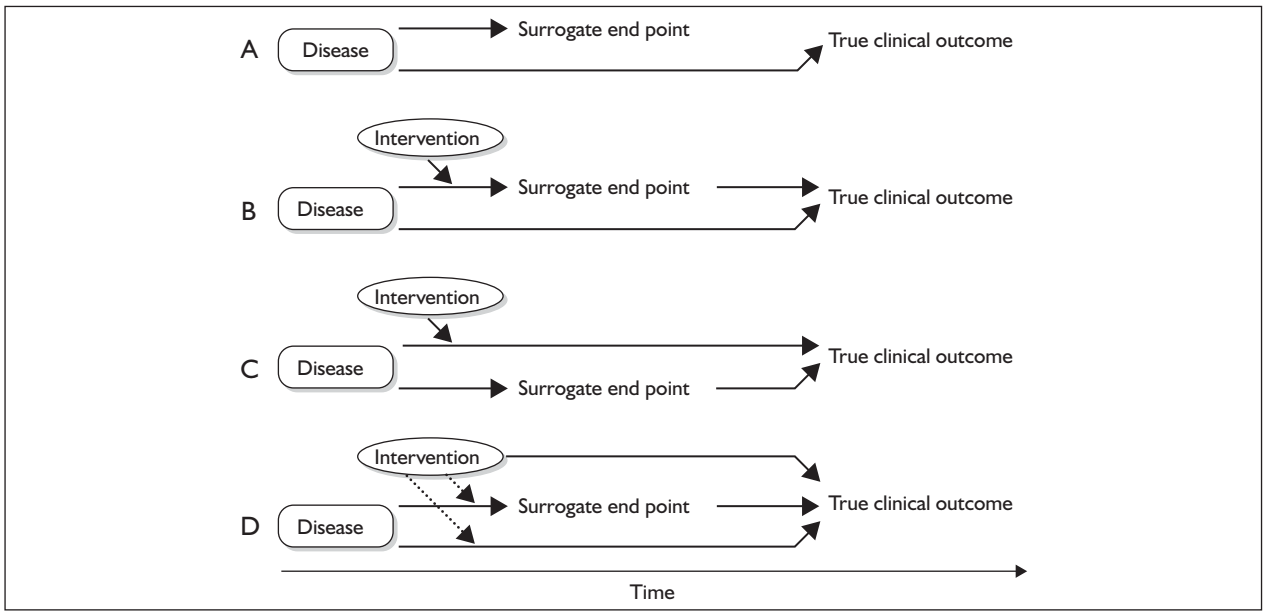

FIGURE 1 *Examples of the reasons for failure of surrogate outcomes. A. The surrogate is not on the causal pathway of the disease process. B. There are several causal pathways leading to the disease but the intervention affects only the pathway mediated through the surrogate. C. There are several causal pathways leading to the disease but the surrogate is not on the pathway that the intervention affects or is insensitive to its effects. D. The intervention may also have a mechanism of action that is independent of the disease process (dotted lines), affecting the final outcome directly. Adapted from Fleming and DeMets.*[6]

> clinical outcome and (iii) evidence from clinical trials that treatment effects on the surrogate correspond to effects on the clinical outcome.
>
> ICH-9,[10] p. 9

In passing, it is interesting to note the overlap between this hierarchy and Bradford Hill's criteria for inferring causation versus association, as first stated in 1965.[11]

The sources of evidence necessary to attain each of the three levels are summarised in *Table 3*.

At the lowest level (level 3), understanding of the biology and pathophysiological studies makes it plausible that changes in the surrogate will lead to changes in the final patient-related outcome. Level 2 requires evidence of the association between the surrogate outcome and the final patient-related outcome. Typically, this evidence would come from cross-sectional observational studies in which both surrogate and final patient-related outcomes are available. The strength of association is reflected in statistics such as a correlation coefficient or relative risk. The larger the correlation, the more likely the causal link between the surrogate and final outcomes. In addition to the strength of association, the validity of the association depends on whether it is consistent across studies and, given the observational basis of the evidence, following adjustment for known confounders. Level 1 validation requires controlled trial evidence showing that the treatment-related change in the surrogate outcome is associated with a concomitant change in the final outcome.

Although we are unaware of a single internationally agreed checklist for the validation of surrogate outcomes, our literature searches identified two groups that have independently published criteria for judging the adequacy of surrogate outcomes.

JAMA User's Guide (XIX) to the use of surrogate end points

Bucher and colleagues,[12] as part of the *JAMA Users' Guides to the Medical Literature* series, produced advice on using journal articles reporting intervention effects based on a surrogate outcome. They propose that the validity of a surrogate depends on two issues. First, to be consistently reliable the surrogate must be on the causal pathway from the intervention to the final outcome. Second, in considering a particular intervention there must be confidence that there are no important effects of that intervention on the final outcome that are not mediated through, or captured by, the surrogate. The guide provides

TABLE 3 *Validation of surrogate outcomes*

Hierarchical level	Evidence requirement[a]	Source of evidence
Level 3	Biological plausibility of relationship between surrogate outcome and final patient-related outcome	Pathophysiological studies and understanding of disease process
Level 2	Consistent association between surrogate outcome and final patient-related outcome	Epidemiological (observational) studies demonstrating an association between the surrogate outcome and final patient-related outcome
Level 1	Treatment effects on the surrogate correspond to effects on the patient-related outcome	Clinical trial(s) showing that change in surrogate outcome with treatment is associated with a commensurate change in final patient-related outcome

a To fulfil the evidence requirement for level 2 or level 3 necessitates the fulfilment of the requirements of the previous evidence levels.
Based on ICH-9 guidelines[10] and the US NIH Biomarkers Definitions Working Group[4]

three questions to determine the validity of a surrogate outcome (*Table 4*).

Although they do not mention the requirement for biological plausibility, the *JAMA User's Guide* questions are otherwise directly related to the levels of surrogate validation presented in *Table 3*, i.e. guide 1 is equivalent to level 2 evidence and guides 2 and 3 are equivalent to level 1 evidence. According to Bucher *et al.*,[12] for a surrogate to be considered valid there needs to be a positive response to guide 1 and one of guide 2 or guide 3.

By splitting level 1 evidence into two components, the *JAMA User's Guide* provides an extension to the validation of surrogates, as RCT evidence may be available for the surrogate and final outcome from another drug (or other medical technology) class but not for the actual drug or another drug within the same class. However, this further level of validation may well be contrary to the desire of analysts and policy-makers for a more generic use of a surrogate outcome across treatments within a disease area.

OMERACT biomarker and surrogate end point evidence schema

The OMERACT (Outcomes Measures in Rheumatology Clinical Trials) Working Group recently published a quantitative scoring system that evaluates and ranks the surrogacy status of biomarkers.[13] Scoring was developed through literature review and therefore is again broadly based on the validation hierarchy in *Table 4*. The OMERACT scoring schema is based on four domains (*Table 5*).

In this schema the authors propose that a biomarker be recognised as a surrogate outcome only if it achieves a total score of 10 or more.

TABLE 4 JAMA User's Guide *for surrogate outcomes*

Guide	Requirement questions
1	Is there a strong, independent, consistent association between the surrogate outcome and the final outcome?
2	Is there evidence from randomised controlled trials in other drug classes that improvement in the surrogate outcome has consistently led to improvement in the final outcome?
3	Is there evidence from randomised controlled trials within the same drug class that improvement in the surrogate outcome has consistently led to improvement in the final outcome?

Modified from Table 1 in Bucher *et al.*[12]

TABLE 5 *OMERACT scoring schema for surrogate outcomes*

Domain	Definition	Scoring
A. Target	The final outcome that the surrogate substitutes for[a]	0–5
B. Study design	The level of evidence for the relationship between the surrogate outcome and the final outcome	0–5
C. Statistical strength	The strength of the association between the surrogate outcome and the final outcome and its statistical significance	0–5
D. Penalties	Lack of, opposing or inconsistent evidence from biology, clinical epidemiology or therapeutic trials	–1 to –3
		Total –3 to –15

a Whether the final outcome can range from death to disease-specific and reversible end points; the full OMERACT surrogate scoring schema is shown in Appendix 2.
Adapted from Lassere *et al.*[13]

No rationale for the weighting of domains in the scoring system is provided. Furthermore, the authors emphasise the current very limited application of the schema and the need for its further development. Until such application takes place, the validity and acceptability of the OMERACT tool remains uncertain.

Finally, the last decade has seen considerable efforts made in the development of statistical methods for the validation of surrogate outcomes. Detailed discussion of these statistical methods is beyond the scope of this report but can be found elsewhere.[14,15] These statistical methods include concepts such as the proportion of treatment effect explained (PTE), which is intended to indicate the proportion of the treatment effect mediated by the surrogate outcome, and the relative effect (RE), which is the ratio of the effects of treatment upon the surrogate and final outcomes. The application of these methods in single trials has often faced the problem of low statistical power, which in turn has been overcome by further developments in approaches that allow multicentre patient-level data analysis and meta-analysis.

Regulatory consideration of surrogate outcomes

With growing pressure to reduce the time to regulatory approval for new medical technologies, surrogate outcomes are frequently used as the basis for marketing licence applications for drugs and medical devices, particularly when they affect patients with life-threatening diseases for which no effective therapy exists. This has particularly been the case for the regulatory authority in the US, the FDA, although less so for the European regulatory authority, the European Medicines Agency (EMEA).[15,16] A summary of the current policies of both agencies is given below.

US Food and Drug Administration

In 1992 the FDA formulated a new regulatory process – the accelerated approval process – for diseases that are serious or life threatening and for which no effective therapies exist. Part of the accelerated approval process ('subpart H') allows marketing approval for a new drug product to be granted on the basis of:

> adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate end point that is reasonably likely, based on epidemiological, therapeutic, pathophysiologic and other evidence, to predict clinical benefit or on the basis of an effect on a clinical end point other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate end point to clinical benefit, or of the observed clinical benefit to ultimate benefit outcome. Post-marketing studies would usually already be under way. When required to be conducted such studies must also be adequate and well controlled. The applicant shall carry out such studies with due diligence.
>
> Johnson *et al.*,[15] p. 1404

European Medicines Agency

In the European Union there is a different 'accelerated approval' process. Current European legislation allows for granting of marketing authorisation under 'exceptional circumstances' when comprehensive data cannot be provided at the time of the submission (e.g. orphan conditions when the disease is rare) and provided that the applicant agrees to a further programme of studies which will be the basis of a post-authorisation review of the benefit–risk profile of the drug. Although this primarily refers to situations in which RCTs are lacking or difficult to undertake, it equally applies to absence of data on an appropriate clinical end point. Although less formalised than the FDA accelerated approval process, in such circumstances the European accelerated approval of drugs may also accept evidence that uses surrogate outcomes to support applications.[16]

In other international jurisdictions the regulatory acceptance of surrogates may differ. For example, in Japan proof of surrogacy through at least two RCTs collecting the final outcome is required as part of the post-marketing process.[16]

Use of surrogate outcomes in Health Technology Assessment

The Centre for Reviews and Dissemination (CRD) at the University of York[17] defines HTA as follows:

> HTA considers the effectiveness, appropriateness, cost and broader implications of technologies using both primary research and systematic review. It seeks to meet the information needs of those who manage and provide care.

