
CHAPTER 1

Principles and methods

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MODELLING IN ECONOMIC EVALUATION



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Clinical efficacy trials seldom provide all the data required for economic evaluation. Modelling is needed to combine different types of data from different sources.

The most straightforward way to estimate the costs and consequences of a new treatment or drug would be to use resource utilisation and efficacy data from a randomised clinical trial. This approach retains the high internal validity of the trial, ensures that both the costs and the effects are measured within the same setting, and allows variability in cost and effect estimates to be explored using confidence intervals for the incremental cost-effectiveness ratio [1].

However, there are several reasons why this approach may not be suitable in practice. Firstly, in many diseases it is impossible to fund a study enrolling enough subjects for a long enough time period to collect the necessary data. Secondly, the special circumstances of

defined group of patients, as specified in the protocol, and resource consumption may not be available for the patient with the condition which will be treated in clinical practice. Also, the difference between, for example, a treatment and placebo may not be entirely representative of the broader patient population.

These characteristics may mean that the efficacy results from trials are of limited generalisability beyond the trial to effectiveness in routine clinical practice. Moreover, there will be situations in which there are no experimental data on costs and effects relating to the question that the decision maker wants to address, perhaps because trials have been based on placebo controls rather than a comparator relevant to treatment decisions made in practice.

The choice of a modelling technique is driven by the type of question to be solved and by data that are available.

clinical studies will influence patient management and some costs will be entirely protocol-driven, preventing a relevant comparison to clinical practice. Thirdly, many studies enrol patients in a large number of countries and trials are powered for the full sample. The individual national groups are, therefore, generally too small to reach significance and to assess country-specific costs, as would be needed for an economic evaluation. The way to handle this latter problem is, in general, to use the quantities of resources from the entire trial and apply country-specific unit costs to them. However, this may not be a completely satisfactory solution as patient management between countries may be different. Lastly, participation in a clinical trial will tend to be restricted to a narrowly

Thus, modelling costs and effects by synthesising data from different sources (epidemiological, clinical, and economic) becomes necessary [2, 3]. Indeed, national guidelines by health technology assessment offices or reimbursement agencies explicitly state the acceptance of modelling and provide the details as to which type of models are desirable and the methodology that should be used. Examples are the guidelines from the Canadian Agency for Drugs and Technology as well as the National Institute of Clinical Excellence in the UK [4, 5].

Within models, it is possible to combine different data sets, extrapolate to a longer time frame than clinical trials, test different assumptions about risk, effectiveness, costs, etc. Economic evaluations generally use three types of models:

- For cost-effectiveness analysis in diseases with distinct events that occur with a given probability, either by decision or by chance, within a relatively limited time frame, decision tree models are used [2].
- For analyses in diseases with an ongoing risk, over a long time frame, Markov models are more appropriate [6, 7].
- For analyses where the timing and chronology of events is important discrete event simulations are more practical.

DECISION ANALYSIS

Decision analysis was developed as a discipline for examining choices under uncertainty and has long been applied to clinical decision-making. It enables complex problems and processes to be broken down into component parts, each of which can be analysed individually in detail, before they are recombined in a logical, quantitative and temporal way to indicate the best course of action. Analyses can be depicted as a decision tree that incorporates strategic choices, probabilities of subsequent events and final outcomes. An example is given in Figure 1.

Several steps are required to construct a clinical decision tree:

