Modelling in the economic evaluation of health care: selecting the appropriate approach

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***Objectives*: To provide an overview of alternative approaches to modelling in economic evaluation, and to highlight situations where each of the alternative modelling techniques should be employed.**

***Methods*: A review of the available approaches to modelling in the economic evaluation of health care interventions with a leading discussion of examples of published studies leading to guidance in the selection of an appropriate approach in different circumstances.**

***Results*: The main approaches to modelling used in economic evaluations in health care are decision trees, Markov models and individual sampling models. These methods assume independence of individuals within the model. Where interaction between individuals is important, other methods such as discrete-event simulation or system dynamics are preferable.**

***Conclusions*: The paper highlights the crucial question to be answered when selecting the approach to modelling: can the individuals being simulated in the model be regarded as independent? This issue is very commonly not recognised by analysts but is fundamental to the appropriate application of modelling in economic evaluation.**

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Introduction

Economic analyses are increasingly used to inform health policy decisions. This can be seen in the UK, for example, in the form of technology appraisal determinations by the National Institute for Clinical Excellence (NICE), which represent national policy decisions on whether appraised health technologies are to be available through the public health care system. All technology appraisal decisions by NICE are informed by a commissioned economic analysis undertaken by an independent academic review team.[1] Such analyses almost always use a decision analytic modelling approach since it 'offers a framework that can be used to achieve some of the key tasks in reimbursement decisions'.[2] More generally, mathematical modelling approaches are now common practice in economic evaluations of health care technologies.[3]

In its broadest sense, the term 'modelling' can be taken to include anything beyond the direct application of observed data. However, in the context of economic evaluation, the term is generally understood to refer to studies that 'employ an analytic methodology to account for events that occur over time'.[4] This definition excludes purely statistical models such as regression models and meta-analyses. The types of models used in economic evaluation allow the analyst to combine information from a variety of sources and to assess the policy implications. The purpose of these models is to synthesise data for the purpose of making a decision. This sets them apart from statistical models.

As Buxton et al[5] indicate, the economic analyst is commonly faced with a number of circumstances where he may wish to employ a mathematical model. These may be described as:

- The 'temporal extrapolation' of cost and effectiveness parameters beyond the data observed in a clinical trial.
- The linking of intermediate clinical end-points to final health outcomes.
- The 'contextual extrapolation' of the results obtained in one clinical setting to other, possibly quite different, settings.
- The analysis of head-to-head comparisons of alternative competing interventions where such direct comparisons have not been made in clinical trials.
- The attempt to inform resource allocation policy decisions in the absence of so-called 'hard data'.

Whilst there is now a general acceptance that in many situations modelling is a necessary requirement, concerns have been expressed about the appropriateness and validity of the modelling undertaken.[6,7] The focus for current debate in this area should, therefore, be the identification of best modelling practice in economic evaluation. This represents a very broad topic and is an issue that has been explored by several

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authors.[8–11] Sculpher et al[11] suggest a framework for the assessment of quality in decision analytic cost-effectiveness models which includes: model structure; time horizon; data identification and incorporation; internal consistency (i.e. model testing and checking); and external consistency (i.e. consistency between model predictions and primary research).

This paper addresses the first of these issues, namely the selection of an appropriate modelling approach for the clinical question being considered. Earlier papers have provided introductions to particular modelling approaches, notably Markov models,[8,12] and others have explored specific methodological issues in modelling, such as the importance of data sources.[13,14] The purpose of this paper is to provide an overview of alternative approaches to modelling in economic evaluation, using examples of published studies to illustrate the working of the various methods, and to highlight situations where each of the alternative modelling techniques should be employed.

There are two quite distinct aspects of model-based economic evaluation. First, it is necessary to produce the mean estimate of cost-effectiveness (or other outcome measures) for a given set of parameters. Second is the issue of exploring the effects of uncertainty in the model inputs. The first issue is concerned with model structure (or type of model), whereas the second relates to sensitivity analysis. A common feature of all health care modelling is the need for extensive sensitivity analysis to handle the inevitable uncertainties. In principle, decisions on the type of model and the approach to sensitivity analysis are completely independent of one another, although in practice there may be limitations imposed by the available computing power and time.