This definition emphasises two key aspects of HTA. First, its scope is to systematically review the clinical effectiveness and the cost (effectiveness) of a drug (or other form of health technology). Second, HTA aims to inform policy and has been increasingly used by governments and health-care payers as a means of supporting their reimbursement and funding decisions. Since 1999 the National Institute for Health and Clinical Excellence (NICE) has been responsible for providing guidance to the NHS in England and Wales on the use of health technologies, principally based on their clinical effectiveness and cost-effectiveness. These decisions have drawn on HTA reports commissioned by the Department of Health and undertaken by independent, university-based academic teams. These reports are based on a systematic review of the clinical effectiveness literature and determine cost-effectiveness typically using the common currency of cost per quality-adjusted life-year (QALY) gained. QALYs are a way of measuring both the quality and the quantity of life lived, as a means of quantifying the benefit of a treatment in terms of a universal/comparable health currency. In many instances the nature of clinical evidence is such that these cost-effectiveness analyses are based on a decision-analytic model.

A number of NICE decisions have been based on an estimate of cost-effectiveness predicated from surrogate outcomes, e.g. the use of orlistat and sibutramine in the treatment of obesity (short-term changes in body mass index predicting long-term changes in cardiovascular events and mortality) and the use of ezetimibe/statins in the treatment of primary hypercholesterolaemia (short-term changes in total cholesterol and cholesterol subfraction levels predicting cardiovascular events and mortality).

Laupacis[18] recently commented that it was the experience of the Canadian Common Drug Review (which makes national reimbursement decisions on drugs based on technology assessment submissions from manufacturers) that 'the use of unvalidated surrogates is increasing' and that this presented 'one of the difficult issues that [CDR] has struggled with'. Tappenden and colleagues[19] summed up the importance of the appropriate use of surrogate outcomes in model-based cost-effectiveness analyses for cancer treatments:

> it is imperative that the link between tumour response [surrogate outcome] and final outcome is explicitly quantified and preferably validated alongside the exploration of the uncertainty surrounding this relationship.
>
> Tappenden *et al.*,[19] p. 870

Surrogate outcomes, therefore, have the potential to play an important role in HTA model-based cost-effectiveness analyses and the reimbursement decisions based on these data. A schematic representation of the use of surrogate outcomes in an HTA CEM is illustrated in *Figure 2*.

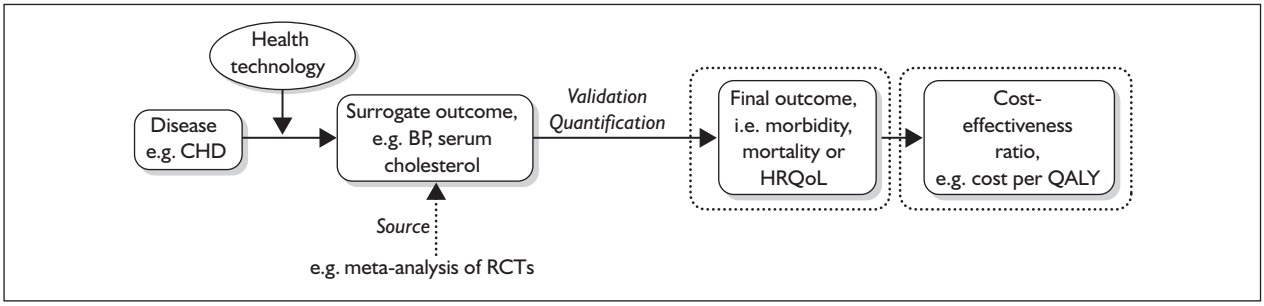

FIGURE 2 *Schematic representation of the use of a surrogate outcome in a Health Technology Assessment cost-effectiveness model. 'Source' refers to the source of the surrogate outcome data (usually a systematic review/meta-analysis of clinical effectiveness literature in an HTA); 'validation' refers to the evidence supporting the relationship between the surrogate outcome and the final outcome; and 'quantification' refers to how this relationship has been quantified. The two dotted boxes show that quantification of the surrogate outcome to final outcome may take place either within or outside the cost-effectiveness model per se. BP, blood pressure; CHD, coronary heart disease; HRQoL, health-related quality of life; QALY, quality-adjusted life-year; RCT, randomised controlled trial.*

Guidelines for the use of surrogate outcomes in Health Technology Assessment and cost-effectiveness analyses

In spite of their potential role, current guidance on the use (and validation) of surrogates in HTA reports, systematic reviews and cost-effectiveness analyses is variable. The recommendations from selected guidelines are summarised in *Table 6*.

The International Network of Agencies for Health Technology Assessment (INAHTA) guidance for the reporting of HTA makes no mention of the methodological issues associated with the use of surrogate outcomes.[20] The European Collaboration for Assessment of Health Interventions (ECHTA) Working Group 4 report on good practice in HTA recommends that surrogate outcomes should be avoided or at least used with extreme care.[21] The CRD[17] and the *Cochrane Handbook for Systematic Reviews of Interventions*[22] both comment on the issue of surrogacy ('intermediate outcome' or 'marker') and the need for caution in interpreting the validity and reporting of outcomes.

Cost-effectiveness methods guidelines, on the other hand, are generally more accepting of the need for surrogate outcomes in CEMs. Drummond and colleagues,[23] in the third edition of *Methods for the Economic Evaluation of Health Care Programmes*, stress the importance of evidence of the linkage between the intermediate (surrogate) and final outcomes. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Good Modelling Practice guidelines[24] additionally highlight the need to undertake sensitivity analyses to assess the robustness of cost-effectiveness to structural assumptions around the relationship between the surrogate and final patient-related outcomes. Philips and colleagues[25] (based on their systematic review of modelling good practice guidelines) stress the importance of transparency in describing the rationale for extrapolation between the surrogate ('intermediate') outcome and final outcome. Finally, the current NICE *Guide to Methods of Technology Appraisal*[26] mentions the inclusion of evidence based on surrogate outcomes but provides no guidance on methods for the validation or reporting of such outcomes. The Pharmaceutical Benefits Advisory Committee (PBAC) guidelines for manufacturers' submissions (updated 2007) provide detailed consideration of the use of surrogates.

Our literature searches found no empirical studies examining the use of surrogate outcomes in HTA and CEMs therein.

TABLE 6 *Guidelines for the use of surrogate outcomes in Health Technology Assessment reports, systematic reviews and cost-effectiveness analyses and modelling*

Guidelines document	Recommendation
Health Technology Assessment	
The International Network of Agencies for Health Technology Assessment (INAHTA) checklist for HTA reports, 2000[20]	No guidance on the use of surrogate outcomes
European Collaboration for Assessment of Health Interventions (ECHTA) Working Group 4 report, 2002[21]	'when assessing efficacy and effectiveness of therapeutic interventions, health-related outcomes (e.g. mortality) should be used. Using physiological or biochemical outcomes (i.e. "surrogate" outcomes) should be avoided as far as possible as they may not correlate with the health-related outcomes. Thus, if surrogate outcomes are used, the underlying assumptions have to be clearly stated, and results should be regarded carefully. Reliance on surrogate outcomes may be harmful and even lethal'
Systematic reviews	
Centre for Reviews and Dissemination (CRD) systematic review guidelines, 2001[17]	'Use of intermediate, surrogate or proxy outcomes (e.g. intraocular pressure as a surrogate for visual field damage in ocular glaucoma or loss of bone mineral content as a surrogate for fractures in hormone replacement therapy) can lead to misleading conclusions from reviews' (section 1.2.2.1)
Cochrane Handbook for Systematic Reviews of Interventions, 2006[22]	'One type of evidence that can be helpful in considering the likelihood of a cause–effect relationship between an intervention and an important outcome is indirect evidence of a relationship. This includes evidence relating to intermediate outcomes (such as physiological or biochemical measures that are markers for risk of the outcome of interest), evidence from studies of different populations (including animal studies) and evidence from analogous relations (i.e. similar interventions). Because conclusions regarding the strength of inferences about the effectiveness of an intervention are essentially causal inferences, reviewers might want to consider guidelines for assessing the strength of a causal inference, such as those put forward by Hill (Hill, 1971)' (section 9.1) 'In addition to identifying limitations of the applicability of the results of their review, reviewers should discuss and draw conclusions about important variation in results within the circumstances to which the results are applicable. Is there predictable variation in the relative effects of the intervention, and are there identifiable factors that may cause the response or effects to vary? These might include … biochemical markers' (section 9.2.4)
Cost-effectiveness analyses and modelling	
Drummond 2005[23]	'The success of this approach depends on the extent to which the link between intermediate [surrogate] and final outcomes has been established. In some cases, where the size of the relative risk (for example, of death) comparing individuals with and without the risk factor is large, it may be possible to establish the link through observational or case–control studies …. However, in many situations it might be necessary to establish the link through studies of stronger methodology, such as intervention studies with random assignment of subjects to treatment groups … When undertaking a CEA using effectiveness data relating to an intermediate end point the economic analyst should either (1) make a case for the intermediate end point having value of clinical relevance in its own right, (2) be confident that the link between intermediate and final outcomes has been adequately established by previous research, or (3) ensure that any uncertainty surrounding the link is adequately characterized in the economic study' (Chapter 5, pp. 108–9)

TABLE 6 *Guidelines for the use of surrogate outcomes in Health Technology Assessment reports, systematic reviews and cost-effectiveness analyses and modelling*

