NICE DSU TECHNICAL SUPPORT DOCUMENT 15: COST-EFFECTIVENESS MODELLING USING PATIENT-LEVEL SIMULATION

REPORT BY THE DECISION SUPPORT UNIT

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ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) is a collaboration between the Universities of Sheffield, York and Leicester. We also have members at the University of Bristol, London School of Hygiene and Tropical Medicine and Brunel University. The DSU is commissioned by The National Institute for Health and Care Excellence (NICE) to provide a research and training resource to support the Institute's Technology Appraisal Programme. Please see our website for further information www.nicedsu.org.uk

ABOUT THE TECHNICAL SUPPORT DOCUMENT SERIES

The NICE Guide to the Methods of Technology Appraisal is a regularly updated document that provides an overview of the key principles and methods of health technology assessment and appraisal for use in NICE appraisals.[1] The Methods Guide does not provide detailed advice on how to implement and apply the methods it describes. This DSU series of Technical Support Documents (TSDs) is intended to complement the Methods Guide by providing detailed information on how to implement specific methods.

The TSDs provide a review of the current state of the art in each topic area, and make clear recommendations on the implementation of methods and reporting standards where it is appropriate to do so. They aim to provide assistance to all those involved in submitting or critiquing evidence as part of NICE Technology Appraisals, whether manufacturers, assessment groups or any other stakeholder type.

We recognise that there are areas of uncertainty, controversy and rapid development. It is our intention that such areas are indicated in the TSDs. All TSDs are extensively peer reviewed prior to publication (the names of peer reviewers appear in the acknowledgements for each document). Nevertheless, the responsibility for each TSD lies with the authors and we welcome any constructive feedback on the content or suggestions for further guides.

Please be aware that whilst the DSU is funded by NICE, these documents do not constitute formal NICE guidance or policy.

Professor Allan Wailoo
Director of DSU and TSD series editor.

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CONTENTS

Tables and figures

Abbreviations

ATF	Accelerated time failure
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence interval
DES	Discrete event simulation
DSU	Decision Support Unit
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ISPOR-SMDM	International Society for Pharmacoeconomics and Outcomes Research - Society for Medical Decision Making
NICE	National Institute for Health and Care Excellence
OR-MS	Operational Research – Management Science
pEVPI	Partial expected value of perfect information
PSA	Probabilistic Sensitivity Analysis
TA	Technology Appraisal
TSD	Technical Support Document
QALY	Quality adjusted life-years

1. INTRODUCTION

Economic models which estimate the relative costs and benefits of alternative technologies are an essential element of the National Institute for Health and Care Excellence's (NICE's) Technology Appraisal (TA) process. Such models are designed to estimate the mean costs and benefits of alternative health technologies for the population likely to be affected by a particular decision. In some cases a single decision is made for the whole population falling within the scope of the TA, whilst in other cases, where the costs and benefits are expected to differ within the population, different decisions are made for different subgroups of the population specified in the scope. However, in both cases the TA Committee's guidance is based on the average costs and benefits across some specified population rather than the individual outcomes occurring at the patient level.

Economic models can use either a patient-level or cohort-level modelling approach to estimate the expected costs and outcomes across a particular population. In a patient-level simulation, the outcomes are modelled for individual patients and then the average is taken across a sufficiently large sample of patients, whilst in a cohort-level model the outcomes are estimated for the cohort as a whole without considering the outcomes for individual patients within that cohort. The optimal approach will depend on the particular nature of the decision problem being modelled and therefore needs to be assessed on a case-by-case basis.[2] It is important that the choice between using a patient-level simulation and a cohort-level modelling approach is given careful consideration and is properly justified in the model description, as the models used to inform NICE TAs have sometimes been criticised on this basis.[3]

The decisions of NICE Technology Appraisal Committees are dependent on both the mean expected costs and benefits and the uncertainty in those means, arising from uncertainty in the evidence used to inform the economic model. Therefore it is important that decision uncertainty is correctly estimated regardless of the choice of model structure.[4] The standard way to assess the decision uncertainty associated with the model parameters is through probabilistic sensitivity analysis (PSA), in which samples are taken from distributions reflecting the uncertainty in the model parameters and this uncertainty is propagated through the model. In the past this has been viewed as a barrier to the use of patient-level simulation due to the computational requirements of simulating both a large number of patients to obtain

a precise estimate of the expected costs and benefits, and a large number of parameter samples to evaluate the uncertainty surrounding the expected costs and benefits.[5] However, we describe here how patient-level simulation can be combined with PSA to meet the information needs of NICE TA Committees.