Methods for sensitivity analysis have been well described elsewhere[15] and are much the same for all types of model. Therefore, sensitivity analysis is not the focus of this paper. However, issues relating to uncertainty are discussed later.

Models based on independent individuals

The first issue to be addressed in selecting a model type is whether the individuals in the model can be regarded as independent. Interaction between individuals can arise from causes such as infection or limitations on the rate at which treatments can be given. In practice, the majority of modelling in economic evaluation of health care does not involve interaction between individuals. The most common types of model that do not involve interaction are decision trees and Markov models, although some other types are used occasionally. This section describes the working of these types of model in more detail. Model types involving interaction between individuals are discussed later.

Decision trees

The decision tree has the simplest and most familiar structure. All possible patient pathways are shown explicitly on decision trees, with associated probabilities and outcome measures. In general, if the time frame is short and if the mortality of patients does not differ across strategies, a simple decision tree is usually appropriate. A good example of such a model is given by Evans et al[16] (see Figure 1). This is designed to compare oral sumatriptan with oral caffeine/ergotamine as treatments for a migraine attack. Any individual suffering a migraine attack follows a path from left to right, finishing at one of the outcomes A–J. The outcomes follow the full course of a single attack, which is taken to be limited in duration. 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'.

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

In principle, any decision problem satisfying the assumption of independence between patients can be represented by a decision tree. It is usual to construct such trees with a single decision node at the root of the tree, which then becomes a set of linked probability trees, one for each policy option.

In practice, however, there is a limit to the manageable size of a probability tree. Consider, for example, a situation where the only issue of interest is the survival time after some treatment. To avoid an infinite number of branches in the tree, it is necessary to consider survival times as belonging to a finite number of ranges. For example, Figure 2 shows a tree covering a period of one year, where survival is considered quarterly. Given the repetitive structure of the tree, it may be redrawn as shown in Figure 3. The structure implied by Figure 3 is a simple example of a Markov model.

Markov models

Markov models are increasingly being used in economic evaluation. Their main benefit is the easy representation of recurrent events, but they do not allow for interaction between individuals. A good example of how a Markov model works is given by Chancellor et al,[17] illustrating the progress of HIV infection and AIDS, in accordance with the state of medical knowledge when the paper was written (see Figure 4). 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.