Guidelines document	Recommendation
International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Modelling Good Practice, 2003[24]	'If evidence regarding structural assumptions is incomplete, and there is no universally accepted theory of disease process, then the limitations of the evidence supporting the chosen model structure should be acknowledged. If possible, sensitivity analyses using alternative model structures – for example, using alternative surrogate markers or intermediate variables – should be performed'
Philips 2004[25]	'The methods and assumptions that are used to extrapolate short-term results to final outcomes (e.g. trial-based intermediate outcomes to survival) should be documented and evidence should be provided that the methodology is valid'
NICE 2004[26]	'4.4.1 Evidence submitted to NICE 4.4.1.2 The written submissions provide a unique contribution outlining the professional view of the place of the technology in current clinical practice. This includes evidence that relates to some or all of the following: – the identification of appropriate outcome measures and the appropriate use of surrogate outcome measures'
Use of surrogate outcomes to estimate final outcomes	
PBAC 2007[64]	'The claim that an incremental treatment effect on a surrogate outcome measured with the proposed drug quantitatively predicts a subsequent incremental treatment effect on a final outcome is more persuasively shown if attention is given to the following issues. *Step 1* Present a systematic review of the literature to examine whether epidemiological evidence and biological reasoning has established that there is a relationship between the surrogate outcome and the final outcome independent of any intervention. In a few instances, relationships have been established, or have been proposed, between surrogate outcomes and final outcomes. Examples include blood, left ventricular ejection fraction and survival after myocardial infarction, or viral load and cure of viral hepatitis. *Step 2* Present a systematic review of the literature to examine whether randomised trial evidence using other drugs has shown that there is a basis to conclude that a treatment effect on the surrogate outcome has satisfactorily predicted a treatment effect on the final outcome. (If there is evidence of this type for the proposed drug, this might help support a biological argument for the treatment.) Based on this evidence, quantify the relationship between these treatment effects with an assessment of the uncertainty of the relationship. Discuss the reproducibility of these findings (e.g. whether they have been consistently shown across more than one trial and for more than one alternative drug and mechanism of action). *Step 3* Explain why this relationship between the treatment effects on these outcomes with these other drugs is likely to apply to the proposed drug. Refer in this explanation to the mechanism of action of the proposed drug compared with the mechanism(s) of action of the drugs contributing evidence to Step 2 (a so-called "class effects" argument). At present, it is difficult to give categorical advice. Consider which outcomes are most appropriate and most feasible, given the data available. The clinical importance and patient relevance of the outcomes should be established and, where possible, supported with data. Having addressed the three steps above in transforming a treatment effect on a surrogate outcome to a treatment effect on a final outcome, explain in response to Subsection D.4 how this is included in the economic evaluation, including by specifying and referencing the sources of the longer term natural history (e.g. longitudinal population studies) as well as the transformed treatment effects' (extracted from Section C2)

Chapter 3
Methods

Sampling frame

Reports published in the UK HTA Programme monograph series in 2005 and 2006 formed the sampling frame for this study. This period was chosen to reflect recent HTA practice and was limited to 2 years because of time and resources available for this project.

Selection of reports

Reports were selected on the following basis:

- Inclusion criteria – the report addressed a treatment effectiveness/efficacy question and included a CEM and the CEM was primarily based on a surrogate outcome.
- Exclusion criteria – the report addressed a diagnostic, screening, aetiology or prognostic question or the report was a methodological study.

A structured proforma was developed to ensure the consistent application of the selection criteria and piloted on five HTA reports (see Appendix 1). Piloting identified that it was not always possible to judge whether the CEM in an HTA report was based on a surrogate outcome. We initially used the US NIH Biomarkers Definitions Working Group definition of a surrogate end point (see *Table 2*), that is, 'a biomarker that is intended to substitute for a clinical (final) outcome, and that a surrogate end point is expected to predict clinical benefit.' However, this definition was difficult to operationalise in practice as the outcomes used in HTA reports were not what could be described as 'biomarkers' but were instead patient-related end points. A pragmatic approach was therefore taken that permitted such reports to be included if they otherwise fulfilled the definition of a surrogate outcome (i.e. substitution for and prediction of a final outcome). The inclusion and exclusion criteria were applied independently to all reports by the two authors (RST and JE).

Data extraction

The following categories of information were extracted from included CEM surrogate outcome reports:

- characteristics of report (i.e. type of technology, disease area and whether report was on behalf of NICE)
- summary of CEM [i.e. type of model and base-case incremental cost-effectiveness ratio(s) (ICER)]
- characterisation of surrogate outcome used in CEM and identification of derived final outcome
- source of surrogate outcome evidence used in CEM (e.g. systematic review of clinical trials)
- evidence of validation of surrogate outcome
- methods used in report to quantify link between surrogate outcome and final outcome (e.g. regression-based approach)
- consideration of the uncertainty associated with using surrogate outcomes in the results or conclusions or elsewhere in the report.

Information was extracted by one of the authors using a standardised proforma (see Appendix 1) and checked by the second author.

Surrogate outcome scoring

In those reports identified as using surrogate outcomes, the evidence linking the surrogate and final outcomes was assessed according to the JAMA criteria[12] and the OMERACT scoring schema.[13] Full copies of these scoring systems are provided in Appendix 2.

Data analysis and reporting

Information on all included and excluded reports was entered into a Microsoft Excel spreadsheet and summarised using counts and percentages.

A narrative synthesis of the included reports was undertaken, presented in the form of tabular summaries and illustrative qualitative quotations from the text of the reports. Exploratory chi-squared analyses were planned to identify potential predictors of the use of surrogate outcomes across the included HTA reports.

Chapter 4
Results

Selection of reports

A total of 100 HTA monograph reports were published between 2005 and 2006. The characteristics of these reports are summarised in *Table 7*.

The majority of the HTA reports (52%) assessed either drugs or diagnostic/screening tests. The disease areas that were most frequently addressed were cancer, cardiovascular disease and mental health. About two-thirds (67%) of the reports addressed a secondary (or systematic review) research question and 50% of all the reports contained a CEM.

The process of report selection is summarised in *Figure 3*. A number of reports were initially

TABLE 7 *Characteristics of HTA reports published between 2005 and 2006*

Category	Number of reports
Technology type	
Drug	30
Medical device	11
Surgical procedure	8
Education or counselling	9
Diagnostic or screening	22
Methodological	11
Other[a]	9
Disease type	
Cancer	12
Cardiovascular	14
Mental health	11
Skeletomuscular	9
Dermatological	6
Renal urinary	6
Gastrointestinal	5
Infectious disease	5
Other diseases	21
Not applicable	11
Type of report	
Primary research	33
Secondary research	66
Both primary and secondary	1
Contains a cost-effectiveness decision model (CEM)	50
Report undertaken on behalf of NICE	31

a Includes evaluation of service and organisation interventions, other types of intervention (e.g. electroconvulsive therapy and blood transfusion) and prognostic questions.

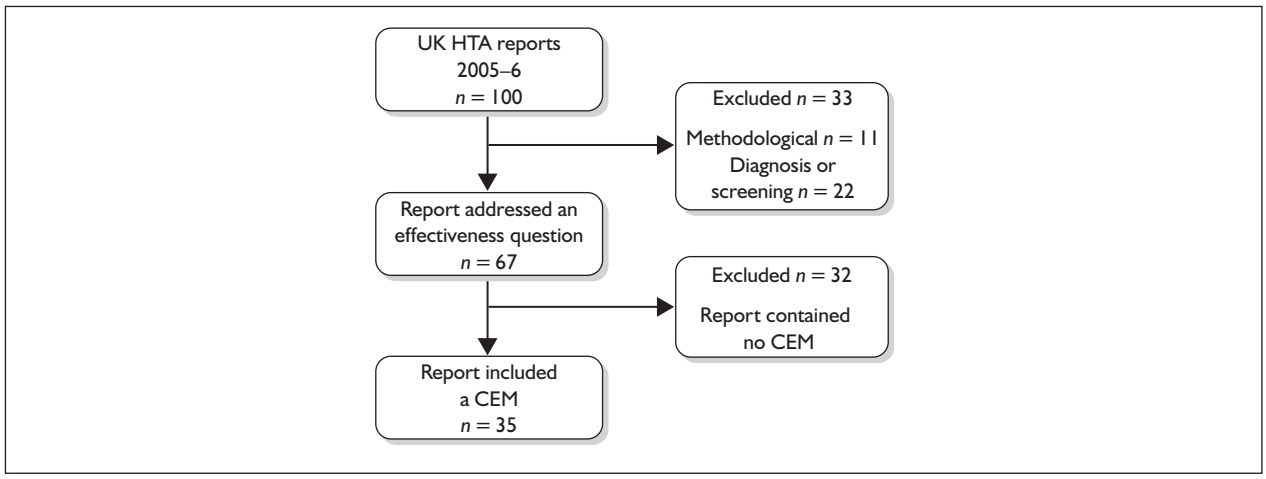

FIGURE 3 *Selection of reports. CEM, cost-effectiveness model.*

excluded on the grounds that they addressed either a methodological or a diagnostic/screening question. Of the remaining 67 HTA reports, a further 32 reports were excluded as they did not contain a CEM. Appendix 3 contains the list of excluded reports and reasons for exclusion.

Details of the 35 included HTA reports are summarised in *Table 8*. The majority (31/35) were secondary research reports undertaken on behalf of NICE. All except one of the included reports undertook a cost–utility (QALY) analysis. In the assessment that did not undertake a cost–utility analysis – the study by Thomas *et al.*[50] assessing the clinical effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts – cost-effectiveness was reported as a cost per percentage of warts cured.

Four[32,43,52,61] of the 35 reports (11%) were identified as using an outcome in the CEM based on prediction of a different end point reported in the clinical effectiveness review. These reports were therefore judged to be examples of the use of surrogate outcomes (highlighted in grey in *Table 8*) and are discussed in further detail below.

The remaining 31 HTA reports used a range of 'final outcomes' in their CEMs, including mortality or definitive clinical events (e.g. myocardial infarction, fracture) ($n = 17$), patient-related measures of disease severity (e.g. eczema severity scale) ($n = 7$) and functional status [e.g. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)] ($n = 4$). Six reports directly used a health-related quality of life (HRQoL) outcome in their CEM. Of these, four primary research reports used the EQ-5D generic utility measure and two secondary research reports used either a disease-specific [i.e. Minnesota Living with Heart Failure (MLWHF) scale] or a generic [i.e. Short Form 36 questionnaire (SF-36)] HRQoL measure, mapped to EQ-5D.

In those reports that did not use a direct measure of mortality or HRQoL in their CEM, changes in clinical outcome (i.e. disease severity, functional status) had to be converted into utility scores. Reports broadly used two conversion approaches: (1) a judgement on health states based on the clinical outcome (e.g. treatment response) to which specific utility values were then applied and (2) direct mathematical mapping of the clinical outcome to utility values. A more detailed analysis of the conversion of clinical outcome into utility in these reports was deemed to be outside the scope of this report; however, this issue will be discussed again in Chapter 5 of this report. The remainder of this section focuses on the four HTA reports that used surrogate outcomes.

Reports with a CEM based on a surrogate outcome

Characteristics of reports

All four HTA reports[32,43,52,61] based on surrogates were commissioned on behalf of NICE. They covered a range of diseases: two reports (from the same academic team) were on renal transplants; one was on Alzheimer's disease; and one was on chronic hepatitis B infection.

