The use of modelling in the economic evaluation of health care

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INTRODUCTION

An analytical framework that employs a mathematical modelling component is increasingly being used in economic evaluations of health care technologies (Karnon and Brown, 1998). Such models are developed in order to combine information from a variety of sources and assess the policy implications. Whilst there have been some concerns expressed about the use of modelling (Sheldon, 1996), there is now a growing acceptance that some degree of modelling is required when undertaking economic analyses, even where data are available from clinical trials (Buxton *et al*, 1997).

Earlier papers have provided introductions to particular modelling approaches, notably Markov models (Sonnenberg and Beck, 1993; Briggs and Sculpher, 1998), and others have explored specific methodological issues in modelling, such as the importance of data sources (Jefferson and Demicheli, 1998; Nuijten, 1998). The purpose of this paper is three-fold: (1) to provide an overview of alternative approaches to modelling in economic evaluation, using examples of published studies; (2) to review current modelling practice by identifying all health economic evaluations published in 1997 that used a modelling approach; and (3) to use case-studies to highlight situations where each of the alternative modelling techniques should be employed.

DIFFERENT MODEL TYPES

Decision Trees

The first type of model to be considered is the decision tree, a good example of which is given by Evans *et al* (1997). This is designed to compare oral sumatriptan with oral caffeine/ergotamine as treatments for a migraine attack. See Figure 1 for the decision tree used in this case. Any individual suffering a migraine attack follows a path from left to right, finishing at one of the outcomes A to J. The first split is at a *choice node* (sometimes called a decision node); here the path followed is determined by the choice of treatment. Later splits occur at *chance nodes*.