The aims of this Technical Support Document (TSD) on patient-level simulation are to:

- Increase awareness of patient-level modelling approaches and highlight the key differences between patient-level and cohort-level modelling approaches.
- Provide guidance on situations in which patient-level modelling approaches may be preferable to cohort-level modelling approaches.
- Provide a description of how to implement a patient-level simulation illustrated with example models.
- Provide guidance on good practice when developing and reporting a patient-level simulation to inform a NICE TA.

The example models are built in the standard software packages (Microsoft Excel®, TreeAge Pro®, R[6]) accepted by NICE without prior agreement.[7,8] We have also provided one example of a discrete event simulation implemented in a bespoke simulation package (SIMUL8®). It should be noted that permission from NICE must be sought in advance to submit a model implemented in a non-standard software package such as a bespoke simulation package.

The focus of this document is on the use of economic models to inform NICE TAs. Systems incorporating interactions between patients are not a common feature within TA and therefore this document focuses on the application of patient-level simulation to systems where patients can be assumed to be independent. However, a brief discussion of the application of patient-level simulation to situations involving patient interaction is given in section 3.5.

2. A TAXONOMY OF MODELLING APPROACHES

2.1. DEFINING PATIENT-LEVEL AND COHORT MODELLING APPROACHES

Economic models estimate the costs and benefits across the target population by considering the outcomes for a group of patients which represent the target population. Here we define a

patient-level simulation as any model which estimates the mean costs and benefits for that group of patients by considering the costs and benefits of each individual within the group. (These types of models have sometimes been referred to as 'individual sampling models').[9,10] Conversely a cohort model is any model which estimates the outcomes for the group of patients without explicitly considering the outcomes of each individual patient. A cohort model may allow for some variability in patient outcome according to patient characteristics defined at the start of the model, but it is not a patient-level simulation unless the outcomes are evaluated at the patient-level. For example, a cohort model may evaluate outcomes for a group of patients in which 40% of the starting cohort is female and may apply different mortality rates for males and females, or it may allow different treatment pathways for subgroups who are unable to tolerate a particular second-line treatment. In both cases this would require certain subgroups of the cohort to be tracked separately through the model. Therefore, a cohort modelling approach does not imply that there is no variation in patient characteristics or outcomes within the cohort, although any variation in outcomes is likely to be captured for broad categories of patients rather than at an individual level.

2.2. DEFINITION OF STOCHASTIC AND ANALYTIC EVALUATION

Models that can be evaluated without the need to randomly sample from parameter distributions are said to be evaluated analytically. Stochastic evaluation refers to the process of allowing certain values within the model to vary randomly according to a specified distribution and taking the mean model outcome over a large number of model runs. Stochastic evaluation allows the distribution of outcomes to be estimated in addition to their mean value, which may also be of interest to decision makers. Different types of stochastic variation can be incorporated within a decision analytic model.

In models which consider individual-level patient heterogeneity, stochastic variation can be incorporated at the level of patient characteristics. In such models, the mean model outcomes are estimated across a group of patients whose starting characteristics are sampled from distributions.

Stochastic variation may also occur at the decision node, state-transition or time-to-event level allowing random variation in the model trajectory for an individual patient, in a manner

which does not necessarily depend on the patient's characteristics at the start of the model. This type of stochastic variation is referred to here as stochastic uncertainty.

Finally, stochastic variation can occur at the parameter level, where parameter values are sampled from a distribution reflecting the uncertainty in their population mean value and this uncertainty is propagated through the model to determine the resulting uncertainty in the expected model outcomes. This type of stochastic evaluation of parameter uncertainty is generally referred to in this context as probabilistic sensitivity analysis (PSA).[11] PSA is a requirement of models submitted to the NICE Technology Appraisal Programme.[1]

Care should be taken when discussing the appropriate modelling approach to distinguish between the different types of stochastic evaluation that can be incorporated within the model to avoid confusion between patient heterogeneity, stochastic uncertainty and parameter uncertainty.[12] For example, it is important not to include parameters which reflect patient heterogeneity within the PSA. Koerkamp *et al.* provide a clear description of the different types of stochastic variation that can be incorporated and combined within a health economic evaluation and how these can be evaluated to provide different information on the uncertainty and variability associated with expected model outcomes.[12]