***Woodroffe* et al. *2005*[32]**

This report examined the clinical effectiveness and cost-effectiveness of a number of new immunosuppressive therapies (tacrolimus, basiliximab, daclizimab, mycophenolate mofetil and sirolimus) compared with existing therapy (ciclosporin and azathioprine) in adults undergoing kidney replacement. A systematic review identified a total of 33 RCTs across the various drugs comparisons. Most trials were short term (≤12 months) and were therefore of insufficient sample size and duration to detect differences between drugs in terms of relevant patient-related final outcomes, i.e. survival of the kidney graft and mortality. However, virtually all trials reported biopsy-confirmed acute rejection (BPAR). The authors of the report describe BPAR as 'acute episodes heralded by a reduction in graft function (seen on biochemistry), and clinical features such as fluid retention and occasionally graft tenderness and fever and confirmed through a histological sample taken of the effected graft.' Furthermore, 'the importance of acute rejection is not only the risk of acute graft loss, but also that it may be more likely that a patient will subsequently lose the [kidney] graft.' BPAR was used as a surrogate outcome to predict graft survival.

***Shepherd* et al. *2006*[52]**

The aim of this study was to assess the clinical effectiveness and cost-effectiveness of two antiviral agents [adefovir dipivoxil (ADV) and pegylated interferon alpha-2a (PEG)] for the treatment of adults with chronic hepatitis B infection. The report's systematic review identified seven RCTs that assessed the effectiveness of ADV and three trials evaluating the effectiveness of PEG. These trials reported treatment effects as the short-term biochemical response [e.g. levels of alanine aminotransferase (ALT) for liver function], virological response [e.g. presence of hepatitis B virus (HBV) DNA as evidence of viral replication] and seroconversion [e.g. hepatitis B virus e antigen (HBeAg) loss/anti-HBe; hepatitis B virus surface antigen (HBsAg) loss/anti-HBs]. The authors used seroconversion rates as a surrogate outcome in a transition natural history model to predict liver cirrhosis, liver cancer, liver transplant and death.

***Loveman* et al. *2006*[43]**

This study assessed the clinical effectiveness and cost-effectiveness of new drugs (donepezil, rivastigmine, galantamine and memantine) for Alzheimer's disease. A total of 12 RCTs were included. The four drugs were shown to be effective when assessed by a cognitive function outcome measure, i.e. the Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-cog) score. The ADAS-cog score was used as a surrogate by the authors to predict the outcome of needing full-time care.

***Yao* et al. *2006*[61]**

This sister report to that of Woodroffe *et al.*[32] examined the clinical effectiveness and cost-effectiveness of a number of new immunosuppressive therapies in children. The analysis was undertaken by the same academic group and an adaptation of the CEM developed in the previous report was used. The same group of drugs were compared and the systematic review identified 14 RCTs and non-RCTs. As in the Woodroffe report,[32] BPAR was used as a surrogate outcome to predict graft survival.

Surrogate validation

The evidence supporting the use of surrogate outcomes (*Table 9*) was assessed according to the evidence framework presented earlier in this report (see *Table 3*).

Woodroffe *et al.*[32] provided evidence from a systematic review and meta-analysis of observational studies to demonstrate the relationship between BPAR (surrogate outcome) and graft survival, i.e. level 2 evidence:

> A key assumption in the cost-effectiveness modelling framework of this review is the linkage between BPAR, graft and patient survival, quality of life and costs. The selection of acute rejection is supported by a systematic review of potential prognostic predictors for graft survival (Novartis submission, Addendum 7).
>
> Woodroffe *et al.*,[32] p. 68

Yao *et al.*[61] updated this systematic review to include evidence in children. To limit bias and confounding, the authors limited the systematic review to observational studies with multivariate analyses with 5-year or longer follow-up times. The authors identified one of two studies in children that confirmed the relationship between the surrogate outcome (BPAR) and the final outcome (graft survival) – level 2 evidence:

> In summary, this updated review of surrogate outcome predictors in children appears to support the findings that acute rejection is a strong predictor of future graft loss.
>
> Yao *et al.*,[61] p. 7

TABLE 8 *Summary of the included Health Technology Assessment (HTA) reports and the outcomes used in cost-effectiveness models (CEMs)*

Study	Report volume (issue)	Primary/ secondary research	NICE TAR	Population	Intervention	'Outcome(s)' used in CEM
Greenhalgh 2005[27]	9 (9)	Secondary	Yes	Depressive illness, schizophrenia	Electroconvulsive therapy	Treatment response as assessed by depression Treatment response as assessed by psychotic symptoms
Green 2005[28]	9 (11)	Secondary	Yes	Severe sepsis	Drotrecogin alpha	Overall mortality
McCormack 2005[29]	9 (14)	Secondary	Yes	Inguinal hernia	Laparoscopic surgery	Hernia recurrence, pain and return to usual activities
Wilby 2005[30]	9 (15)	Secondary	Yes	Epilepsy in adults	Antiepileptic drugs	Treatment response as assessed by reduction in seizures
Hartwell 2005[31]	9 (17)	Secondary	Yes	Acute myocardial infarction	Immediate angioplasty	Overall mortality and cardiovascular events
Woodroffe 2005[32]	9 (21)	Secondary	Yes	Adults undergoing renal transplantation	Immunosuppressive drugs	Biopsy-confirmed acute rejection
Stevenson 2005[33]	9 (22)	Secondary	Yes	Postmenopausal osteoporosis	New drugs	Fractures (hip, vertebral, wrist and proximal humerus)
Wilson 2005[34]	9 (25)	Secondary	Yes	Gastrointestinal stromal tumours	Imatinib	Overall mortality and functional status as assessed by Eastern Cooperative Oncology Group (ECOG) performance status
Robinson 2005[35]	9 (27)	Secondary	Yes	Acute coronary syndrome	Glycoprotein antagonists	Overall mortality, MI, vascularisation and GI bleeding
Tillin 2005[36]	9 (28)	Primary	No	Bowel incontinence	Electrically stimulated neosphincter surgery	HRQoL as assessed by EQ-5D
Garside 2005[37]	9 (29)	Secondary	Yes	Atopic eczema	Pimecrolimus and tacrolimus	Severity scale – Investigator Global Assessment (IGA) and assessment of treatment response with Physician Global Evaluation (PGE)
Cochrane 2005[38]	9 (31)	Primary	No	Lower limb osteoarthritis	Water-based therapy	Pain and functional status assessed on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale and HRQoL assessed by SF-36 and EQ-5D

	'Final outcome' classification					
Source of outcome	**Death**	**Clinical event**	**Disease severity**	**Function**	**HRQoL**	**Commentary on the approach to the use of outcome in the CEM**
Meta-analysis of RCTs			✓			Utility values applied to health states based on treatment response
Single RCT			✓			
Single RCT	✓					Utility values applied to survivor health state
Meta-analysis of RCTs and non-RCTs		✓				Utility values applied to health states based on recurrence and pain
Meta-analysis of RCTs		✓				Utility values applied to health states based on seizure response
Meta-analysis of RCTs	✓	✓				Fixed utility value applied to health states associated with cardiovascular events
Meta-analysis of RCTs	[a]	[a]	[a]	[a]	[a]	Biopsy-confirmed acute rejection used to predict graft survival. QALYs were then driven by graft survival rates
Meta-analysis of RCTs		✓				Mortality and utility applied according to site of fracture
Single uncontrolled trial	✓			✓		ECOG used to map to HRQoL utility
Meta-analysis of RCTs	✓	✓				Fixed utility value applied to health states associated with cardiovascular events
Non-RCT study					✓	Trial EQ-5D used directly
Meta-analysis of RCTs			✓			Utility values applied to health states based on severity
Single RCT				✓	✓	Trial EQ-5D used directly

continued

TABLE 8 *Summary of the included Health Technology Assessment (HTA) reports and the outcomes used in cost-effectiveness models (CEMs) (continued)*

Study	Report volume (issue)	Primary/ secondary research	NICE TAR	Population	Intervention	'Outcome(s)' used in CEM
Castelnuovo 2005[39]	9 (43)	Secondary	Yes	Atrioventricular block and sick sinus syndrome	Dual chamber pacemakers	Overall mortality, atrial fibrillation, pacemaker syndrome and complications
Clegg 2005[40]	9 (45)	Secondary	Yes	End-stage heart failure	Left ventricular assist devices	Overall mortality and HRQoL as assessed by Minnesota Living with Heart Failure (MLWHF) score
Clar 2005[41]	9 (47)	Secondary	Yes	Cartilage defects in knee joints	Autologous chronocyte implantation	HRQoL (SF-36)
Dretzke 2005[42]	9 (50)	Secondary	Yes	Conduct disorder in children	Parent training	Child behaviour as assessed by the Child Behaviour Checklist (CBCL) and the Eyberg Child Behaviour Inventory (ECBI)
Loveman 2006[43]	10 (1)	Secondary	Yes	Alzheimer's disease	Donepezil, rivastigmine, galantamine and memantine	Cognitive function as assessed by the Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-cog) score
Connock 2006[44]	10 (7)	Secondary	Yes	Epilepsy in children	Antiepileptic drugs	Treatment response as assessed by freedom from seizures and side effects
Main 2006[45]	10 (9)	Secondary	Yes	Advanced ovarian cancer	Topotecan, doxorubicin and paclitaxel	Overall mortality and progression-free survival
Connock 2006[46]	10 (20)	Secondary	Yes	Fabry's disease and mucopolysaccharidosis	Enzyme replacement therapy	None
Wright 2006[47]	10 (21)	Primary	No	Mild chronic hepatitis C	Alpha-interferon and ribavirin	HRQoL assessed by EQ-5D
King 2006[48]	10 (23)	Secondary	Yes	Attention deficit disorder in children and adolescents	Methylphenidate, dexamphetamine and atomoxetine	Treatment responses as assessed on global symptom improvement (GSI-I) and severity (GSI-S) scales
Connock 2006[49]	10 (24)	Secondary	Yes	Gaucher's disease	Enzyme replacement therapy	Disease severity as assessed by the Severity Score Index (SSI)
Thomas 2006[50]	10 (25)	Secondary	No	Cutaneous warts	Salicylic acid and cryotherapy	Cure rate
Buxton 2006[51]	10 (27)	Secondary	No	Risk of sudden cardiac death due to arrhythmias	ICD	Overall mortality, arrhythmia, hospitalisation