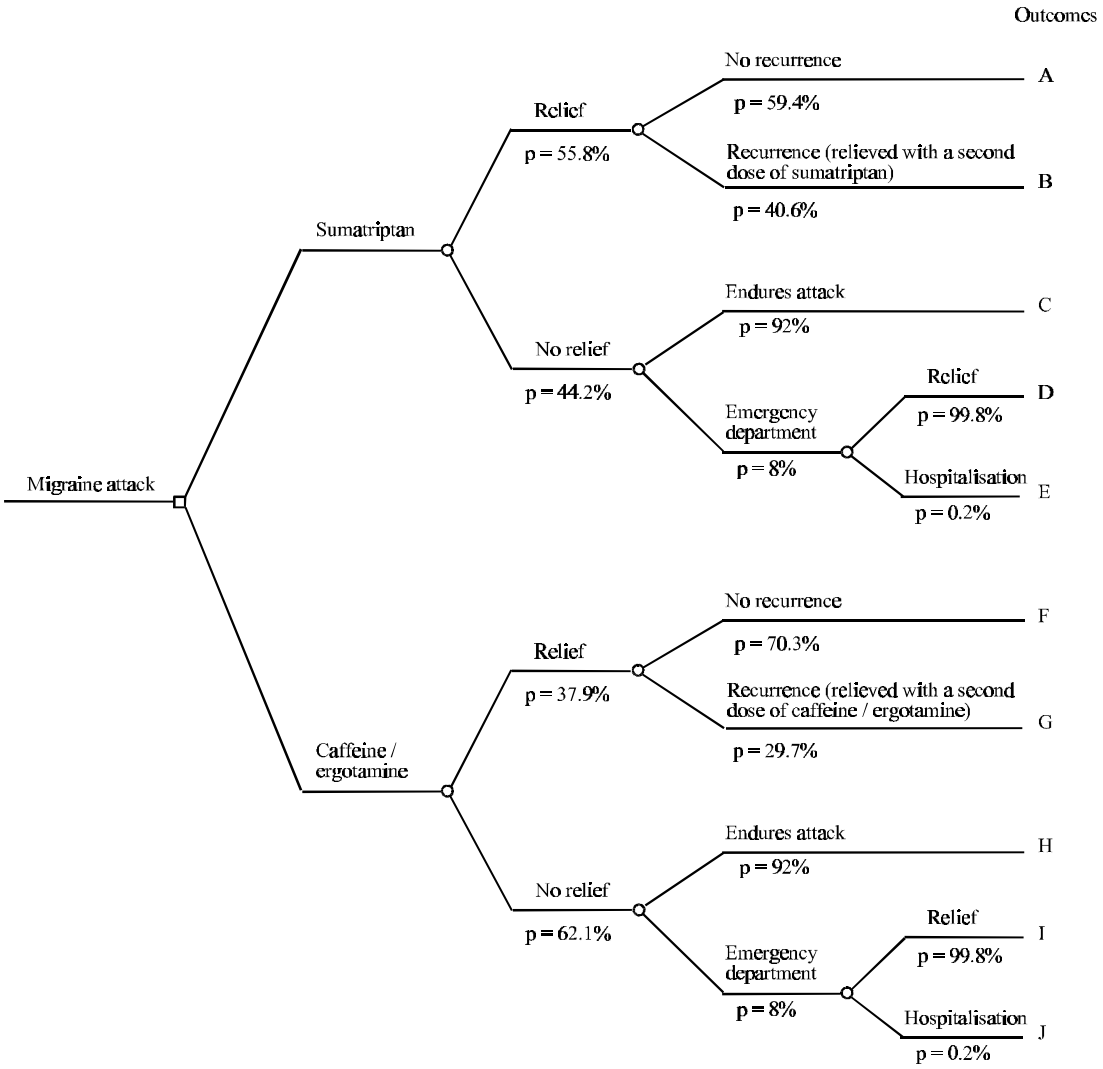


Figure 1. Decision tree (adapted from Evans *et al*, 1997)

The probabilities on each branch (here given as percentages) indicate how many individuals follow that branch, as a proportion of the number reaching the preceding chance node. The total probability for all the branches leaving a chance node must be 1 (or 100%). For each outcome, the cost and effectiveness (in this case given as a utility) can be determined. These are then weighted by the overall probability of the outcomes and summed to provide the expected cost and effectiveness of each option.

Beyond Decision Trees

When a decision tree contains a single decision node, the branches form probability trees. Each such probability tree is then a description of the possible outcomes of a specific policy option. In effect, it provides a simulation model for that policy option.

In the example considered here, the two probability trees have the same essential structure, merely different sets of parameters. Other forms of simulation model may be used in place of probability trees.

Some forms of simulation model may appear naturally at any point in a decision tree; for others, the model represents a single policy option. Different options may be represented by separate models, or by different parameter lists within a single model; the difference may simply be a matter of how the modelling has been done.

Markov Models

One of the best known types of simulation model is the Markov chain. An example is given by Chancellor *et al* (1997), illustrating the progress of HIV infection and AIDS. At any time, each patient is in one of a finite number of "states"; in this case, there are two levels of non-AIDS HIV infection (States A and B) with State C representing AIDS and State D representing death (see Figure 2).

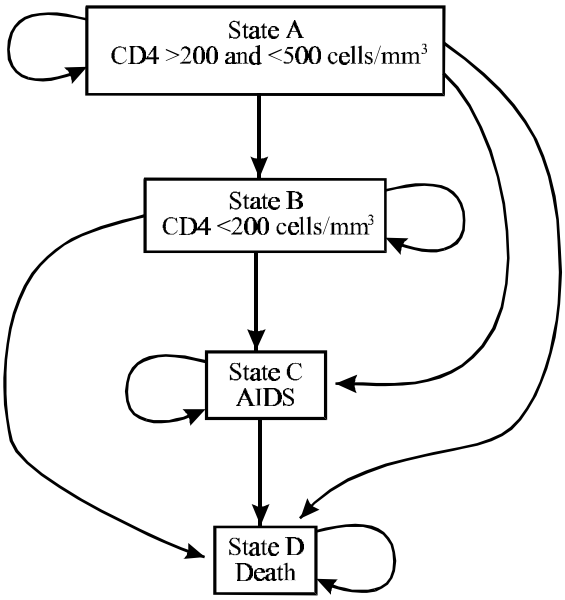


Figure 2. State transition diagram for a Markov model
(adapted from Chancellor *et al*, 1997)

A fixed time cycle is used, in this case of one year. For each of States A, B and C, a patient who is in that state at the start of a year may remain in that state or change to a

different state. State D is called a *sink state*; a patient reaching state D remains there. For each ordered pair of states there is a *transition probability*, which is the conditional probability that a patient will be in the second state at the end of any time cycle, given that the patient was in the first state at the start of the cycle. For any state, the sum of the transition probabilities out of that state must be equal to 1. Note that the transition probability depends only on the state in which the patient is at the start of the cycle; this statement is known as the *Markov assumption*. The Markov assumption does not allow the transition probability to depend either on the time a patient has spent in a given state, or the patient's previous history before entering that state.