2.3. DECISION TREE ANALYSIS

Decision tree analysis estimates the likelihood of various outcomes occurring using a probability tree and then applies associated pay-offs, the costs and benefits in this context, for each branch of the tree. Decision tree analysis does not explicitly model the timing of outcomes, making it necessary for the analyst to adjust pay-offs for events occurring in the future to allow for discounting. In the past, decision tree analysis was commonly employed to model a cohort of homogeneous patients analytically using mean parameter values.[5] However, NICE's requirement for PSA has resulted in probabilistic evaluation of parameter uncertainty becoming common place. It should however be noted that decision trees can also be evaluated stochastically allowing each individual to follow a unique path through the decision tree based on samples drawn from statistical distributions, as opposed to estimating the proportion following each path in the traditional manner.[10] Therefore, a decision tree framework can be compatible with a patient-level simulation approach.

2.4. STATE-TRANSITION MODELS

State-transition models consist of a discrete set of mutually exclusive health states which are evaluated at regular intervals to determine the population of each health state. The flow of patients through the model over time is determined by the application of a transition matrix which defines the probability of moving between each state within one cycle. State-transition models are often synonymously referred to within a health economic context as 'Markov models', although strictly the use of the term 'Markov' should be limited to models which display the 'Markovian property' in which transitions are dependent only on the state in which the patient resides and not on anything that occurred before they arrived in that state or the duration of time they have occupied that state. This is sometimes referred to as a 'memoryless' process. The simplest form of a state-transition model is one in which a fixed transition matrix is applied every cycle giving a time homegenous Markov chain, although this approach can also be extended to give a Markov process in which time varying transition matrices are allowed. The term 'Markov model' has often been used synonymously with the term 'cohort model' within the health economic context because Markov state-transition models are so often employed to model cohorts of patients. Cohort state-transition models evaluate the proportion of patients within the cohort who reside within each of the model states for each model cycle. They are also widely combined with PSA to provide an estimate of the distribution of costs and benefits expected for a cohort of homogeneous patients with average characteristics. However, as with decision trees, they can also be evaluated stochastically using samples drawn from statistical distributions to determine whether an individual patient experiences a particular transition given the probability of that transition occurring in that particularly cycle.[13] Therefore, a state-transition model framework is also compatible with a patient-level simulation approach.

Guidance on developing state-transition models has been produced by the ISPOR-SMDM Modeling Good Research Practices Task Force.[14]

2.5. DISCRETE EVENT SIMULATION

A discrete event simulation (DES) is concerned with the events that occur during the lifetime of individual entities. As the individual entities are usually patients in this context, DESs are inherently patient-level and the expected outcome for the population of interest can only be

reliably estimated by simulating a sufficiently large number of patients. The simulation maintains a list of the time to each possible event, as sampled for each individual patient, and the simulation clock is advanced from one event to the next. Therefore, unless events are scheduled to happen at regular intervals, the simulation clock will step forward at irregular intervals which are dependent on the sampled times between subsequent events. The simulation tracks patient attributes (both continuous and categorical) and global variables such as total costs and quality adjusted life-years (QALYs). These are updated each time an event occurs. Individual entities can experience an event of the same type more than once if after the first event is processed another event of the same type is scheduled. The time to future events can be made dependent on patient attributes including their history of previous events. Continuous patient attributes can be updated at specified time intervals by setting up events which occur at regular intervals such as annual increases in age.

It is also possible within a DES framework to allow patients to interact with other patients or with other entities which are defined as resources within the simulation such as doctors, appointment slots, equipment etc. These resources may be constrained leading to the formation of queues where the next event can only be processed when a particular resource is available. Such flexibility allows for very complex systems to be modelled incorporating factors such as infection and service capacity, although these are often not necessary within a TA context.[15] (See section 3.5 for a brief discussion of model structures which are suitable for modelling systems with interaction between individuals or constrained resources.)

Discrete event simulations are inherently patient-level and must be evaluated stochastically to produce precise estimates of the expected costs and benefits across a specific patient population. This is the key trade-off against the increased level of flexibility they provide. The main model inputs driving flow through the model are the distributions of time-to-event for each event type. In DES these time-to-event values are sampled for individual patients from probability distributions.