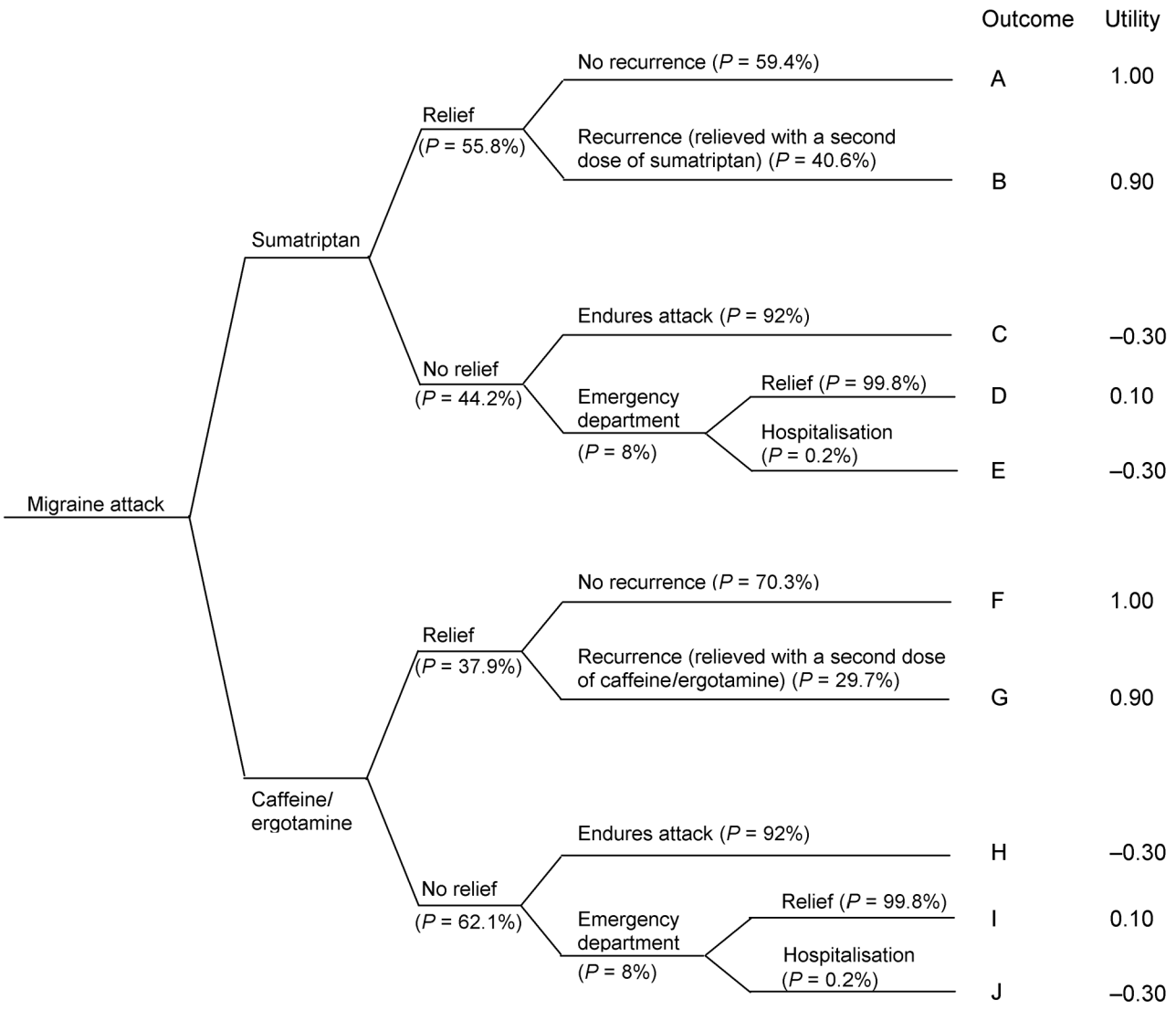

Figure 1 Decision tree. Adapted from Figure 1 in Ref. 16.

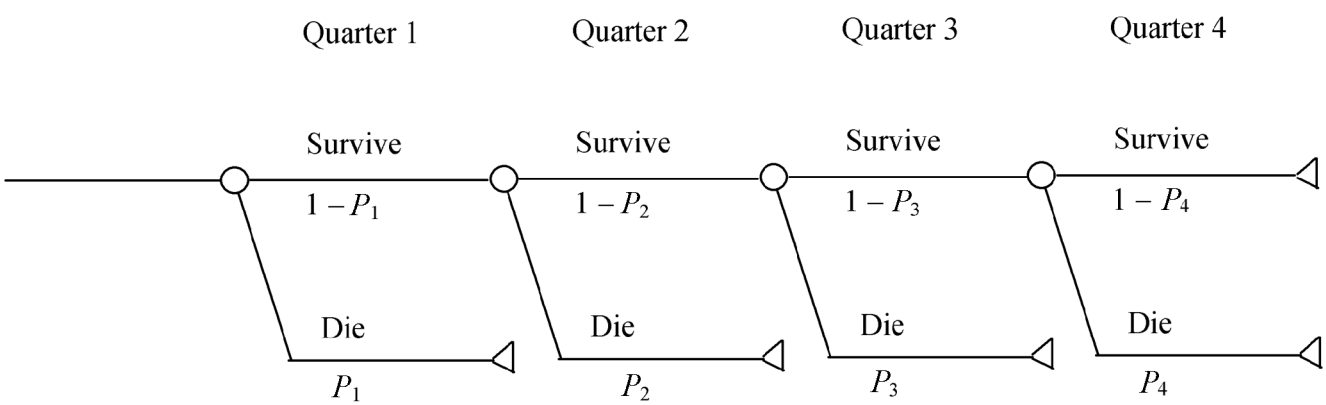

Figure 2 Survival tree.