	'Final outcome' classification					
Source of outcome	**Death**	**Clinical event**	**Disease severity**	**Function**	**HRQoL**	**Commentary on the approach to the use of outcome in the CEM**
Meta-analysis of RCTs	✓	✓				Utility applied to health states based on cardiovascular outcomes
Single RCT, controlled and uncontrolled data	✓				✓	MLWHF mapped to utility scores
RCTs and uncontrolled data					✓	Illustrative threshold analysis to assess change in utility necessary to achieve cost-effectiveness
Meta-analysis of RCTs			✓			Examined what the QALY gains would have to be for unit change in behavioural outcomes needed to achieve cost-effectiveness
Meta-analysis of RCTs	[a]	[a]	[a]	[a]	[a]	ADAS-cog used to predict outcome of need for full-time care
RCTs		✓				Utility values applied to health states based on treatment response and side effects
RCTs	✓	✓				Utility values applied to health states based on disease state
Not applicable	[a]	[a]	[a]	[a]	[a]	Assumed that on treatment patients regain full health
Single RCT					✓	Trial EQ-5D values used directly
Meta-analysis of RCTs			✓			Utility values applied to health states based on treatment response
Non-RCTs			✓			Utility values mapped from severity scores
Meta-analysis of RCTs		✓				ICER is cost per 1% cure
RCTs and survey	✓	✓				No utility gain with ICD assumed in base case

continued

TABLE 8 *Summary of the included Health Technology Assessment (HTA) reports and the outcomes used in cost-effectiveness models (CEMs) (continued)*

Study	Report volume (issue)	Primary/ secondary research	NICE TAR	Population	Intervention	'Outcome(s)' used in CEM
Shepherd 2006[52]	10 (28)	Secondary	Yes	Chronic hepatitis B	Adefovir dipivoxil and pegylated interferon alpha-2a	Response to treatment as assessed by alanine aminotransferase (ALT) and hepatitis B virus (HBV) levels and seroconversion rates
Woolacott 2006[53]	10 (31)	Secondary	Yes	Psoriatic arthritis	Etanercept and infliximab	Function/disability assessed by Health Assessment Questionnaire (HAQ)
Pandor 2006[54]	10 (41)	Secondary	Yes	Colon cancer	Oxaliplatin and capecitabine	Progression-free survival and overall mortality
Kaltenthaler 2006[55]	10 (33)	Secondary	Yes	Depression and anxiety; obsessive–compulsive disorder	Computerised cognitive behaviour therapy	Depression severity as assessed by the Beck Depression Inventory (BDI) Treatment response as assessed by the Yale–Brown Obsessive Compulsive Scale (YBOCS)
Chen 2006[56]	10 (42)	Secondary	Yes	Rheumatoid arthritis in adults	Adalimumab, etanercept and infliximab	Function/disability assessed by HAQ
Davies 2006[57]	10 (44)	Secondary	No	Individuals undergoing non-urgent surgery	Cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion	Need for transfusion, overall mortality, morbidity and adverse events
Murray 2006[58]	10 (45)	Secondary	Yes	Colorectal cancer	Laparoscopic surgery	Mortality, cancer recurrence, complications
Woolacott 2006[59]	10 (46)	Secondary	Yes	Psoriasis	Etanercept and efalizumab	Disease severity assessed by Psoriasis Area and Severity Index (PASI)
Sharples 2006[60]	10 (48)	Primary/ secondary	No	Severe heart failure	Ventricular assist devices	Mortality and HRQoL as assessed by EQ-5D
Yao 2006[61]	10 (49)	Secondary	Yes	Children undergoing renal transplantation	Immunosuppressive drugs	Biopsy-confirmed acute rejection

CV, cardiovascular; GI, gastrointestinal; HRQoL, health-related quality of life; ICD, implantable cardioverter defibrillator; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; QALY, quality-adjusted life-year; RCT, randomised controlled trial; TAR, technology assessment report.
a No final outcome.

Source of outcome	'Final outcome' classification					Commentary on the approach to the use of outcome in the CEM
	Death	**Clinical event**	**Disease severity**	**Function**	**HRQoL**	
RCTs	[a]	[a]	[a]	[a]	[a]	Cirrhosis, liver cancer, liver transplant and death predicted from seroconversion rates based on natural history model. Utility values applied to health states based on disease state
RCTs				✓		Utility values predicted from HAQ
RCTs	✓	✓				Utility values applied to health states based on disease state
RCTs			✓			Utility values mapped to severity categories via BDI
			✓			Utility values mapped from YBOCS
Meta-analysis of RCTs				✓		Utilities predicted from HAQ
Meta-analysis of RCTs	✓	✓				External source of utility values applied to morbidity and adverse events
	✓	✓				Fixed utility values applied to health states associated with disease states
RCTs			✓			HRQoL utilities predicted from PASI
Non-RCT study	✓				✓	EQ-5D used directly
Meta-analysis of RCTs	[a]	[a]	[a]	[a]	[a]	Biopsy-confirmed acute rejection used to predict graft survival

TABLE 9 *Validation of surrogate outcomes*

Report	Evidence of validation?	Evidence	Level of evidence
Woodroffe 2005[32]	Yes	Systematic review of observational evidence of relationship between surrogate outcome and final outcome	2
Loveman 2006[43]	Yes	Observational study of individual patient data comparing cognitive function and need for full-time care	2
Shepherd 2006[52]	Yes	Systematic review of disease natural history	3
Yao 2006[61]	Yes	Systematic review of observational evidence of relationship between surrogate outcome and final outcome	2
		Comparison of change in surrogate outcome in one RCT	1

In addition, Yao *et al.*[61] examined whether the relationship between the surrogate outcome and the final outcome held up in a trial setting:

> To investigate the level of extrapolation between observational data and RCTs for this review, we compared the change in surrogate levels to the change in graft survival seen in the paediatric RCT by Filler and colleagues.
>
> Yao *et al.*,[61] p. 7

They found that:

> In this trial, an improvement in 2-year graft survival with tacrolimus ($p = 0.04$) was associated with improvements in both GFR and the incidence of acute rejection at 6 months to 1 year in the tacrolimus group.
>
> Yao *et al.*,[61] p. 7

that is, level 1 evidence.

The report of Shepherd *et al.*[52] recognises the limitations of the outcomes assessed in the trials and the need to predict a more final outcome of chronic hepatitis B:

> Clinical trial data relating to the effectiveness of interventions included in this appraisal are limited to measurements of short-term serological, virological and histological changes. In order to estimate the impact of these intermediate effects on final outcomes for patients, a natural history model for CHB was required.
>
> Shepherd *et al.*,[52] p. 81

Following a literature search on the natural history and epidemiology of chronic hepatitis B the authors developed a Markov disease state transition model. These epidemiological data were judged to represent level 3 evidence:

> the principal effect of antiviral treatment is to change patients' serological, biochemical, histological or virological status to place them in health states where they are less likely to develop progressive liver disease.
>
> Shepherd *et al.*,[52] p. 82

Loveman *et al.*[43] based their decision to use cognitive function as a predictor for full-time care on a previously developed CEM for Alzheimer's disease (AHEAD model). The authors state that the relationship between cognitive function and full-time care is based on individual patient data analysis undertaken by the developers of the AHEAD model.[62] On checking this source reference, the study concerned was identified to be a cohort comparison of cognitive function outcome and full-time care in Alzheimer's disease, i.e. level 2 evidence.

Surrogate quantification

A range of approaches was used across the four reports to quantify the relationship between the surrogate outcome and the final outcome. The CEM in both the Woodroffe *et al.*[32] and the Yao *et al.*[61] reports used a hazard ratio [derived from a systematic review of observational studies examining the patient-level relationship between the surrogate outcome (BPAR) and the final

outcome (graft survival)] to numerically represent this relationship.

> The authors reported that the pooled hazard ratio (HR) for allograft survival based on an acute rejection episode was 1.95 (95% confidence interval (CI):1.42 to 2.67).
>
> Yao *et al.*,[61] p. 6, referring to Woodroffe *et al.*[32]

> The adult BSA model was adapted for paediatrics … [and] … use made of a paediatric-specific HR of 1.41, 95% CI: 1.15 to 1.74.
>
> Yao *et al.*,[61] p. 43

Shepherd *et al.*[52] assessed the relationship between seroconversion rate (surrogate outcome) and final outcome (e.g. chronic hepatitis, liver cancer) within a natural history CEM. The link between the surrogate outcome and the final outcome was quantified as a transition probability within this model, as shown in *Table 10*.

Loveman *et al.*[43] quantified the impact of cognitive function (surrogate outcome) on full-time care (final outcome) using a predictive risk equation developed by the AHEAD model authors.[59] This equation was developed using a Cox proportional hazards model and contains coefficients for cognitive function, age at disease onset and the presence of psychotic symptoms (PSY) and extrapyramidal syndrome (EPS) and treatment duration (*Table 11*).

TABLE 10 *Transition probabilities for the natural history model for patients with HBeAg-positive chronic hepatitis B*

Health state		
From	**To**	**Transition probability**
HBeAg	HBsAg	0.02
	HBeAg	R
	CHB	0.03
	CC	0.01
	HCC	0.001

CC, compensated cirrhosis; CHB, chronic hepatitis B; HBeAg, seroconverted; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; R indicates a residual probability (i.e. 1 minus the sum of all the other probabilities at the node) – typically, the residual probability is that for remaining in the current health state.
Adapted from Table 34 of Shepherd *et al.*[52]

Handling uncertainty

In their discussion, Woodroffe *et al.*[32] identified the link between surrogate outcome (BAPR) and final outcome (graft survival) in their model as a potential limitation:

> In contrast, certain limitations were placed on the review … to estimate long-term effectiveness (and cost-effectiveness), extrapolation from trial 1-year BAPR to graft survival was undertaken.
>
> Woodroffe *et al.*,[32] p. 68

In addition, in the executive summary of their report they state that:

> The absence of both long-term outcome and quality of life from trial data makes assessment of the clinical and cost-effectiveness of the newer immunosuppressants contingent on modelling based on extrapolations from short-term trial outcomes.
>
> Woodroffe *et al.*,[32] p. xi

Yao *et al.*[61] took a quantitative approach to handling the uncertainty associated with the use of a surrogate outcome in their CEM. Using sensitivity analysis, they explored how the ICER would alter when varying the hazard ratio for the relationship between the surrogate outcome and the final outcome. Two hazard ratio values were chosen: (1) 1.41, based on a single paediatric observational study (base-case value); and (2) 1.69, taken from a meta-analysis of adult observational studies. Sensitivity analysis shows that the ICER for each of the pairwise comparisons remains relatively consistent (i.e. either dominant or > £50,000/QALY), providing evidence that the CEM results are relatively insensitive to the quantification of the relationship between the surrogate outcome and the final outcome (*Table 12*).