One of the benefits of using a DES approach is that it may have more face validity with clinicians and patients who may appreciate the transparency of being able to visualise (or, with some software packages, see animations of) individual patients experiencing disease outcomes and accruing costs and health benefits. Although care should be taken that this

additional realism does not result in more trust being placed in the model than is warranted and that the desire for face validity does not result in models that are unnecessarily complex.

Guidance on developing DES has been produced by the ISPOR-SMDM Modeling Good Research Practices Task Force.[16]

2.6. HANDLING OF TIME WITHIN THE MODEL

Decision tree analysis estimates the likelihood of various outcomes occurring and the associated pay-offs without explicitly modelling the timing of outcomes. It is therefore generally used to model events occurring over a short time-horizon or where the exact timing of the event is unimportant. State-transition models employ a discrete time approach to estimate the number of patients experiencing particular health states at fixed time-points which are determined by the cycle length and the time horizon. Given that real-life clinical events can occur at any point in time, the discrete time approach employed within a state-transition model essentially provides a numerical approximation to the real-life scenario. The accuracy of the approximation can be increased by incorporating continuity corrections such as a half-cycle correction and by reducing the cycle length.[17] Reducing the cycle length until there is no appreciable effect on the model outcomes is recommended.[17] This may be achieved at longer cycle lengths if a continuity correction is applied.[17] Discrete event simulations progress through the times at which specific events happen for particular individual entities, based on samples from discrete or continuous distributions, allowing events to occur at any time point. However a DES cannot be considered to be a true continuous time model as it simulates events according to intervals in which the state of the system is known to have changed.[18]

3. IDENTIFYING WHEN A PATIENT-LEVEL SIMULATION MAY BE PREFERABLE TO A COHORT APPROACH

3.1. MODEL NON-LINEARITY WITH RESPECT TO HETEROGENEOUS PATIENT CHARACTERISTICS

If there are factors which vary between patients (e.g. age) which have a non-linear relationship with the model outcomes (e.g. costs and QALYs), then estimating the model outcomes for a cohort of patients using only average characteristics (e.g. mean age at starting treatment) will provide a biased estimate of the average outcome across the population to be treated.

Where such factors can be identified in advance of starting treatment, it may be possible to conduct subgroup analysis to determine the average outcome in subgroups of patients defined using broad categories of the factor of interest (e.g. 5 year age bands), provided the outcomes within those subgroups are expected to be reasonably homogeneous. This would allow either for separate recommendations to be made for each subgroup, or for a weighted average to be taken across the subgroups to make a single recommendation across the whole population. The latter may be necessary in situations where legal or ethical considerations would make separate recommendations unacceptable.

In some cases it is known that a certain factor affects outcomes, but it cannot be determined which patients will be affected prior to treatment initiation, making separate recommendations impossible. Griffin *et al.* give disease progression rate, within the context of a cancer screening program, as an example of one such variable.[5] It may not be possible to know which patients are likely to experience faster disease progression prior to offering screening, but if disease progression has a non-linear relationship with outcomes, it would be necessary to include the variability in disease progression within the model to obtain an unbiased estimate of the mean outcomes across the cohort offered screening. In these situations an approximate solution may sometimes be obtained by averaging across analytically evaluated models, in a manner similar to the averaging of outcomes across subgroups described above.

The use of subgroup analysis and model averaging to address patient heterogeneity becomes problematic when the number of categories required to define groups with homogeneous outcomes becomes large, either due to the presence of continuous variables requiring granular categorisation or due to the presence of many interacting factors. In such cases, a patient-level simulation may be preferable, as a group of patients can be simulated with characteristics sampled from the relevant population distributions. The expected costs and benefits across the sampled group should then provide an unbiased estimate provided that a sufficiently large sample is simulated and any covariance between the different patient characteristics is correctly taken into account.

When deciding on an appropriate modelling approach, consideration should be given to the likely relationship between characteristics which may vary within the population and the model outcomes. In some cases it may be possible to see before building the model that such a non-linear relationship exists by considering the proposed model structure and the functional form of any relationships that are to be included within the model. In other cases it may be necessary to build the model and test it for linearity with respect to patient characteristics. Where the relationship between patient characteristics and model outcomes is found to be, or could reasonably be expected to be non-linear, a patient-level simulation which incorporates patient heterogeneity should be conducted to obtain an unbiased estimate of the mean outcomes unless this can be avoided through appropriate subgroup analysis.