A fixed time cycle is used, in this case 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 (or an absorbing 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

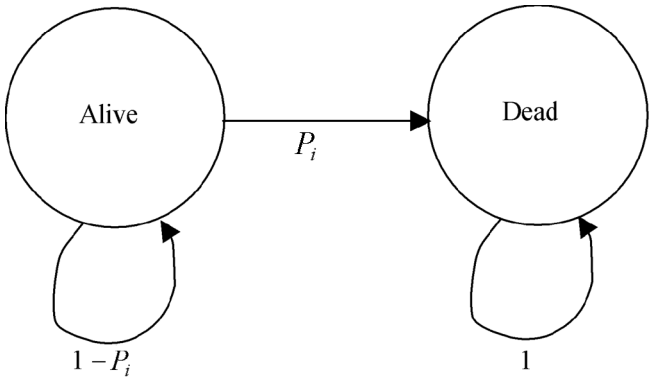

Figure 3 Markov process equivalent of survival tree.

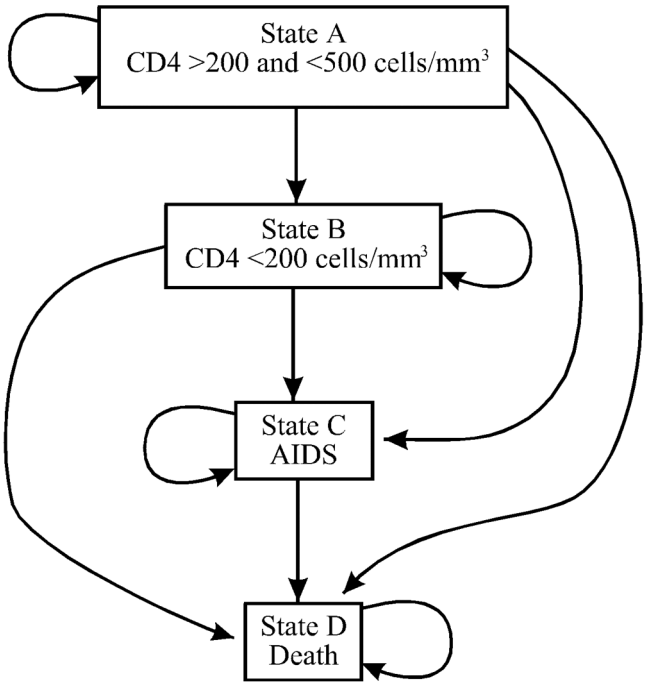

Figure 4 State transition diagram for a Markov model. Adapted from Figure 1 in Ref. 17.

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. Markov models thus assume that patients in a given state can be treated as homogeneous groups. This homogeneity assumption is inherent in Markov models. In its most general form, a Markov process does allow the probabilities to vary with time; technically, the term 'Markov chain' is used when the transition probabilities remain the same for each cycle. In practice, many Markov models are thus Markov chains.

For any given policy, the proportion of patients in each state can be calculated sequentially for each time cycle over a period of simulated time. Costs are then 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.

Use of Monte Carlo simulation

For both decision trees and Markov models, the usual approach works in terms of identifying the proportions of the total number of patients in particular states, at various points in the model. 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 sequence of health states is followed over time by the individual patient under consideration.

When Monte Carlo simulation is used, the result of the simulation represents a sample from the population of all possible outcomes in the model. Results from the simulation are thus subject to variation resulting directly from this sampling approach. Following Briggs,[18] we recommend the use of phrases such as 'quasi-standard errors' to describe such variation. Quasi-standard errors have nothing to do with uncertainty in the input parameters to the model, and can be reduced by increasing the number of virtual patients on whom the model is run. They should be quoted simply as a means of confirming that enough replications have been made.

Scope of Monte Carlo simulation models versus Markov models

Models designed to use Monte Carlo simulation can accommodate a richer structure than decision trees and Markov models whilst remaining manageable in size. For example, a well-known method of overcoming the homogeneity assumptions inherent in Markov models is to increase the number of states in the model. The same effect can be achieved with a Monte Carlo simulation by attaching attributes to the individuals within a model. The transition probabilities can be made to vary according to these attributes in any way that is desired. Furthermore, attributes can be updated while the model is running. Consider, for example, the model of a recurrent illness shown (as a Markov model) in Figure 5.