For any given policy, the proportion of patients in each state is calculated sequentially for each time cycle over a period of simulated time; costs are accumulated according to the number of patients in a given state in each cycle. Different policies may be tested by changing the costs and transition probabilities.

Stochastic Simulation

For both decision trees and Markov models, the usual approach gives the proportion of all patients reaching each point in the simulation. An alternative approach is to consider the progress of individual patients through the model. Wherever probabilities are used, the output from a (pseudo-)random number generator is used to determine which path is chosen by the individual patient under consideration.

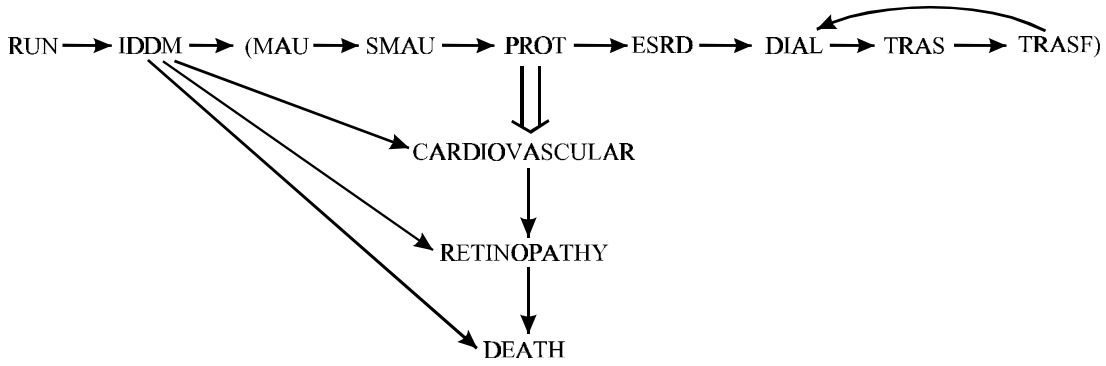
Models built on this basis are known as *stochastic models*; they can be considerably more general than decision trees and Markov models. Where a patient may remain in a given state for a variable length of time, a single random number may be matched against a statistical distribution to determine how long the patient remains in that state; the time spent in a state need not be an exact multiple of a fixed cycle time. Further, patients may carry attributes which affect the probabilities involved; these may include information about the previous progress of the patient through the model.

The term *discrete event simulation* (DES) is used for those models in which changes to the state of the system happen only at events which themselves are deemed to take

no time. For example, a patient who is considered to be ill in the model may progress through a number of stages of illness, each progression occurring at a specific time. DES models are usually, but not necessarily, stochastic.

DES models may consider a single individual at a time, or may allow large numbers of patients to be considered simultaneously. In the latter case, interaction between the patients can be modelled. For example, patients may have to wait until a hospital bed becomes available as a result of a previous patient's treatment having finished.

An example of a DES model is that used by Hart *et al* (1997). The model is designed to assess the cost of insulin-dependent diabetes mellitus (IDDM) in Spain. Figure 3 shows the various states considered in the model.



RUN, initialisation; IDDM, onset of IDDM; MAU, microalbuminuria; SMAU, significant microalbuminuria; PROT, proteinuria; ESRD, endstage renal disease; DIAL, dialysis; TRAS, renal transplant; TRASF, transplant failure

Figure 3. States in a DES model (adapted from Hart *et al*, 1997)

For each patient, a time of onset of IDDM is selected from a distribution based on empirical data. Following onset of IDDM, a patient may progress to microalbuminuria, or may die without such progression. Random numbers are used for each individual to determine which of these happens, and at what time. Similar principles are used for each of the other disease states in the model. Costs are assigned to the individuals according to the states reached, thus producing a total cost for each individual, both with and without discounting. When the model is run, each individual's cost is a sample from the population distribution. The model must be run

for a sufficiently large number of individuals that the average cost estimate may be taken as representative of the population as a whole.