Furthermore, in the report's discussion the authors raise the dependence on surrogate outcome as a specific limitation of the CEM:

> Surrogate outcomes – The short duration of follow-up of RCTs necessitated the prediction of long-term graft loss [final outcome] and all-cause mortality from 1-year BPAR [surrogate outcome]. The authors of this report updated a previous systematic review of the literature in order to source the predictive value of BPAR associated with children [see section 'Surrogate outcomes and prediction of long-term graft survival' (p. 6)].
>
> Yao *et al.*,[61] p. 55

TABLE 11 *AHEAD model predictive risk equation for full-time care*

	Variable	EPS	PSY	< 65 years at disease onset	Cognitive function	Duration
Risk equation index	Coefficient	–0.9419	–0.4027	–0.4848	–0.0724	0.0617

EPS, extrapyramidal syndrome; PSY, psychotic symptoms.
Adapted from Table 47 of Loveman *et al*.[43]

TABLE 12 *Sensitivity analysis of varying the hazard ratio for surrogate–final outcome*

Drug comparison	Hazard ratio	ICER
CAS vs TAS	1.41	£145,540/QALY
	1.69	£58,801/QALY
CAS vs CMS	1.41	£194,559/QALY
	1.69	£76,958/QALY
CAS vs BCAS	1.41	Dominant
	1.69	Dominant
CAS vs DCAS	1.41	Dominant
	1.69	Dominant
TAS vs BTAS	1.41	Dominant
	1.69	Dominant

BCAS, regime of basiliximab, ciclosporin, azathioprine and steroid; BTAS, regime of basilixmab, tacrolimus, azathioprine and steroid; CAS, regime of ciclosporin, azathioprine and steroid; DCAS, regime of daclizumab, ciclosporin, azathioprine and steroid; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TAS, regime of tacrolimus, azathioprine and steroid.
Adapted from Table 57 of Yao *et al*.[61]

In addition, they note that there was inadequate validatory evidence to use two other possible markers as surrogate outcomes in the CEM:

> We found insufficient evidence to support the predictive use of graft function outcomes (i.e. serum creatinine and [glomerular filtration rate] GFR [surrogate outcomes].
>
> Yao *et al*.,[61] p. 55

Shepherd *et al*.[52] quantified the impact of uncertainty associated with the use of surrogates through sensitivity analysis, varying the assumptions of the structure of the CEM, as shown in *Table 13*.

Also through sensitivity analysis, Loveman *et al*.[43] assessed the impact of a 1-point shift (in both directions) for the surrogate outcome (ADAS-cog) (*Table 14*).

Furthermore, in the discussion section the authors highlight the limitation of the use of surrogate outcomes:

> It is difficult to know what the changes [in cognitive function] demonstrated on each measure really mean.
>
> Loveman *et al*.,[43] p. 14

OMERACT scoring schema and JAMA criteria

The scoring on the OMERACT surrogate schema domains for the four reports is summarised in *Table 15*. The low OMERACT schema score of 4 for the Shepherd *et al*.[52] report reflects the fact that, although the authors 'embedded' the relationship between seroconversion (surrogate outcome) and chronic hepatitis/liver cancer (final outcome) in the disease history CEM, they did not present specific biological or epidemiological evidence to support this link. The reports of Woodroffe *et al*.,[32] Loveman *et al*.[43] and Yao *et al*.[61] each scored 9 out of the potential maximum OMERACT score of 15; however, they all just failed to meet the threshold cut-off score of ≥ 10 that the authors of the schema deemed to represent the minimum level of

TABLE 13 *Sensitivity analysis of structural change in the hepatitis C virus disease model*

	Cost per QALY			
	IFN	**PEG**	**LAM**	**ADV**
Baseline analysis	£5994	£6119	£3685	£16,569
Structural assumption:				
Zero transition probability from compensated cirrhosis to HBeAg seroconverted state	£5275	£5696	£3513	£30,494
Zero transition probability from HBeAg seroconverted state to HCC	£5864	£6047	£3615	£16,220

ADV, adefovir dipivoxil; HCC, hepatocellular carcinoma; IFN, interferon; LAM, lamivudine; PEG, pegylated interferon alpha-2a.
Adapted from Table 42 of Shepherd *et al*.[52]

TABLE 14 *Sensitivity analysis of changes in Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-cog)*

	Cost per QALY		
	Donepezil 10 mg	**Rivastigmine 6–12 mg**	**Galantamine 24 mg**
Base case	£96,797	£70,438	£81,910
+1 point on base-case ADAS-cog	£66,505	£49,065	£57,119
–1 point on base-case ADAS cog	£150,214	£120,915	£122,571

QALY, quality-adjusted life-year.
Adapted from Table 74 of Loveman *et al*.[43]

TABLE 15 *OMERACT surrogate schema scoring*

Domain	**Woodroffe 2005**[32]	**Shepherd 2006**[52]	**Loveman 2006**[43]	**Yao 2006**[61]
A. Target[a]	4 (renal graft survival)	4 (chronic hepatitis, liver cancer)	4 (need for full-time care)	4 (renal graft survival)
B. Study design	2 (at least one prespecified population-based study)	0 (review of disease natural history)	2 (at least one prespecified population-based study)	2 (at least one prespecified population-based study)
C. Statistical strength	3 (at least good association between marker change and target change in all individual studies)	0 (no relevant data)	3 (at least good association between marker change and target change in all individual studies)	3 (at least good association between marker change and target change in all individual studies)
D. Penalties	0	0	0	0
Overall score	9	4	9	9

a The target score of '4' represents 'at least one patient-centred target of irreversible organ morbidity or major irreversible clinical burden of disease'.

evidence that an end point should reach to support its use as a surrogate outcome.

The studies of Woodroffe *et al.*,[32] Loveman *et al.*[43] and Yao *et al.*[61] were judged to broadly meet the JAMA level of guide 1, i.e. strong, independent, consistent association between the surrogate outcome and the final outcome. With RCT evidence showing the relationship between surrogate and final outcomes, the report of Yao *et al.*[61] also fulfilled the level of guide 2 and thus met the JAMA requirement of a valid surrogate.

Predictors of the use of surrogate outcomes

Given the small number of HTA reports with CEMs based on surrogate outcomes, an analysis of predictive factors was not possible.

Chapter 5
Discussion

This study aimed to examine the use of surrogate outcomes in CEMs in HTA by undertaking both a non-systematic review of the literature on the use of surrogate outcomes in HTA and a survey of the use of surrogate outcomes in CEMs in UK HTA reports published in 2005 and 2006.

The terms 'surrogate outcome or end point', 'biomarker' and 'biological marker' are often used interchangeably, which has led to confusion over the identification of what may be considered a surrogate outcome and the role of surrogate outcomes. For the purposes of this report we applied the following definition of a surrogate outcome: an end point that substitutes for and predicts a patient-relevant final outcome (i.e. mortality, important clinical events or health-related quality life).

Findings

Review of the literature

There is a long tradition of the use of surrogate outcomes (e.g. blood pressure, tumour size reduction) in clinical trials and drug regulation. However, the use of surrogate outcomes is controversial and a number of cases have been documented in which use of a surrogate outcome has led to the adoption of a health technology that has later been found to be harmful.[6,7] UK and international guidelines on HTA methods currently provide little or no specific advice on the appropriate selection and use of surrogate outcomes.[20,21,26]

Through a synthesis of ICH-9 guidelines[10] and the work of the US NIH Biomarker's Definitions Working Group[4] an evidence hierarchy for surrogate validation can be derived: level 1 – controlled trial evidence showing that the treatment-related change in surrogate outcome is associated with a concomitant change in the final outcome; level 2 – evidence from observational studies of an association between the surrogate outcome and the final patient-related outcome; and level 3 – understanding of the biology and pathophysiological studies make it plausible that the changes in the surrogate outcome will lead to changes in the final patient-related outcome.

Survey of UK HTA reports

Out of a total of 100 HTA UK reports published between 2005 and 2006, 35 addressed an effectiveness/efficacy question and contained a CEM. Of these, four (11%) reports were found to have based their cost-effectiveness analysis on a surrogate outcome: two reports[32,61] of patients undergoing kidney transplantation used an outcome of biopsy-confirmed acute rejection (BPAR) (final outcome – graft survival); one report[43] of Alzheimer's disease used the cognitive function score (final outcome – need for full-time care); and one report[52] of chronic hepatitis used seroconversion (final outcome – chronic hepatitis/liver cancer).

All four reports sourced treatment-related changes in surrogate outcomes through a systematic review of the literature, in some cases also undertaking meta-analysis. However, there was some variability in the consistency and transparency by which these reports provided evidence of the validation for the surrogate–final outcome relationship. Most usefully, some reports used sensitivity analyses to explore the impact of the potential uncertainty of the surrogate–final outcome relationship on cost-effectiveness. Only one of the reports[61] undertook a systematic review to specifically seek the evidence base for the surrogate–final outcome link. Furthermore, this was the only report to provide level 1 surrogate–final outcome validation evidence, i.e. RCT data showing a strong association between the change in surrogate outcome (BPAR) and the change in final outcome (graft survival) at an individual patient level. Two of the other three reports reported level 2 evidence, i.e. observational study data showing the relationship between the surrogate outcome and the final outcome.[32,43] However, none of the reports achieved a sufficient score on the OMERACT schema to be judged to have acceptable evidence of a surrogate outcome by its authors. Having been only recently developed, the OMERACT schema requires further testing against a range of surrogate outcomes to fully assess its suitability as a practical tool.

It is interesting to note that the four reports based on the use of surrogate outcomes were all undertaken on behalf of NICE, whose reference case seeks a cost per QALY analysis.[26] There may therefore be a particular pressure on HTA analysts when undertaking work directly for policy-makers to extrapolate from surrogate outcomes to QALYs to formally quantify the cost-effectiveness of a health technology.

The 31 remaining reports used a wide range of patient-relevant final outcomes in their CEMs. In total, 17 reports used what might be regarded as a 'definitive' final outcome, i.e. death or important clinical events (e.g. myocardial infarction, fracture). Six reports used a HRQoL outcome as assessed by the EQ-5D or a non-preference HRQoL measure (e.g. SF-36). Seven reports used outcomes that, although potentially important to patients, were not what might be regarded as a 'final outcome' in that disease area, e.g. improvement in osteoarthritis function assessed on the Health Assessment Questionnaire (HAQ) or reduction in severity assessed on the Psoriasis Area and Severity Index (PASI).[53,59] A number of authors called these near final outcomes 'intermediate' outcomes. In CEMs these outcomes require some process of further translation to quantify the health benefit and determine the cost-effectiveness. For example, one HTA report used a previously published algorithm to compute the utility gain from the observed change in functional outcome score (HAQ) in arthritis patients. Other reports derived utility by linking the outcome to a particular disease state (e.g. pain). This process of extrapolating clinical outcomes from intermediate outcomes to utility is known as 'mapping'.[63] Although outside the direct scope of this study, it is noteworthy that the process of utility mapping shares the same issues of outcome translation as surrogate outcomes. For example, it cannot be assumed that outcome measures that can be partially or fully perceived by patients at a point in time linearly map on to HRQoL outcomes at a later stage. This raises the question as to whether the evidence requirements for utility mapping should be similar to those applied to the surrogates.