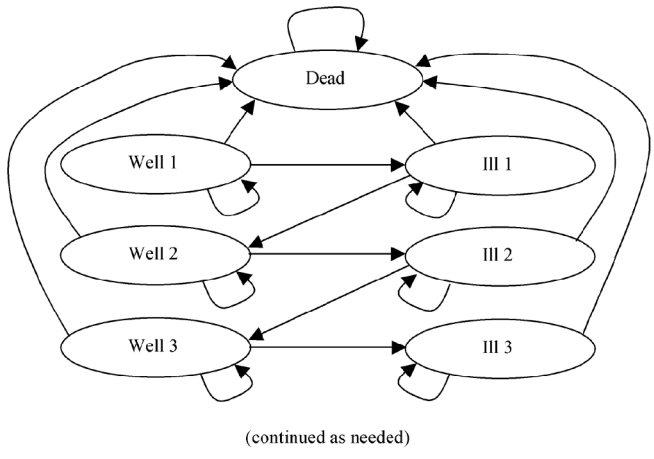

Figure 5 Markov model for a recurrent illness.

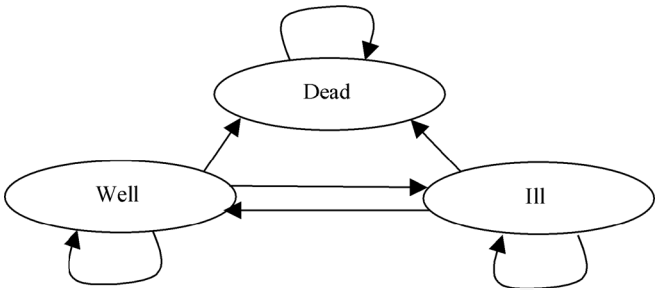

Figure 6 States required for recurrent illness model using Monte Carlo simulation.

Here the probability of becoming ill in any time period depends on the number of times the patient has previously been ill. In principle, the number of states required is unlimited, although in practice it is necessary to stop at some maximum. By contrast, the Monte Carlo simulation version requires only the three states shown in Figure 6.

The transition probabilities can be allowed to vary according to the time the patient has been in a particular state, or according to the total time for which the patient has been ill, simply by recording such times as attributes. To do so without Monte Carlo simulation would require a further increase in the number of states in the model.

Another limitation of Markov models is the need to operate with cycles of fixed length. Using Monte Carlo simulation, where a patient may remain in a given state for a variable length of time, a single random number may be matched against a probability 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-length cycle.

An example of a model that tracks individuals through Monte Carlo simulation is that used by Hart et al.[19] The model is designed to assess the cost of insulin-dependent diabetes mellitus (IDDM) in Spain. Figure 7 shows the various states considered in the model.

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.

Clarifying terminology

There is considerable variation in the terminology applied by authors to describe modelling types. For example, consider the papers by Warner et al[20] and Paltiel et al.[21] The modelling approach adopted and the form of simulation used are virtually identical in both cases: time is advanced in fixed steps, and individuals are tracked through the model using Monte Carlo simulation techniques. However, Warner et al describe their model as a discrete-event simulation (DES), whereas Paltiel et al describe their model as a state-transition model. We believe that a new term is needed to describe models in which the ability to track individuals is an essential part of the model structure, but in which only one individual is modelled at a time. We propose the use of the term 'individual sampling models'.

Another problem of terminology arises when the same term is used with different meanings. For example, the term 'stochastic simulation' is used in management science to mean DES where random numbers are used to determine individual outcomes (see, for example, Pidd[22]). The same term is often used in health economics to mean probabilistic sensitivity analysis. We urge authors to avoid using the term 'stochastic simulation' when probabilistic sensitivity analysis is being referred to.