When two or more strategies are to be compared, a stochastic model may simply be run twice, obtaining the average cost and effect for each strategy within suitable confidence intervals and hence an incremental cost-effectiveness ratio (ICER) within its own confidence interval.

LITERATURE REVIEW

Aim and Objectives

The principal aim of the literature review was to establish current practice in the use of modelling techniques in the economic evaluation of health care interventions.

The first specific objective was to identify all papers published in English that:
(a) reported an economic evaluation,
(b) employed a modelling framework, and
(c) were published in the calendar year 1997.

The second objective was to establish which of the modelling techniques were being used most commonly and to what extent basic requirements of 'good practice' in modelling were being observed.

Methods

Relevant papers were identified through the searching of three computerised bibliographic databases: the National Health Service Economic Evaluation Database (NHS EED), MEDLINE and Office of Health Economics / International Federation of Pharmaceutical Manufacturers' Association (OHE-IFPMA) Health Economic Evaluations Database (HEED). Search strategies were devised, using appropriate keywords and index terms, to identify all relevant economic evaluation modelling papers. It was not possible to use precisely the same search strategy across the three

databases because of variation in indexing rules and search engine in the different databases.

The search of the NHS EED first involved identifying all economic evaluation records for the year 1997; a total of 853 papers. In order to identify those studies where a model had been used, the NHS EED structured review of the paper was used. This records whether or not some form of modelling was undertaken. A total of 69 such papers were identified. Due to the rather general nature of MEDLINE indexing, a problem also identified by other authors (Briggs and Gray, 1999), a search strategy using both index terms and keywords was devised. The MEDLINE index terms used for papers identified from the search of NHS EED informed this process. This search revealed 169 potentially relevant papers. The OHE-IFPMA Database has 'modelling' as an index term and this was used to as part of the search strategy that identified a total of 98 such papers published in 1997.

All papers identified from the search of the three databases were retrieved and underwent an initial screen. Retrieved papers were only included in the main review if they reported a full economic evaluation (i.e. they compared at least two different strategies for the management of a group of patients, and the comparison was made in terms of both costs and consequences) and they used one of the modelling techniques described above.

The total number of papers reviewed in the study was 119. Figure 4 identifies the bibliographic database from which each paper was identified.

The review process involved each of the 119 papers being read by at least one of the authors who completed a checklist of questions. In order to establish consistency in the completion of the checklist, a sample of 15 papers were reviewed by all three authors and the responses compared. The checklist had questions relating to various aspects of the economic evaluation itself (type of study, effectiveness measures used, price year and discount rate), questions specific to the modelling component (type of model, diagrammatic presentation used, parameter list reported, sources for values indicated and software used), and questions on the sensitivity analysis (type of sensitivity analysis, basis for defining ranges).