In summary, in spite of the importance and risks of the use of surrogate outcomes in CEMs, the four HTA reports identified in this survey varied considerably in their approaches to handling and reporting surrogates. The strength of evidence for the surrogate–final outcome relationship, transparency of quantification and exploration of uncertainty of this relationship were found to vary considerably. Recommendations for handling and reporting of surrogate outcomes in CEMs in future HTA reports are made below.

Report strengths and limitations

We believe this to be the first empirical study of the use of surrogate outcomes in HTA. Previous surrogate outcome surveys have focused on their use in clinical trials and often used a purposive sampling strategy to identify examples that have led to surrogate failure.[6,7,9] This report provides an overview of the various issues relating to the use of surrogate outcomes in HTA, including definitional uncertainty, a framework for surrogate validation and a summary of current methodological guidelines for the use of surrogates.

However, because of limited resources and time, the sample of HTA reports surveyed was relatively small and limited to the UK. The small sample size and the limited number of HTA reports with a CEM based on a surrogate outcome potentially limits the generalisability of the findings of this study. The report focused on inclusion of HTA reports in which there was clear evidence of the dependence of the CEM on a surrogate outcome. We may have therefore excluded reports that used surrogate outcomes but which were unclear about this in their CEM description or reports in which the CEM depended on a mix of final and surrogate outcomes (in terms of the operational definition of this review). Documentary analysis was used to assess the content of included reports. It is therefore important to acknowledge that the absence of mention of an issue in the text should not necessarily imply the absence of consideration of that issue by the report's authors. Finally, for the purposes of this report we have focused on identifying HTA reports with CEM models that have used definitive examples of surrogate outcomes. However, we recognise that rather than a dichotomy there is effectively a continuum between what might be regarded as 'true surrogate outcomes' and what might be regarded as 'true final outcomes'. Nevertheless, we would contend that the recommendations remain applicable.

Proposed recommendations for studies selecting and/or using surrogate outcomes in HTA reports

Recommendations are proposed for the use of surrogate outcomes (any end point that substitutes for and predicts a final patient-related outcome, i.e. mortality, important clinical events or HRQoL) in future HTA reports. These recommendations are based on the findings of the review of the literature on the use of surrogate outcomes, the experience of the survey of the use of surrogates in UK HTA reports and feedback and discussion on the draft recommendations from InterTasc [UK HTA groups who undertake technology assessment reports commissioned by the National Institute for Health Research (NIHR) HTA Programme] and the technology assessment team at NICE. The rationale and source of each recommendation are shown in parentheses. These recommendations are intended to act as a list of considerations that policy-makers and HTA analysts should take into account when faced with the use of surrogate outcomes in CEMs in HTA reports. It is acknowledged that the practicalities and resource implications of implementing these recommendations have not been formally tested within this project.

1. Ideally, the assessment of clinical effectiveness and cost-effectiveness of a health technology should be based on final patient-related outcomes (i.e. mortality, important clinical events and HRQoL) (for rationale see Chapter 2, Risks of surrogate outcomes). To minimise the risk of bias this evidence should be identified from a systematic review (and meta-analysis) of well-conducted RCTs.
2. When this is not possible and there is a requirement to use a surrogate outcome[2] the following should be undertaken:
   i. A review of the evidence for the validation of the surrogate–final outcome relationship (for rationale see Chapter 2, Validation of surrogate outcomes). To minimise the risk of bias such a review should be systematic.
   ii. The evidence on surrogate validation should be presented according to an explicit hierarchy such as the following: level 1: evidence demonstrating treatment effects on the surrogate correspond to effects on the patient-related outcome (from clinical trials); level 2: evidence demonstrating a consistent association between surrogate outcome and final patient-related outcome (from epidemiological/observational studies); level 3: evidence of biological plausibility of relationship between surrogate outcome and final patient-related outcome (from pathophysiological studies and/or understanding of the disease process) (for rationale see Chapter 2, Validation of surrogate outcomes). To achieve level 1 classification a surrogate must fulfil the level 1 and level 2 and level 3 criteria. To achieve level 2 classification a surrogate must fulfil the level 2 and level 3 criteria.
   iii. Consideration should be given to carrying out a CEM analysis based on a surrogate outcome when there is level 1 or 2 validation evidence (for rationale see Chapter 2, Risks of surrogate outcomes).
3. When a CEM analysis based on a surrogate outcome is undertaken:
   i. Provide a transparent explanation as to how the relationship between the surrogate and final outcomes is quantified within the CEM (for rationale see Chapter 4, Reports with CEMs based on a surrogate outcome).
   ii. Explicitly explore and discuss the uncertainty associated with use of the surrogate outcome in the CEM, especially through sensitivity analysis (for rationale see Chapter 4, Reports with CEMs based on a surrogate outcome). In accordance with recent HTA methodological developments, such uncertainty may be quantified using probabilistic sensitivity analysis.
   iii. Make specific research recommendations regarding the need for future research on the surrogate–final outcome relationship (for rationale see Chapter 4, Reports with CEMs based on a surrogate outcome). In accordance with recent HTA methodological developments, the impact of the surrogate outcome on decision uncertainty may be quantified by value of information analysis.
   iv. Include the term 'surrogate outcome' in the report executive summary/abstract to assist bibliographic identification (for rationale see Chapter 4, Reports with CEMs based on a surrogate outcome).

Areas for future research

The following areas are suggested for further research:

- Given both the UK focus and relatively small number of HTA reports with a CEM explicitly based on surrogate outcomes identified, the generalisability of the findings may be limited. This supports a more extensive survey of the use of surrogate outcomes in HTA across international jurisdictions. Consideration should be given to the role of surrogate outcomes in both the clinical effectiveness and the cost-effectiveness components of these reports. Furthermore, future empirical studies need to address those situations in which HTA reports may combine both surrogate and final outcomes and the validity of using surrogates across technology classes.
- The review of the literature in this report identified only two previous empirical studies designed to quantify the potential bias associated with the use of surrogate outcomes. Further empirical studies are needed to assess the potential biases of the use of surrogate outcomes in HTA and cost-effectiveness analyses, for example a comparison of the findings of cost-effectiveness analyses based on surrogate outcomes versus cost-effectiveness analyses based on final outcomes.
- Testing of the new OMERACT surrogate scoring schema and the development of similar tools.
- Explore the transferability of the hierarchy of evidence framework for surrogate–final outcomes to the process of mapping disease-specific outcomes to HRQoL utility in CEM analyses.

Chapter 6
Conclusions

Policy decisions on the adoption of health technologies should be based on evidence of effectiveness and cost-effectiveness from well-conducted RCTs that report final patient-relevant outcomes, i.e. death, morbid end points (such as myocardial infarction, stroke) or impaired HRQoL. Contrary to this there is increasing pressure on health-care policy-makers to reduce the time to health technology regulatory approval and reimbursement by the use of surrogate outcomes (that substitute for and predict final patient-related outcomes). However, given that reliance on surrogate outcomes can ultimately lead to harmful patient outcomes, the use of such outcomes in HTA remains controversial.

In this survey of UK HTA reports about 10% of the CEMs therein were explicitly based on surrogate outcomes. The strength of evidence for the surrogate–final outcome relationship, transparency of quantification and exploration of uncertainty of this relationship were found to vary considerably. Recommendations are made for the use of surrogate outcomes in future HTA reports.

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Contribution of authors

Rod Taylor devised and led the study, drafted the initial version of the protocol and report, assessed reports for inclusion and exclusion, extracted data and had overall responsibility for the project. Julian Elston contributed to the development of the protocol, contributed to the editing of the report, assessed reports for inclusion and exclusion and extracted data.

About PenTAG

PenTAG is part of the Institute of Health Services Research at the Peninsula Medical School. PenTAG was established in 2000 and carries out independent health technology assessments for the UK HTA Programme and other local and national decision-makers. The group is multidisciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Peninsula Medical School is a school within the Universities of Plymouth and Exeter. The Institute of Health and Social Care Research is made up of discrete but methodologically related research groups, among which health technology assessment is a strong and recurring theme. Projects to date include:

The effectiveness and cost-effectiveness of imatinib (STI 571) in chronic myeloid leukaemia: a systematic review. *Health Technol Assess* 2002;**6**(3).

Screening for hepatitis C among injecting drug users and in genitourinary medicine (GUM) clinics: systematic reviews of effectiveness, modelling study and national survey of current practice. *Health Technol Assess* 2002;**6**(31).

Systematic review of endoscopic sinus surgery for nasal polyps. *Health Technol Assess* 2003;**7**(17).

The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling. *Health Technol Assess* 2004;**8**(3).

The effectiveness and cost-effectiveness of imatinib for first line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis. *Health Technol Assess* 2004;**8**(28).

Do the findings of case series studies vary significantly according to methodological characteristics? *Health Technol Assess* 2005;**9**(2).

The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema – a systematic review and economic modelling. *Health Technol Assess* 2005;**9**(29).

The effectiveness and cost-effectiveness of dual chamber pacemakers compared to single chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome – systematic review and economic evaluation. *Health Technol Assess* 2005;**9**(43).

Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling. *Health Technol Assess* 2006;**10**(8).

The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end stage renal disease patients on dialysis: a systematic review and economic evaluation *Health Technol Assess* 2007;**11**(18).

The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation. *Health Technol Assess* 2007;**11**(45).

The effectiveness and cost-effectiveness of cardiac resynchronisation therapy for heart failure: a systematic review and economic evaluation. *Health Technol Assess* 2007;**11**(47).