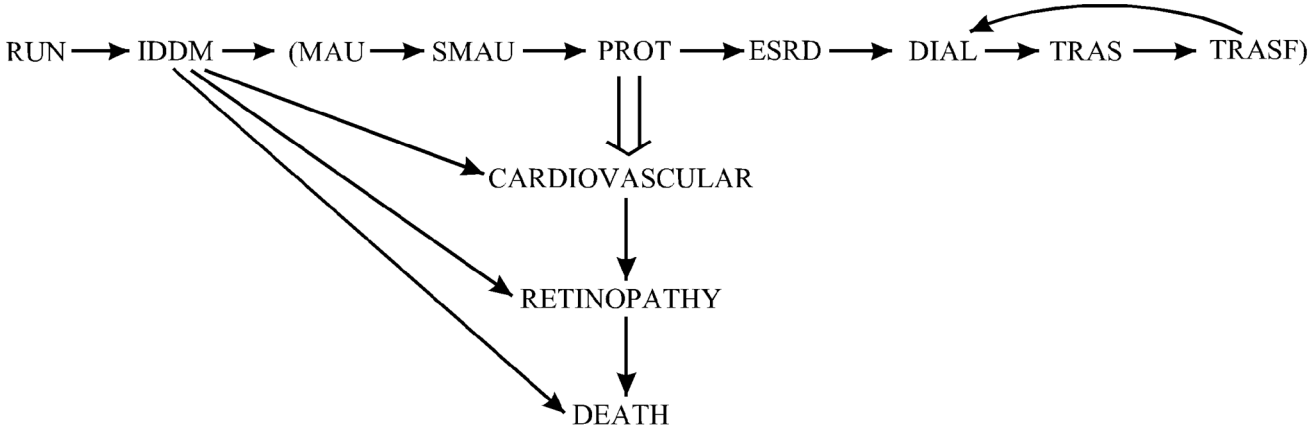

Figure 7 States in a discrete-event simulation model. RUN, initialisation; IDDM, onset of insulin-dependent diabetes mellitus; MAU, microalbuminuria; SMAU, significant microalbuminuria; PROT, proteinuria; ESRD, end-stage renal disease; DIAL, dialysis; TRAS, renal transplant; TRASF, transplant failure. Adapted from Figure 2 in Ref. 19.

Models that account for interaction between individuals

Interaction between individuals needs to be taken into account in two main circumstances: when modelling infectious diseases, where the risk of an individual catching the disease depends on how many other people already have it; and when constraints on resources mean that the choice of treatment for one patient affects what can be given to another.

Where interaction is a significant issue in modelling, methods such as DES and system dynamics (SD) are required. DES works at an individual level, whereas SD works at an aggregated level. DES models allow full representation of each individual's history and the interaction between specific individuals. The price that must be paid for the ability to model in such detail is that these models require specialist software or programming skill to construct, and running times are very much longer than for other types of model. SD (and similar) models also allow for some forms of interaction between individuals but, as with Markov models, although they can be computed quickly, they can take only limited account of individuals' histories. See, for example, Pidd[22] for a fuller description of DES and SD models.

SD and DES approaches have been applied appropriately in the context of screening for infectious diseases.[23–25] In the particular case of screening for *Chlamydia trachomatis*, these more sophisticated dynamic approaches allowed for the inclusion of re-infection rates and partner notification, which challenged the cost-effectiveness results reported in earlier papers.

When modelling a situation in which patients have to queue for treatment, the modeller must decide whether to include the queuing as a part of the model. If queuing time is very short compared to other time scales in the model, it may be appropriate to omit the queuing. If queuing time has to be modelled, two approaches are possible. If the patients in the model form a queue in their own right (e.g. a waiting list to see a specialist), then it is likely that different treatment strategies will affect the queuing time, in which case the interaction between patients represented by the queue will be an important part of the model. If, however, the patients in the model form a small part of a larger queue (also containing patients with other conditions), it may be possible to represent individual patients' waiting times as following a statistical distribution. This approach avoids the need to handle interaction between patients. A good example of a model involving queuing is the study reported by Ratcliffe et al,[26] who investigated the cost-effectiveness of liver transplant surgery using a DES model.

Handling uncertainty

It is important that proper regard be given to any uncertainty in the modelling of a system if the results are to be used for decision-making. In the special case where the model structure is known to be adequate, and uncertainty about the model parameters can be objectively represented through a joint probability distribution, the effect of uncertainty can be measured using probabilistic sensitivity analysis. Claxton[27] has argued that the mean values estimated from such analysis should be used as the basis for decisions relating to today's patient, and that the question of whether to conduct further research is an entirely separate one. His assertion that the decision relating to today's patient cannot be deferred is self-evidently true. However, two strong assumptions need to be true if such decision-making is to lead to optimal decisions over time. First, policy must be fully reversible. Second, the expected values calculated from the model must be unbiased estimates of the expected costs and benefits of applying the treatment in practice, or at least of the difference between expected costs and benefits of the alternatives up for consideration. If a system is oversimplified in order to allow a probabilistic analysis to be carried out, it is not possible to have confidence in the results of such analysis.