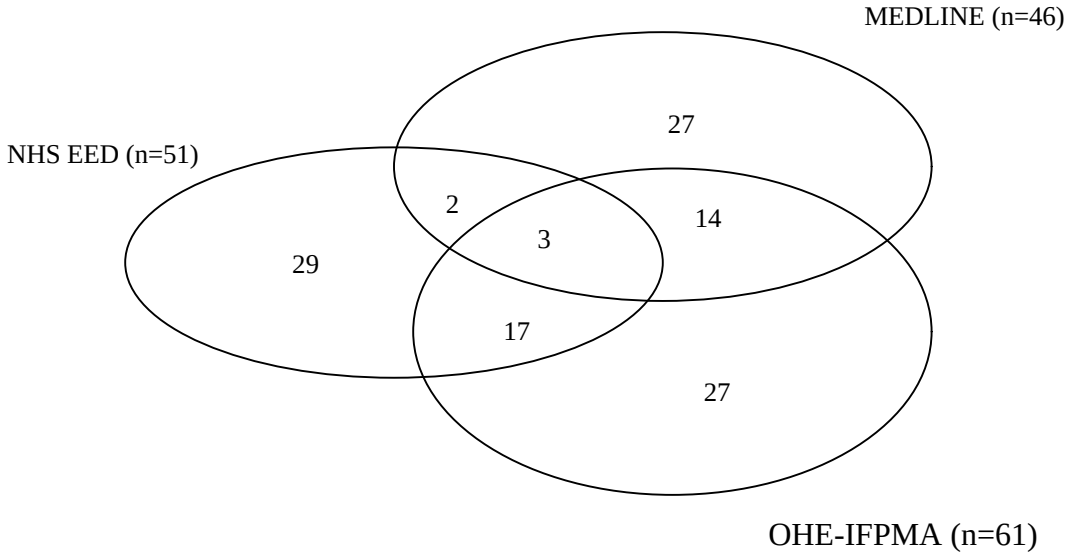


Figure 4. Identification sources for the 119 reviewed economic evaluations

Results

Table 1 reports the descriptive details for the reviewed cohort of studies. The vast majority of studies used either a cost-effectiveness or cost-utility framework, a finding consistent with that of the more general review of economic evaluations reported by Pritchard (1998). The most commonly employed modelling technique was the decision tree, and whilst a large number of studies used a Markov model, only two studies modelled using stochastic simulation.

In terms of general 'good practice' in modelling, 87% of papers provided a detailed parameter list and provided an indication of the sources for values of those parameters. However, only a minority of papers reported the software package on which the model was constructed and run. If other researchers are to be able to replicate the reported analysis, for example as part of a quality assurance process, then such information is clearly important.

As part of the review process possible case studies were identified. The next section of the paper reports three such case studies, each demonstrating examples of good practice of Decision Tree, Markov and Stochastic modelling techniques.

Study characteristics		Number of papers (% of all 119 papers)
Type of economic evaluation[1]	CCA	18 (15%)
	CMA	7 (6%)
	CEA	71 (60%)
	CUA	45 (38%)
	CBA	2 (2%)
Modelling technique[2]	Decision tree	76 (64%)
	Markov	43 (36%)
	Stochastic simulation	2 (2%)
Model details	Diagram provided	96 (81%)
	Parameter list provided	104 (87%)
	Source for values stated	106 (89%)
	Software reported	47 (40%)
Sensitivity analysis	Reported	118 (99%)
Type of sensitivity analysis	One-way	105 (88%)
	Multi-way	33 (28%)
	Extreme scenario	14 (12%)
	Threshold	40 (34%)
	Probabilistic	0

[1] 12 papers used two economic evaluation types

[2] 2 papers reported both a decision tree and a Markov model

Table 1: Descriptive details of the 119 reviewed studies

CASE STUDIES

Case Study 1 – Decision Tree

Kalish *et al* (1997) describe a decision tree model concerned with one aspect of the treatment of dyspepsia, namely the conversion of histamine$_2$ antagonists to over-the-counter use in the USA. Dyspepsia is a condition that can arise from a number of different causes, and whose symptoms can be treated by various classes of drugs, whose effectiveness depends on the underlying cause of the dyspepsia. Among these

drugs are histamine$_2$ antagonists (H_2As), which first became available in the 1970s, and which are far more effective than antacids at controlling dyspepsia. The decision tree has two branches, according to whether H_2As are available over the counter or not. Since the two branches have the same structure, it is sufficient to diagram one of them (see Figure 5).

