

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

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Executive summary

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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.

Publication

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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.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

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.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

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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The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

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