On the other hand, probabilistic sensitivity analysis may not be necessary to guide a decision. If a correctly specified model gives a policy recommendation that is robust to extreme changes in parameter values, then the decision can be made with confidence and without the need to estimate the mean costs and benefits of the alternative that is not chosen. In such cases, there is no need to undergo the considerable effort required to produce a joint distribution for model parameters which properly reflects current uncertainty.

Issues of computational feasibility

Even with the computing power available in the early years of the 21st century, the time taken to run a full DES can be appreciable. The problem is made worse by the need to run a sufficient number of replications with the same parameter set to ensure that the results are a fair reflection of the population mean for that parameter set. If there is substantial uncertainty in the input parameters, it may not be possible to perform a full probabilistic sensitivity analysis using a DES model. However, this does not mean that DES models should be abandoned in favour of simpler models which omit important features of the system being modelled. There is a real trade-off in directing limited analytic resources between correct specification of the model structure and precise specification of the parameter distributions if probabilistic analysis is to avoid misleading answers. Where effort is best directed in a particular case is an empirical issue and should be decided case by case. In cases where there is significant interaction between individuals and a need to work at an individual level, a DES approach is the only way to represent the system adequately. In such cases, it is likely that any estimate from a DES model will be closer to 'the truth' than the mean estimate from a full probabilistic sensitivity analysis on an inappropriate model.