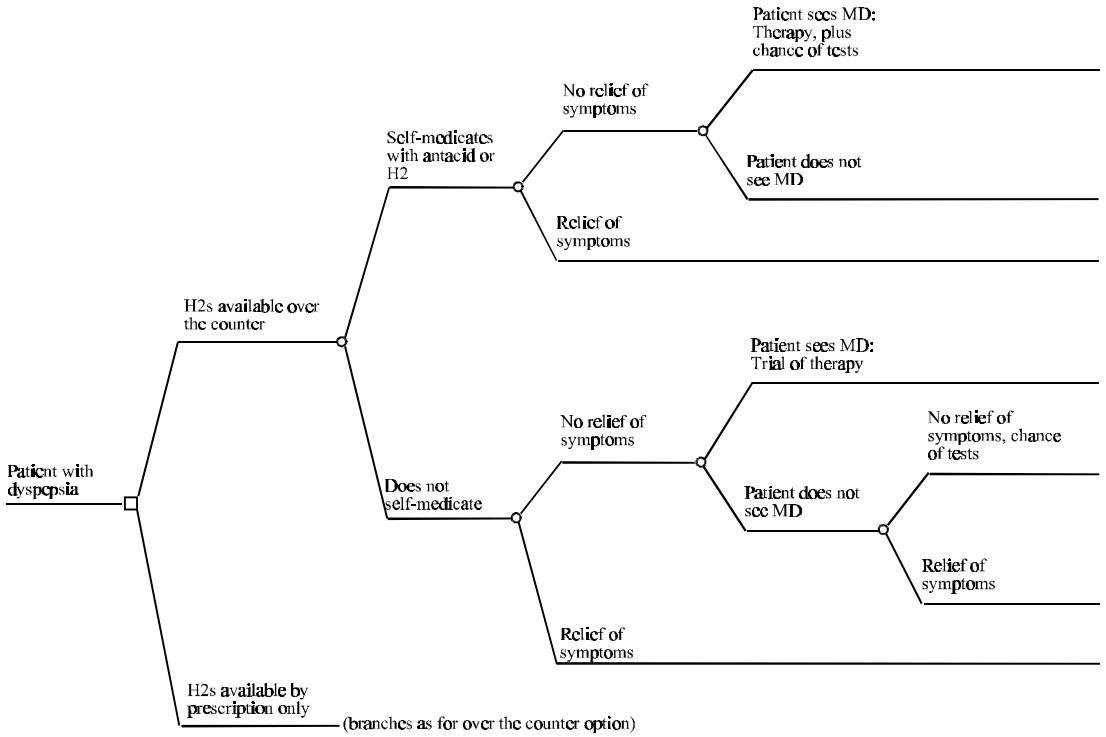


Figure 5. Decision tree for histamine$_2$ antagonists (adapted from Kalish *et al* 1997)

Although dyspepsia is a chronic condition, the long-term consequences may be represented by average outcomes for the purpose of this model. Since the outcomes are the same in both policies, a cost-minimisation analysis was used.

It should be noted that the population of dyspeptic patients is far from homogeneous, but that this is not a problem in the decision-tree approach. In fact, Kalish *et al* carried out separate analyses for each of the main causes of dyspepsia, and then reported overall results in the form of a weighted average. Base-case results were reported for each underlying cause of dyspepsia, including both societal costs and costs borne by health maintenance organisations. From the societal perspective, there would be a very small extra cost from making H_2As available over the counter ($204 rather than $203 per episode of dyspepsia) although this average conceals variation in both

directions for the different causes of dyspepsia. Note that for the base case it would have been perfectly possible to include suitably weighted average probabilities directly on the tree; there is no assumption of homogeneity involved. However, if non-homogeneous populations are represented on a decision tree, then care must be taken in adapting the results to other populations.

Of course there is uncertainty in the parameters of the model. Kalish *et al* carried out a number of one-way sensitivity analyses for patients with non-ulcer dyspepsia (the most frequent of the causes). Additionally for this group they carried out a two-way sensitivity analysis, simultaneously varying cost and efficacy of over-the-counter H_2As. The results are shown in the form of a graph showing for which combinations of parameter values each policy is cheaper from the societal perspective.

In this case, there are exactly two branches at each node; in principle, there can be any number, but it is always possible to introduce more chance nodes to reduce the number of branches at each node to two. For example, a chance node with three branches “no complications”, “mild complications” and “severe complications” may be replaced by an initial chance node with the two branches “no complications” and “complications”, the latter branch then reaching a further chance node with branches “mild” and “severe”. See Figure 6. An advantage of only using two branches at any node is that if one probability is changed, there is only one way of changing the probability on the other branch. Detsky *et al* (1997) recommend that only two branches should be allowed at any decision node.

