Modelling in prioritising and planning clinical trials

The role of modelling in prioritising and planning clinical trials

Methodology

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Executive summary

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Executive summary

Background

Most decision-analytic models in health technology assessment describe pathways through health states and events in a population. Mathematical models of the natural history of a disease are used to estimate health outcomes, resource usage and costs, and to compare the clinical and economic effectiveness of the technologies under assessment. The most common mathematical techniques used are decision analysis, state transition models and discrete event simulation. The appropriate technique depends on the characteristics of the treatment under evaluation.

Objectives

- To assess modelling methods used in the construction of disease models to support health technology assessment, and methods for their analysis and interpretation.
- To identify the role of mathematical modelling in planning and prioritising trials. 'Trials' is defined as all forms of primary research supporting health technology assessment of the clinical and economic consequence of alternative interventions.

Methods

Systematic reviews of the methodological and case study literature were undertaken. Search strategies focused on the intersection between modelling, health technology assessment, and priorities and prioritisation.

Results and conclusions

Five central questions were addressed.

(1) In what ways can modelling extend the validity of trials?

By:

- generalising from trial populations to specific target groups
- generalising to other settings and countries
- extrapolating trial outcomes to the longer term
- linking intermediate outcome measures to final outcomes
- extending analysis to relevant rather than trial comparators
- adjusting for prognostic factors in trials
- synthesising primary research results.

These conclusions are drawn from the review of methodological and case studies of economic models from the general health technology assessment literature that claims some value in research planning and design. In undertaking modelling or interpreting the results of modelling studies, the degree of reliance that can be placed on these studies is important, so close attention must be paid to guidelines for good practice.

(2) What characteristics of the trial/technology affect the success of modelling?

The review does not highlight specific success factors within the trials or technologies; given analytical expertise, there are no theoretical distinctions between alternative disease areas. Modelling may offer greater benefits as an evaluative tool for certain forms of health technology, such as diagnostics and screening, which may have an impact over a long period and where key disease/technology characteristics may not be directly observable. It may also provide more substantial benefits for technologies with long lead times in research, or for rapidly changing technologies.

A limited evidence base will reduce the 'success' of modelling, if the criterion is usefulness of a model in deciding on the adoption of the technology in practice. However, if the criterion for a model's success is its usefulness in helping to decide on further research, then a limited evidence base is inevitable, and provides the key source material to describe the current uncertainty.

(3) What aspects of trial design can modelling feasibly inform?

Cost-effectiveness modelling and sensitivity analysis can inform research design by: identifying key parameters requiring further investigation, specifying the minimum clinical difference needed for sample size calculations for a proposed trial, and defining the duration and population characteristics of a proposed trial.

Some methodological discussion and case studies use standard methods of sensitivity analysis in informing these aspects, but these methods have weaknesses. Analytical methods focusing on trial design and prioritisation are required. Two methods identified in the literature are payback methods and expected value of information (EVI) analysis.

- Payback methodology presupposes a specific trial design and therefore does not explicitly address this issue. Specific applications have focused on its role in informing the sample size of trials.
- EVI analysis of economics models has been applied in practice and can address all these issues.

(4) How feasible, costly and beneficial might modelling be as part of the prioritisation process?

Although the payback approach has not always been implemented successfully, it has potential feasibility. There are no published results on its implementation costs. The benefits are unproven but are often conceived as increased explicitness of the prioritisation process and improved decision-making. The main requirement for research into payback methods is the implementation of stochastic sensitivity analysis within exemplar case studies.

EVI analyses have been shown to be possible within the financial, resource and time constraints of the NHS HTA R&D Programme. The potential benefits of EVI are:

- The value of further research relates directly to its impact on technology commissioning decisions and the consequential health and economic benefits, and is demonstrated in real and absolute rather than relative terms.
- It avoids the misleading rankings of uncertainties that may result from conventional sensitivity analyses.
- It does not start from a prespecified research design, but identifies key uncertainties and allows the technical efficiency of many different types of research to be assessed. Further research is required to establish the benefits in practice.

(5) How far can modelling substitute for low-priority trials?

Modelling is not a substitute for data collection. By identifying the absolute and relative value of further research on specific parameters, EVI analysis directly identifies trial designs of low priority in informing technology commissioning decisions.

Recommendations for further research

- To report issues of good practice in undertaking and reporting economic modelling. Areas for development include model validation, stochastic sensitivity analyses, and specifically the cost-effectiveness acceptability curve presentation of uncertainty and the explicit reporting of assumptions. The guidelines identified here should be recommended to journals that publish economic evaluations to provide a structure for peer review.
- To develop case studies using stochastic sensitivity analyses within the payback approach to prioritisation of research.
- To encourage the calculation of the overall expected value of perfect information for a decision problem in modelling studies seeking to inform the prioritisation and planning of health technology assessment.
- To identify the potential benefits of EVI analysis and assess whether they can be realised in R&D prioritisation and planning in practice.
- To define an objective function that captures the issues of importance to decision-makers in health technology assessment planning and prioritisation, and includes quantifiable aspects to incorporate into a process that supports the arbitration of subjective judgement.
- To develop approximation methods to allow the general application of EVI methods.
- To develop a general method to estimate expected value and expected net benefit of sample information, through methodological research into updating of prior probability distributions. These methods should be demonstrated in case studies.

Publication

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NHS R&D HTA Programme

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