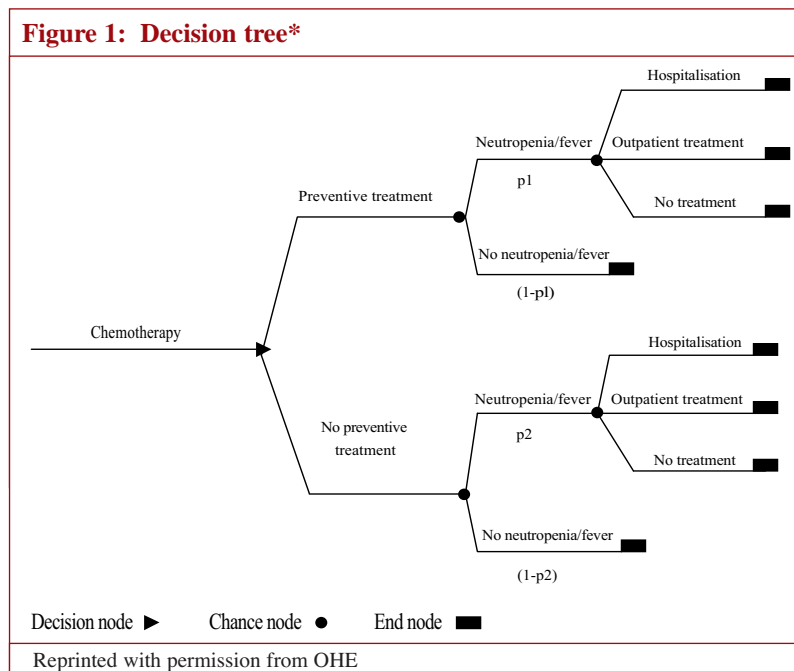
- clear definition of the problem
- description of successful or unsuccessful outcomes
- definition of alternative patient management strategies and their consequences
- estimation of the probabilities
- a time frame.

Decision trees are usually based on data from clinical trials and other sources of empirical evidence, such as systematic reviews and meta-analyses. For the economic evaluation, the expected cost for each strategy is calculated by multiplying the cost for each branch by the overall probability of that branch occurring. The different treatment strategies can then be compared in terms of their different expected costs and outcomes.

*In this example of a decision tree, a decision is made to give or not give a treatment that reduces the risk of chemotherapy-induced neutropenia (decision node). In both cases, patients can have neutropenia, but the probability (chance node) in the intervention group (p1) is lower than in the no-treatment group (p2).

Consequently, costs of treating neutropenia are lower in the intervention group, as fewer patients experience it, assuming that it is treated in the same way in both groups. Expected costs and expected outcomes for each strategy will be estimated by ‘folding back the tree’. Using the decision tree model above, if we assume that the preventive treatment costs Euros 1,000, that the average proportion of patients experiencing neutropenia without prevention is 40%, that treatment reduces this risk by 25%, and that the average cost of treating a neutropenic event is Euros 3,000, then the average cost per patient in the prevention arm would be Euros 1,900 (Euros 1,000 + 0.3 x 3,000) and in the no prevention arm Euros 1,200 (Euros 3000 x 0.4).

The cost-effectiveness of preventive treatment will be estimated by comparing the two strategies. In this example, the incremental cost per neutropenic event avoided would be Euros 7,000 (Euros 700/0.1). In other words, preventive treatment would reduce the absolute proportion of patients with neutropenic events by 10%, thereby saving Euros 300 (Euros 3,000 x 0.1) and leaving an incremental cost for the preventive treatment of Euros 700 (Euros 1,000 minus Euros 300).



MARKOV CHAIN ANALYSIS

Sometimes decision trees are not the best way to describe disease effects and interventions. This is particularly the case in chronic diseases where the risk of, for example, progression of a disease, may be continuously changing over time. For such problems, a Markov model will be more appropriate. Figure 2 illustrates the structure of Markov models.

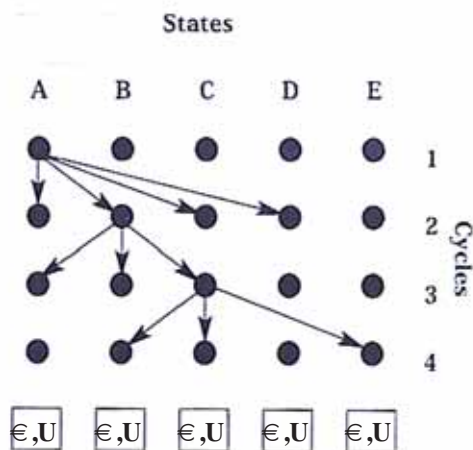
For Markov models, it is assumed that all patients can be classified into a finite number of states, so-called Markov states. States are generally defined by disease parameters, such as severity, which are meaningful to patients and clinicians, but other definitions exist as well. Development of a disease and the effect of treatment are represented as transitions from one state to another. Transition probabilities only depend on the health state patients are in and not on how long they have been in this stage and how they got there. Disease