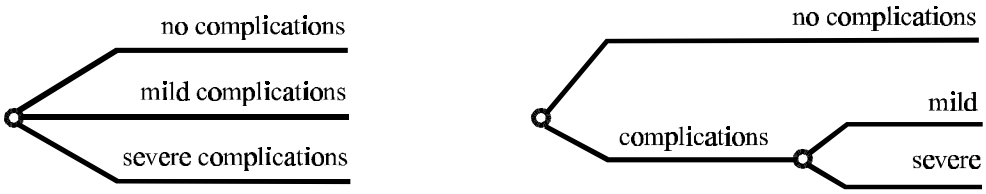


Figure 6. Different ways of showing three possible outcomes

Case Study 2 – Markov Model

Inadomi and Sonnenberg (1997) consider spontaneous bacterial peritonitis (SBP). This is a severe complication which occurs frequently in cirrhotic patients with ascites. Any occurrence of SBP requires inpatient treatment lasting five days; accordingly the model operates to a five-day time-cycle. The model distinguishes seven states as shown in Figure 7.

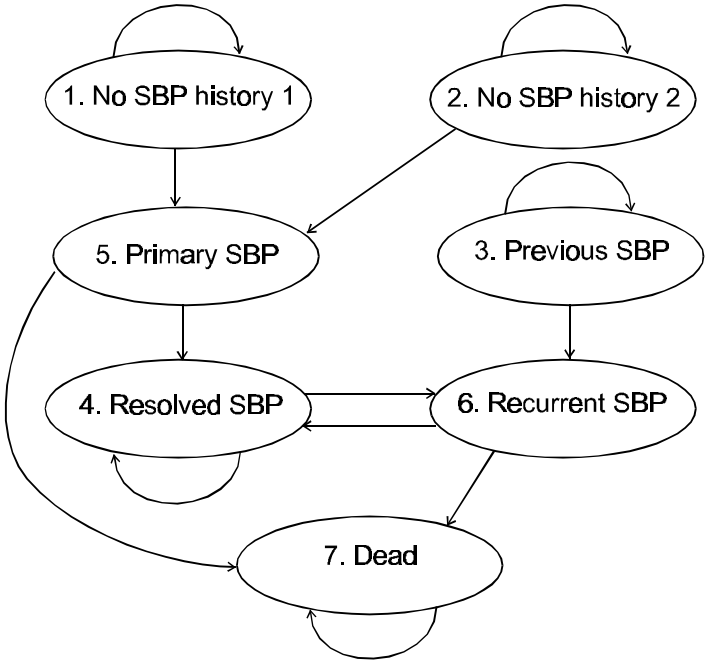


Figure 7. Transition diagram for SBP model
(adapted from Inadomi and Sonnenberg, 1997)

In this model, states 1 to 4 are states in which the patient is in the underlying chronic condition. States 1 to 3 are entry states; for each analysis, the model was run separately with a cohort of patients all starting in the same state. States 1 and 2 are distinguished by the ascitic fluid total protein concentration. Patients with a low protein concentration are in state 2, and have a higher risk of SBP than those in state 1. States 3 and 4 are distinguished so that the proportion of patients starting in state 3 who go through the year without an episode of SBP can be seen in the model. States 5 and 6 represent the episodes of SBP; they are distinguished for the purpose of results. Treatment of SBP is “kill or cure”, thus transition from state 5 or 6 must always be to

another state: state 4 if the treatment is successful, state 7 (death) if not. Note that there are no transitions to state 7 from any of states 1 to 4. Mortality from SBP is so high (31 per cent per episode in the base case) that death from other causes is negligible.

In this model, there are strong homogeneity assumptions. The mortality is assumed to be the same from every case of SBP, although primary SBP could have been given a different mortality. Similarly, risk of recurrence is assumed to be the same for all patients with a previous history of SBP. However, a different risk of recurrence for patients with no history is allowed for by using a separate state for such patients. The fact that these patients themselves do not form a homogeneous group is then taken into account by splitting them into two separate states. For any individual, the time spent between episodes of SBP in the model follows a negative exponential distribution; this will always be the case if the risk is assumed constant over time.