3.2. PATIENT FLOW DETERMINED BY TIME SINCE LAST EVENT OR HISTORY OF PREVIOUS EVENTS

As described earlier, state-transition models often employ a Markovian assumption in which it is assumed that future events are independent of past events. This makes it difficult to model situations where the likelihood of future state transitions is dependent on the time since a previous transition (e.g. time on current treatment) or the history of previous events (e.g. previous fracture increases risk of further fractures). Additional states are sometimes added to state-transition models in order to allow the patients' progress through the model to be dependent on their history as well as their current health state. The history of previous events may be incorporated by replicating states so that patients who have a particular history are handled within a separate replicate state. The dependence on time since the last transition may be incorporated by using a series of replicate states allowing the patient to move to a

different state each cycle to record the passage of time even though there is no change in their actual health state. These are sometimes referred to as 'tunnel states'. Ultimately there is a limit on how many such replicate states can be incorporated before the cohort Markov state-transition approach becomes unwieldy.

One solution is to keep the state-transition framework but to evaluate the model using a patient-level simulation in which a single patient moves between health states stochastically. As only one patient is evaluated at any one time, fewer health states need to be defined as a time /history dependent transition matrix can be employed where the transition matrix for later cycles is dependent on the occupation of health states by that individual patient at earlier time points. In this case the need for a stochastic evaluation is being traded against a reduction in the number of unique health states that are required to be enumerated explicitly as part of the model. It should be noted that, depending on the complexity of the clinical scenario being modelled, the number of logical rules required to make the transition matrices dependent on the patient's previous history, or the occupation time within each state, may make programming errors difficult to detect if the model is implemented within a spreadsheet package. When implemented in TreeAge ("Microsimulation mode"), tracker variables can be used to capture prior events of significance and to drive the transition matrix in a more transparent manner.

One innovative approach that allows factors such as time or patient history to be incorporated in a cohort state-transition model is to define the transition matrix as a multi-dimensional array. This allows a cohort model to be implemented where the transition probability is dependent on more factors than just the start and finishing state giving a non-Markov cohort state-transition model. The additional dimensions may be time since a particular event, patient characteristics or the patient's history of previous events. Hawkins *et al.* used this approach when modelling epilepsy treatments, where the probability of treatment failure declines over time.[19] In their model a unique probability was defined for each possible transition, for each model cycle, giving a 3 dimensional transition matrix (dimensions are starting state, finishing state and time cycle). This method requires the use of software which can support multi-dimensional arrays, and in this case the model was implemented in the statistical programming language R.[6] This approach eliminates the need for stochastic evaluation, and could in theory be applied in more complex situations where other dimensions are used to incorporate patient history or characteristics. However, populating

and validating such a complex transition matrix may prove more difficult that implementing a stochastic patient-level simulation.

An individual patient-level methodology is likely to provide a more efficient and parsimonious solution than trying to implement a cohort model in situations where there is substantial non-Markovian behavior due to its ability to track individual patients and record their event history and use this to update their risk of future events. A further advantage of the DES framework is that where the risk of certain events occurring changes over time, this can be handled by sampling a single time to event estimate from a non-exponential time-to-event distribution which is easier and more efficient than calculating time-dependent transition probabilities for each cycle in a patient-level state-transition model.

3.3. AVOIDING LIMITATIONS ASSOCIATED WITH USING A DISCRETE TIME INTERVAL

As described earlier, a state-transition model is essentially a discrete time approximation to a continuous real-life process. The application of this approximation may introduce bias if not implemented correctly. For example, the transition matrix needs to reflect the fact that multiple transitions may occur within a single cycle giving a non-zero probability for some transitions which cannot occur as a direct transition. Soares *et al.* describe how bias can be introduced by incorrectly discretising a continuous flow process.[17] This bias is reduced if the cycle length is shortened to a value where multiple transitions within one cycle are extremely unlikely and therefore theoretically the bias could be avoided simply by selecting a small enough cycle length. However, as pointed out by Caro, some diseases combine periods of rapid events with long periods where no events occur.[20] In such cases the need for very short time cycles to accurately capture rapidly occurring events may make the model large and slow to evaluate over the required time frame. As the simulation clock within a DES steps forward in time from one event to the next, it may prove to be a more efficient modelling framework in situations such as these where multiple events can occur in quick succession followed by periods of inactivity.