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Figure 2: Markov models**

- All patients are grouped into a finite number of states (Markov states)
- Time progresses in equal increments (Markov cycles)
- All events of progression are represented as transitions from one state to the other, with a certain probability
- Spending one cycle in a given state is associated with a defined cost (€) and a defined utility (U)



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**Markov models illustrate the disease process by distributing patients across a finite number of distinct and mutually exclusive disease states at baseline and then following the development of the cohort during a defined time (number of cycles). For instance, states could be defined by levels of disability, with state A above being 'no disability', B 'mild disability', C 'moderate disability', D 'severe disability' and E 'death' (absorbing state). All Markov models have a state that patients cannot leave, usually death, in order to perform survival analyses. However, often there is not enough detailed information to perform lifetime analyses, and the duration of the model, i.e. the number of cycles as well as their length, is chosen depending on the disease and the epidemiological and clinical data that are available.

Costs and utilities (health status) for these states are assumed to depend on the state only and are therefore the same for all cycles. In such a framework, more severe states are generally associated with higher disease costs and a lower quality of life. Thus, if patients spend more time in the benign states of 'no disability' or 'mild disability', costs within a given time frame will be reduced while quality of life will be improved. The transitions between states, i.e. the probability at each cycle of deterioration, e.g. from moderate to severe disability, or of improvement, e.g. from moderate to mild disability, are calculated from epidemiological or clinical data.

The model will then calculate the average cumulative costs and effects, e.g. the number of quality-adjusted life years (QALYs), over a defined time for an untreated and a treated cohort, and compare the groups to estimate the incremental cost (treatment costs minus cost reductions due to treatment) per QALY gained with the treatment compared with no treatment.

progression will be represented by transitions to more severe states, while the treatment effect will either reverse or slow this progression. The differences or cut-off points between the states must therefore also represent clinically meaningful differences.

The time period covered by a model is divided into equal increments, referred to as Markov cycles. The length of the cycle is chosen to represent a clinically meaningful time interval. For instance, weekly cycles in a model to calculate the effectiveness of a treatment to avoid hip fractures would clearly be too short, while yearly cycles for a treatment of infections would be too long. During each cycle a patient may make a transition from one state to another or remain in the current state. No distinction is made between the different patients within each state.

The probabilities of making a transition from one state to another during a cycle (transition probabilities) are generally calculated from epidemiological data or clinical trials. The Markov process is completely defined by the cohort distribution among the states at the start and the probabilities for the individual transitions allowed during the subsequent cycles. In order for a Markov process to terminate, it must have at least one state that the patient cannot leave. Such states are called absorbing states because, after a sufficient number of cycles, the entire cohort will have been absorbed by those states. In medical examples, death is by far the most common absorbing state. Each state is assigned a utility and a cost, and cumulative utilities and costs for a given cohort are calculated at the end of the Markov process.

Markov models can be analysed deterministically as cohort simulations, e.g. representing a clinical trial cohort, or a specific type of patient or subgroup, etc.; or probabilistically using the underlying distribution in the data sets [8].

DISCRETE EVENT SIMULATIONS

In discrete event simulations (DES) models, similar to Markov models, patients are in states, e.g. levels of disease, different treatments. They remain in the same state until a certain event happens, such as a change in the disease, change of treatment, death. While in a state, patients can have different characteristics over time, and hence different costs and utilities, which provide more flexibility than

using a Markov model where this is not possible. The best way to think about the DES model is as a system (a disease and its treatment) presented as a chronological sequence of events.

DES models are analysed as patient-level simulations. Thus, they contain the full range of information available on patients in the data sets used for building the model.

CONCLUSION

Modelling in economic evaluation in health care has indeed become the rule rather than the exception. It is almost never the case that all required and adequate data for the analysis are found in a single data set. It is thus necessary to combine different types of data from different sources into a framework that includes the relevant issues, but is structured in a logical way that allows making decisions under uncertainty.

The choice of a modelling technique is driven by the type of question to be solved and by data that are available; beyond this, it is mostly a question of convenience. All models should give equal results if they use the same underlying data, provided that they are programmed correctly, since any model can only represent the underlying data.

Both text and diagrams are adapted from the author's book *Health Economics: an introduction to economic evaluation* [1].

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