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Appendix 1

Inclusion/exclusion criteria and data extraction proforma

No.	Question	
1	Identification number of HTA report	Volume: Edition:
2	First author and year (2005/6)	
3	Reviewer:	RT JE
4	Date extracted (format DD/MM/YY)	

Key word search terms	Number of hits in report
surrog*	
biomarker	
intermediate outcome	
marker	
predictive factor	

Section A: General information – to be completed for all HTA reports

No.	Question	Answer
1	Type of health technology (exclude reports addressing non e.g. diagnosis, aetiology) Circle appropriate answer or answers	Drug Surgical procedure Education or counselling Diagnostic or screening Health promotion Medical device Other (specify)
2	Disease area Provide details	
4	Type of research report Circle appropriate answer	Primary Secondary Not sure
5	Undertook economic modelling? Circle appropriate answer	Yes No Not sure
6	NICE TAR? Circle appropriate answer	Yes No Not sure
7a	Was the economic model based on a surrogate outcome(s)? (NIH definition of surrogate end point: a biomarker intended to substitute for a clinical end point. A clinical investigator uses epidemiological, therapeutic, pathophysiological, or other scientific evidence to select a surrogate end point that is expected to predict clinical benefit, harm, or lack of benefit or harm) Circle appropriate answer	Yes No Not sure
7b	If no, name main outcome(s) used in model	
8	Type of decision model Circle appropriate answer or answers	Decision tree Markov model Both Other
9	Base case ICER (£/QALY or £/health outcome gain) List result or results	

If answers to Questions 5 *and* 7a are both yes then include

Include ☐ Exclude ☐ Unsure ☐

Section B: Surrogate HTA report – to be completed only for HTA reports with surrogate outcomes used in the economic model

No.	Question	Answer
10	Characteristics of surrogate	
11a	Surrogate outcome used? Name:	
	Final outcome sought? Name:	
12b	Type of surrogate (specify)	Biochemical
	Circle appropriate answer	Physiological
		Radiological imaging
		Immunological
		Histological
		Other
		Not sure
13c	Source of surrogate data used in model	Meta-analyses of RCT
	Circle appropriate answer	Single study – RCT
		Single study – non-RCT
		Other
		Not sure
14	Evidence of validation of surrogate	
14	Did the authors provide evidence of validation for the use of surrogate outcome used in the report?	Yes
		No
		Not sure
	If yes, which of the following criteria did they mention?	
14a	Biological plausibility/pathophysiology	Yes
		No
14b	Epidemiological (correlation) studies	Yes
		No
14c	Treatment effect studies (RCTs)	Yes
		No
15	Did the authors refer to any validation framework?	Yes
		No
		Not sure
	If yes, which framework did they refer to?	
15a	Bucher criteria	Yes
		No
15b	Prentice criteria	Yes
		No
15c	Other	Yes
		No
15d	Other comments	

No.	Question	Answer
16	Validation scoring To be completed by reviewer	
16a	Bucher framework	Attached
16b	Lassere framework	Attached
17	Quantification of surrogate in the model What statistical methods did the authors use to quantify the surrogate outcome in their economic model?	
	Regression-based approach	Yes No Not sure
	Confidence profile (Eddy) method	Yes No Not sure
	Other methods (give details)	Yes No Not sure
18	Discussion/interpretation of surrogates in report	
18	Did the authors consider uncertainty associated with using surrogate outcomes in the results?	Yes No Not sure
18a	If yes, was this consideration:	Narrative Quantitative Both Not sure
18ai	If narrative, provide quote (or cite relevant page/paragraph numbers) (e.g. did the authors discuss the influence of use on surrogate on interpretation of results?)	
18b	Did the authors consider uncertainty associated with using surrogate outcomes in the conclusions	Yes No Not sure
19	To be selected as a case study? (i.e. was the report a 'good' example of how to use and report use of surrogates in HTA)?	Suitable Not suitable

Appendix 2

Surrogate outcome scoring

JAMA criteria – scoring

Criteria	Circle appropriate response	Comments
1. Necessary but not sufficient: Is there a strong, independent, consistent association between the surrogate end point and the clinical end point?	Yes No Unsure	
2. Is there evidence from randomised trials in other drug classes that improvement in the surrogate end point has consistently led to improvement in the target outcome?	Yes No Unsure	
3. Is there evidence from randomised trials in the same drug class that improvement in the surrogate end point has consistently led to improvement in the target outcome?	Yes No Unsure	
Adapted from Bucher *et al*.[12]		

OMERACT criteria – scoring

Circle appropriate rank for domains A–D and provide total score.

Domain	Rank	Criteria
A. Target (for all studies ranked in domain B)	0	All targets studied are disease centred and reversible
	1	At least one target studied that is disease centred is irreversible
	2	At least one patient-centred target that is reversible
	3	At least one patient-centred target of irreversible minor organ morbidity or minor irreversible clinical burden of disease
	4	At least one patient-centred target of irreversible major organ morbidity or major irreversible clinical burden of disease
	5	Death
B. Study design (requires as baseline appropriate study quality, study power and study duration)	0	Evidence from in vitro or animal studies or case reports or cross-sectional observational or retrospective observational cohorts studies evaluating the relationship between marker and target
	1	At least one prespecified non-population-based prospective observational study with collection of all covariates needed to adjust for known confounding and effect modification evaluating the relationship between marker and target
	2	At least one prespecified non-population-based prospective observational study with collection of all covariates needed to adjust for known confounding and effect modification evaluating the relationship between marker and target or one randomised controlled trial of the same drug class of an intervention evaluating the relationship between marker and target
	3	At least two randomised controlled trials of the same drug class of an intervention evaluating the relationship between marker and target
	4	At least two randomised controlled trials in each of two drug classes of an intervention evaluating the relationship between marker and target
	5	At least three randomised controlled trials in each of three known drug classes of an intervention evaluating the relationship between marker and target or at least three randomised surrogate objective trials

Domain	Rank	Criteria
C. Statistical strength	0	No association/prediction or no relevant data
	1	At least fair association or better between marker change and target change in most single-study analyses
	2	At least fair association or better between marker change and target change in all single-study analyses or fair prediction in an across-study analysis evaluating the effect of treatment on marker change and target change
	3	At least good association or better between marker change and target change in all single-study analyses or good prediction in an across-study analysis evaluating the effect of treatment on marker change and target change
	4	At least very good association or better between marker change and target change in all single-study analyses and very good prediction in an across-study analysis evaluating the effect of treatment on marker change and target change
	5	Excellent association or better between marker change and target change in all single-study analyses and excellent prediction in an across-study analysis evaluating the effect of treatment on marker change and target change
D. Penalties due to lack of evidence or evidence to the contrary	–1	No in vitro or animal study evidence to support surrogacy validity or no epidemiological evidence to support surrogacy validity
	–1	At least one randomised controlled trial that does not demonstrate statistically significant surrogacy validity (i.e. evidence of no effect in at least one adequately powered randomised controlled trial)
	–1	At least one epidemiological study that supports opposite assertion
	–1	At least one epidemiological study that does not demonstrate surrogacy validity (i.e. evidence of no effect in at least one adequately powered epidemiological study)
	–1	At least one randomised controlled trial that demonstrated evidence of significant clinical heterogeneity
	–2	At least one randomised controlled trial that supports opposite assertion
	–3	At least one randomised controlled trial that demonstrates use of marker confers patient harm
	–3	Does not meet the threshold criterion of a rank of 3 in at least one domain if score is 7 or more
Total score		

Note: Marker must meet minimum technical performance criteria as per OMERACT filter.
Adapted from Lassere *et al.*[13]

Appendix 3
Excluded HTA reports

Study	Vol. no.	Issue no.	Primary reason for exclusion
Ozolins 2005	9	1	No cost-effectiveness model
Dalziel 2005	9	2	Methodological report
Wilson 2005	9	3	No cost-effectiveness model
Fowler 2005	9	4	No cost-effectiveness model
Shenfine 2005	9	5	No cost-effectiveness model
Taylor 2005	9	6	Diagnostic and screening question
Grant 2005	9	7	Methodological report
Robinson 2005	9	8	Methodological report
Smith 2005	9	10	Methodological report
Dinnes 2005	9	12	Methodological report
Willis 2005	9	13	Diagnostic and screening question
Peveler 2005	9	16	No cost-effectiveness model
Kalra 2005	9	18	No cost-effectiveness model
Woloshynnowych 2005	9	19	No cost-effectiveness model
Raftery 2005	9	20	No cost-effectiveness model
Smith 2005	9	23	No cost-effectiveness model
Roderick 2005	9	24	No cost-effectiveness model
Glenny 2005	9	26	Methodological report
Newman 2005	9	30	Diagnostic and screening
Price 2005	9	33	No cost-effectiveness model
Symmons 2005	9	34	No cost-effectiveness model
King 2005	9	35	Methodological report
Bryant 2005	9	36	No cost-effectiveness model
Bartlett 2005	9	38	Methodological report
Epps 2005	9	39	No cost-effectiveness model
Hobbs 2005	9	40	Diagnostic and screening question
Durham 2005	9	42	No cost-effectiveness model
Knowles 2005	9	44	Diagnostic and screening question
Kwartz 2005	9	46	Diagnostic and screening question
McDaid 2005	9	48	No cost-effectiveness model
Roderick 2005	9	49	No cost-effectiveness model
Dennis 2006	10	2	No cost-effectiveness model
Black 2006	10	3	Diagnostic and screening question
Whiting 2006	10	4	Diagnostic and screening
Dundar 2006	10	5	Methodological report
Martin 2006	10	6	Diagnostic and screening question
Garside 2006	10	8	Diagnostic and screening question

continued

Study	Vol. no.	Issue no.	Primary reason for exclusion
Szczepura 2007	10	10	Diagnostic and screening question
Wu 2006	10	11	Diagnostic and screening question
Nelson 2006	10	12	Diagnostic and screening question
Michaels 2006	10	13	No cost-effectiveness model
Speight 2006	10	14	Diagnostic and screening question
Goodacre 2006	10	15	Diagnostic and screening question
Brazzelli 2006	10	16	No cost-effectiveness model
Lewis 2006	10	17	No cost-effectiveness model
Rodgers 2006	10	18	Diagnostic and screening question
Kennedy 2006	10	19	No cost-effectiveness model
Nixon 2006	10	22	No cost-effectiveness model
Harvey 2006	10	29	No cost-effectiveness model
Wardlan 2006	10	30	Diagnostic and screening question
Castelnuovo 2006	10	32	Diagnostic and screening question
Williams 2006	10	34	Prognostic question
Brazier 2006	10	35	No cost-effectiveness model
Whiting 2006	10	36	Diagnostic and screening question
O'Dowd 2006	10	37	No cost-effectiveness model
Brown 2006	10	38	No cost-effectiveness model
Waugh 2006	10	39	Diagnostic and screening question
Williams 2006	10	40	Diagnostic and screening question
Brown 2006	10	43	No cost-effectiveness model
Liu 2006	10	47	No cost-effectiveness model
Henison 2006	10	50	Diagnostic and screening question

Health Technology Assessment reports published to date

Volume 1, 1997

No. 1
Home parenteral nutrition: a systematic review.
By Richards DM, Deeks JJ, Sheldon TA, Shaffer JL.

No. 2
Diagnosis, management and screening of early localised prostate cancer.
A review by Selley S, Donovan J, Faulkner A, Coast J, Gillatt D.

No. 3
The diagnosis, management, treatment and costs of prostate cancer in England and Wales.
A review by Chamberlain J, Melia J, Moss S, Brown J.

No. 4
Screening for fragile X syndrome.
A review by Murray J, Cuckle H, Taylor G, Hewison J.

No. 5
A review of near patient testing in primary care.
By Hobbs FDR, Delaney BC, Fitzmaurice DA, Wilson S, Hyde CJ, Thorpe GH, *et al*.

No. 6
Systematic review of outpatient services for chronic pain control.
By McQuay HJ, Moore RA, Eccleston C, Morley S, de C Williams AC.

No. 7
Neonatal screening for inborn errors of metabolism: cost, yield and outcome.
A review by Pollitt RJ, Green A, McCabe CJ, Booth A, Cooper NJ, Leonard JV, *et al*.

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We look forward to hearing from you.

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