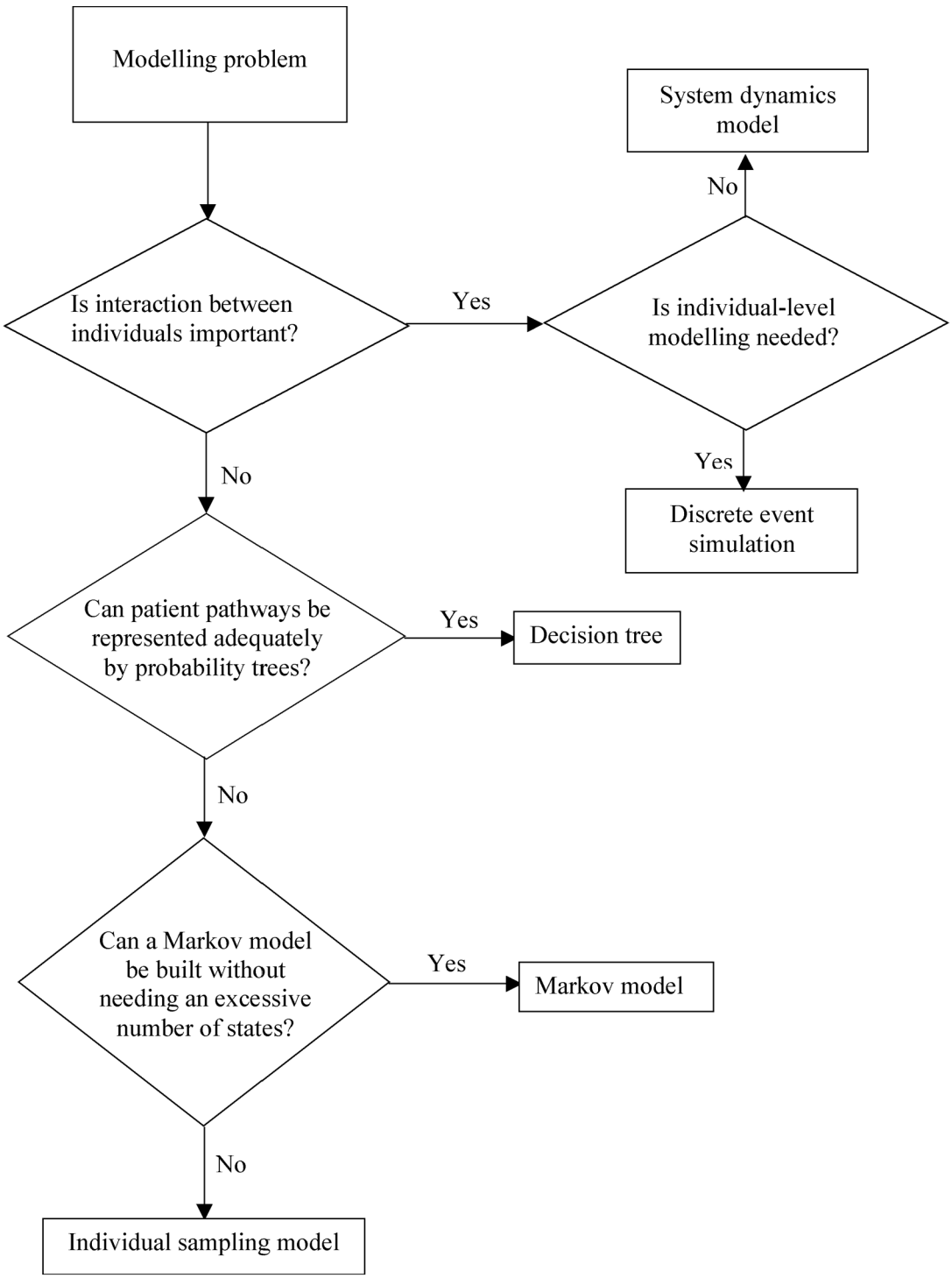

Figure 8 Selecting an appropriate model type.

Selecting the appropriate model type

The selection of the appropriate model type for the evaluation of a health care intervention should be made along the lines shown in Figure 8. As indicated above, the key initial consideration is whether the individuals in the model may be regarded as independent. Where interaction is not thought to be an important issue then the choice is between decision trees, Markov models or individual sampling models. Where interaction is a significant issue in modelling, methods such as DES and SD are required.

Simplicity versus complexity in modelling

Generally, simplicity in models is an advantage.[28] Here, simplicity essentially relates to the size of the model, not to the modelling technique used. The simplest DES 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 necessarily require more data than simple models needs to be challenged. Consider, for example, a model with three states – WELL, ILL, and DEAD – and fixed transition probabilities between the states. If the model is replaced by a two-state model, combining the states WELL and ILL into a single state ALIVE, then the transition probability from ALIVE to DEAD is a weighted average of the transition probabilities from WELL and ILL to DEAD in the three-state model. Since the proportions in the states WELL and ILL can be expected to vary over time, a fixed transition probability from ALIVE to DEAD will no longer be appropriate. Determining how this transition probability varies with time requires the same data as the three-state model.

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 the data are of such good quality that the fixed values given to these parameters are known to be accurate. In this sense, the decision to simplify a model is an empirical issue, the answer to which is unknown without undertaking a more complex model.

Conclusions

Many successful modelling exercises have been undertaken in the field of health care economic evaluation, particularly in cases that are well described by simple models. More complex areas require models that respect complexity. Techniques that 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.

This paper has provided an overview of alternative approaches to modelling in the economic evaluation of health care interventions, and guidelines for good practice in the selection of a model. This should be seen as complementary to the work of others who have suggested broader frameworks for assessing the quality of models,[11] and guidelines for considering the quality of clinical and economic evidence.[29,30] This paper has highlighted the crucial question to be answered when selecting the model type: can the individuals being simulated in the model be regarded as independent? This issue is very commonly not recognised by analysts but is fundamental to the appropriate application of modelling in economic evaluation.

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 DES 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 likely to be well worth paying if the results obtained are more reliable.

In cases where the available data on costs and effects are limited, modelling presents the opportunity for economic analyses still to be conducted. In these circumstances, sensitivity analyses are of critical importance so that the robustness of the results can be extensively explored. Sensitivity analysis should cover all of the possibilities reasonably consistent with existing data. In this way, key uncertainties can be pinpointed, providing a guide to the most useful additional data collection. The model can then be used as a basis for a formal analysis of the value of additional information of the type described by Claxton.[27]

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