The model is used to compare two strategies. Patients with cirrhosis and ascites may or may not receive prophylactic antibiotics. Those who receive antibiotics have a lower risk of contracting SBP, but incur a small cost for the antibiotics. The model shows that the strategy of using antibiotics is cost-saving as well as improving outcomes, in all three patient groups considered (entry in state 1, 2 or 3). Sensitivity analysis used shows that these results are robust to substantial variation.

A Markov model is necessary here as a decision tree would be infeasibly large. While the Markov assumptions are almost never fully satisfied, it must be remembered that any model is a simplification of reality; if the assumptions are close to being satisfied, and, as in this case, the conclusion is robust to variation in the parameters, the conclusions drawn from a Markov model are likely to be reasonable.

In any Markov model, the choice of time cycle is important. Here there is a natural choice of five days. A longer time cycle would prevent separation of time undergoing treatment from other time, while a shorter time cycle would require undergoing treatment to be modelled as a series of linked states, with transition to the “Resolved SBP” state only possible from the last state of treatment.

Case Study 3 – Stochastic Simulation Model

Urban *et al* (1997) describe a model to identify an efficient protocol for ovarian cancer screening. Ovarian cancer is taken as going through four separate stages. The length of time spent in the first stage is taken to follow a lognormal distribution, with the other stages in fixed proportion to the first stage. Distributions are applied for age and stage of disease at clinical detection, in line with known data on the application of a particular strategy.

A cohort of simulated patients is then run through the model, which applies from age 50 to 80. For each patient, it is first determined whether she will contract the disease during the testing period; if so, an age at clinical detection is sampled from an appropriate distribution, as is the stage at which detection occurs. From this, the patient's history is worked backwards as well as forwards. The effect of different screening strategies can then be applied, and the difference in costs and benefits assessed. The process is repeated for a sufficiently large number of patients, to give estimates of the difference in costs and benefits between different strategies, and hence incremental cost-effectiveness ratios. The model indicates that a multimodal strategy is preferable to the use of a single screening method; the results are robust to a range of assumptions.

This model does not conform to the strict definition of a Discrete Event Simulation model, because it does not handle events in time order. The benefit of the approach used is that the results from the same patient under different strategies can be treated as paired data. This allows the difference in costs or effects between strategies to be estimated within smaller confidence intervals for a given simulation sample size than would be the case if the data had to be treated as unpaired.

DISCUSSION

The results from any model are only as good as the data used in its construction. Ideally, sensitivity analysis should cover all possibilities reasonably consistent with existing data. In this way, sensitivity analysis can be used to pinpoint key uncertainties, and to identify where it is most useful to collect additional data.

Generally, simplicity in models is an advantage (Ward, 1989). Here, simplicity essentially relates to the size of the model, not to the modelling technique used. The simplest discrete event simulation models are simpler than the most complex decision trees. Simpler models are usually easier to understand than complex models, and thus easier to validate. However, the widely-held belief that complex models require more data than simple models needs to be challenged. Moving from a complex model to a simpler model is effectively fixing one or more parameters of the model. This can only be justified if either the results are robust to variations in the parameters in question, or if the data is of such good quality that the fixed values given to these parameters are known to be accurate.

Many successful modelling exercises have been undertaken in the field of healthcare economic evaluation, particularly in cases that are well described by simple models. More complex areas require models that respect the complexity, and techniques which can handle that complexity are ready and waiting to be adopted more widely by the health economics community. Such techniques may require more skill in effective model construction, but the answer to this is to acquire or import the skills, rather than risk giving inappropriate advice as a result of an inadequate model.

A rough analogy may be drawn with the field of statistics: non-parametric tests are preferred when the distributional assumptions inherent in parametric tests are not satisfied sufficiently well to allow parametric tests to be used. Similarly, stochastic models such as Discrete Event Simulation models are to be preferred when the assumptions required by a Markov model are not sustainable. There is a price to pay in increased computational requirements, but this is well worth paying if the results obtained are more reliable.

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