

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

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Executive summary

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Executive summary

Background

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

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

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

Objectives

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

Methods

We conducted a review of methodological research related to the inclusion of adverse effects in decision models. Searches were conducted of relevant databases [Cochrane Methodology Register, Health Economic Evaluations Database

(HEED), NHS Economic Evaluation Database (NHS EED), EconLit, EMBASE, Health Management Information Consortium, IDEAS (Internet Documents in Economics Access Service), MEDLINE and Science Citation Index] from inception to September 2007. In addition, relevant organisation websites were browsed for guidelines as potential sources of relevant research literature.

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

Results

Methodological research

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

Review of current practice

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

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

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

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

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

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

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

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

In total, 13 reports (30% of those models that included adverse effects and 16% of all reports)

used withdrawals related to drug toxicity and therefore might be interpreted as using withdrawals to capture adverse effects, but this was explicitly stated in only three reports. However, the remaining 10 models also incorporated adverse effects explicitly through at least one other parameter.

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

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

Conclusions

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

that were reviewed for this project varied greatly.

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

Improved links between the outcomes of the model and the data inputs presented in the systematic review and model description may aid the reader's understanding and support the decision-maker. Even when a systematic review of adverse effect

data is not feasible, summaries of such data should be presented in the clinical effectiveness review.

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

Publication

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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.

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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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