3.4. DEVELOPING A FLEXIBLE MODEL AS AN INVESTMENT FOR FUTURE ANALYSES

Discrete event simulations are particularly flexible models which can be easily adapted to incorporate additional events or patient attributes and as such may lend themselves to iterative decision making processes or repeated use. Adapting decision tree or state-transition models to include additional health states or patient attributes can be time consuming, particularly if the model is implemented within a spreadsheet package, and this may limit the ability of the decision analysts to respond to criticisms raised during the TA process.

If a whole disease model is required which may be used across a range of different decision problems such as prevention, treatment and screening decisions, then it may be easier to develop that whole disease model using a patient-level simulation approach,[21] and in particular a DES framework, as these types of models are generally easier to adapt. Such an investment in a whole disease model may not seem worthwhile in the context of a single technology appraisal, where the economic model is developed by the manufacturer or sponsor of the technology to inform guidance on a single technology with a single indication. However, it may be justifiable for multiple technology appraisals, where Technology Assessment Groups develop models to assess the cost-effectiveness of more than one technology for one or more indications and these models are sometimes updated and re-used across several different TAs. In this context, the development of flexible whole disease models which can be easily adapted to inform several different decisions would increase decision making consistency across NICE's work programme by allowing a consistent set of model assumptions to be applied within a particular disease area. (A similar argument could be made for the development of flexible whole disease models within NICE's Clinical Guideline Programme).

3.5. MODELLING SYSTEMS WHERE PEOPLE INTERACT WITH RESOURCES OR OTHER PEOPLE

Patient-level simulations may be particularly useful when modelling situations where people interact with other people or compete for resources that are constrained in some way such as healthcare staff, appointment slots or equipment. Systems incorporating patient interaction are not a common feature within Technology Appraisals, but are mentioned here for

completeness. State-transition models built using TreeAge can be run as patient-level simulations in parallel to capture interactions between patients or with system resources. However other modelling approaches may be better suited to problems where these are significant components. A DES is an obvious choice of modelling framework in such situations although there are some alternative model structures. The ISPOR-SMDM Modelling Good Research Practices Taskforce highlight dynamic transmission, DES and agent-based models as being applicable in situations where there are interactions between individuals, which may be due to disease transmission or due to the allocation of constrained resources.[2] Both DES and agent-based approaches model at the patient-level whereas many dynamic transmission models employ a cohort-level system dynamics approach.[2,22] Readers are referred to Brennan *et al*.'s paper on model taxonomy which includes a list of questions that can be used to select an appropriate model.[10]

3.6. NEED FOR PROBABILISTIC SENSITIVITY ANALYSIS TO ASSESS DECISION UNCERTAINTY

The need for PSA has in the past been cited as a reason for choosing a model structure which allows analytic rather than stochastic evaluation of the model outcomes.[5] When evaluating the decision uncertainty in a patient-level simulation using PSA it is usually necessary to run two nested simulation loops. The inner loop evaluates the outcomes across the simulated population for the given parameter values, and the outer loop samples those parameter values to reflect uncertainty in the model inputs. In a cohort-level model, only the outer loop is required, thus PSA computation time for a cohort-level model is likely to be lower than for an equivalent patient-level model. However with modern PC specifications this additional computation time may not be overly restrictive. Furthermore, the computation time for the inner loop may be reduced by keeping the patient-level simulation as efficient as possible. A DES, where calculations occur only at the times when events occur is likely to be much more efficient to evaluate stochastically than a patient-level state-transition model where calculations are needed every cycle for every simulated patient.

Further advice on conducting PSA and the relative importance of first and second order uncertainty within patient-level models can be found in section 5.3 and 5.4.

4. IMPLEMENTING A SIMPLE MODEL WHICH INCORPORATES PATIENT HISTORY USING DIFFERENT APPROACHES

Here we introduce a simple model for assessing the cost-effectiveness of osteoporosis treatments in order to demonstrate how such a model could be represented using a variety of modelling frameworks. This model is not a comprehensive model for assessing osteoporosis treatments, but it is intended only as a teaching example. The key model assumptions are:

- Patients start with a history of no previous fractures and a baseline utility of 0.7
- The only types of fractures that can occur are hip fractures and vertebral fractures
- Patients can experience up to one hip fracture
- Patients can experience up to two vertebral fractures
- Fractures result in one-off costs which are incurred at the time of the fracture (£7000 for hip and £3000 for vertebral)
- Fractures result in a life-long utility multiplier being applied to the patient's pre-fracture utility (0.75 for hip fracture, 0.90 for first vertebral fracture, 1 for second vertebral fractures). So for example, a patient who has had a hip fracture and two vertebral fractures will have a utility of 0.7x0.75x0.9x1 =0.4725
- Patients in the control arm incur no costs other than those associated with fractures
- Patients in the intervention arm incur a fixed cost per day for treatment from the start of the model until death (equivalent to £500 p.a.)
- Time (in years) to hip fracture is described as a Weibull distribution with shape of 4 and scale of 10.
- Time (in years) to vertebral fracture is described as a Weibull distribution with shape 2 and scale of 8.
- Intervention doubles the expected time to hip fracture and expected time to first vertebral fractures (Note this is not equivalent to a hazard ratio of 0.5. See section 4.5.4 on calculating acceleration factors from hazard ratios when assuming Weibull time to event distributions)
- Intervention has no effect on time to second vertebral fracture
- Hip fractures have a 0.05 probability of resulting in death at the time of fracture
- Time (in years) to death is normally distributed with mean 12 and standard deviation of 3.
- No side-effects of treatment are modelled

- No treatment withdrawal is modelled
- Costs and benefits are discounted at 3.5% per annum
- Time horizon is patients lifetime (with the exception of the patient-level state-transition model, when a 30 year horizon is applied)

It should be noted that this example model has been adapted from a model previously used by the authors to teach DES and therefore the model assumptions have been framed with a DES implementation in mind. This DES implementation is described in section 4.1 to 4.3 and an equivalent patient-level state-transition implementation is described in section 4.4.

4.1. GENERAL DISCRETE EVENT FRAMEWORK

Within a discrete event framework, events are used to update the patient's health status. Therefore, when specifying a DES model, it is necessary to translate the clinical pathway into a series of sequential events. Events which update the patient's health status are analogous to transitions between health states within a state-transition model. These events are likely to result in a change in the patient's utility value and / or a change in the costs they incur and /or a change in their future event probabilities.

When deciding how to convert the clinical pathway into a series of sequential events, care should be taken to ensure that any competing risks are not ignored. For example, if there is a risk of death during a six month period of chemotherapy treatment, then specifying 'starting chemotherapy' as a separate event from 'finishing chemotherapy' would allow the competing event of death to occur between those two events. Simply specifying 'chemotherapy' as a single event which lasts for six months would fail to incorporate the competing risk of death as during that period no other events would occur.

Attributes are variables which are specific to the individual patient, such as their utility, or their history of previous events. Global variables are those which are not specific to an individual patient. These may be parameters which are fixed for the whole simulation e.g. the cost of hip fracture, or they may be output variables which are updated during the simulation, such as a running total of the costs and QALYs accrued across the whole simulated population. Events are used to update both patient attributes and global variables. For example, when an event occurs, it is necessary to update the running total of costs and

QALYs accrued so far to represent those accrued since the last event, and to update the attributes that track the patient's health status, such as their utility value, so that information is available for later updates of the global variables. In our example model;

Events that can occur are:

- hip fracture,
- vertebral fracture
- death due to hip fracture
- death due to other cause.

Patient attributes are:

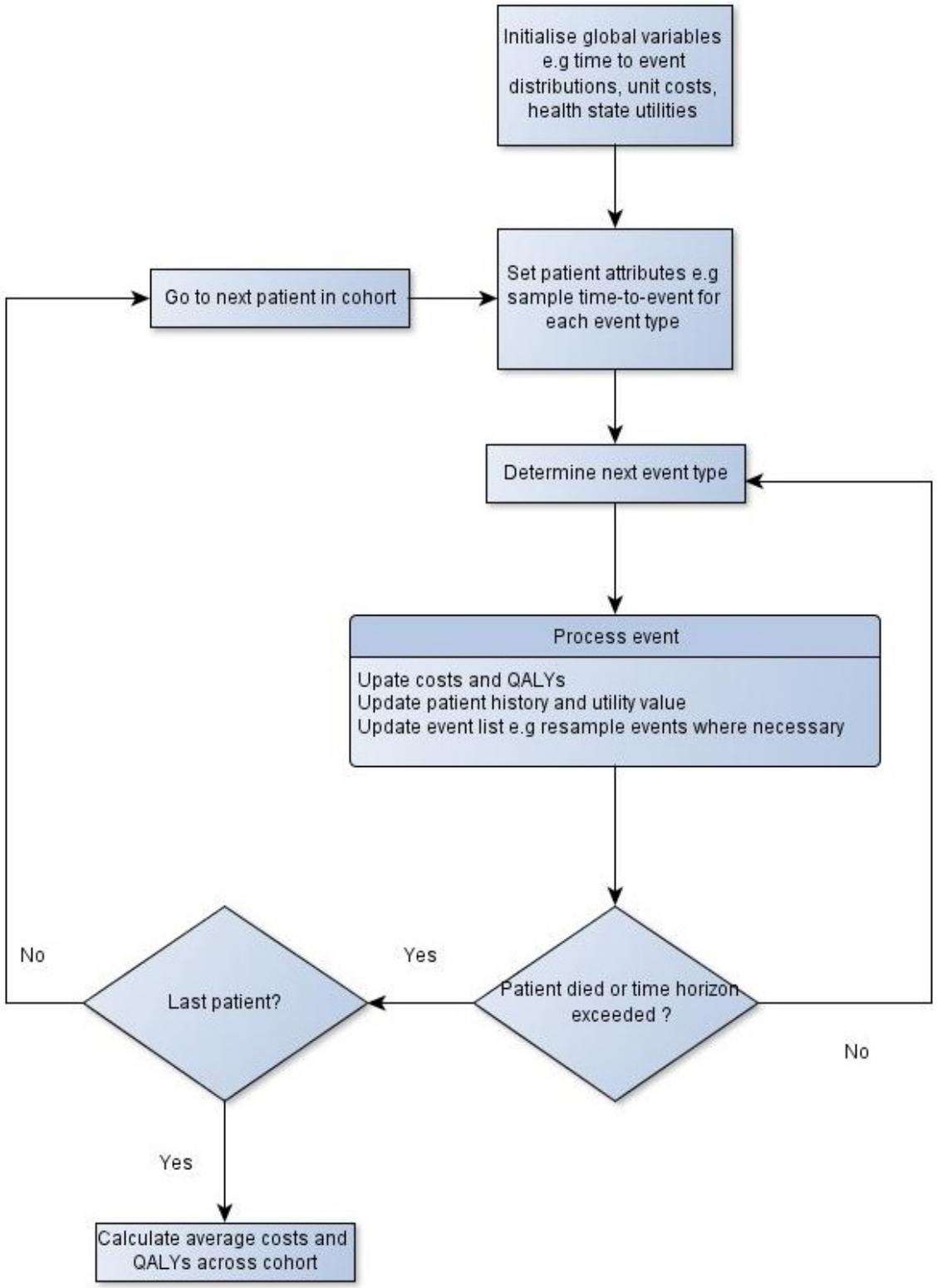
- Time to death
- Time to hip fracture
- Time to vertebral fracture
- Current utility
- History of vertebral fracture
- History of hip fracture
- Time of last event (used to determine duration of time since last event for calculating costs and QALYs accrued since last event)
- Time to next event (this is a dynamic attribute which is updated according to which event is sampled to occur next)
- Router (variable used to route patients from one event to the next)

Global variables are:

- Parameters for each of the time-to-event distributions
- Costs for each fracture type
- Baseline utility
- Utility multipliers for each fracture type
- Intervention costs
- Intervention effects (e.g. acceleration factor or hazard ratio)
- Discounting factors
- Total costs (discounted and undiscounted)
- Total QALYs (discounted and undiscounted)
- Number of patients in simulation

The processes described in Figure 1 can be implemented using bespoke simulation packages, such as ARENA® (Rockwell Automation, Inc, Wexford, PA, USA) or SIMUL8 (Simul8 Corporation, Boston, MA, USA), or generic programming languages such as Visual Basic, C++ or the statistical language R amongst others.[6] TreeAge Pro 2014 now includes time-to-event functionality which may be used to implement a DES. Whilst earlier (pre-2014) versions of TreeAge did not include this explicit DES functionality, there is at least one example of a DES being implemented in TreeAge (TreeAge Pro 2009) using the Markov node function as a cycling facility to resample times between possible events.[23] (Further details on the range of simulation software available is provided by the OR-MS Today survey which is regularly updated.[24])

Figure 1: Key model logic for a DES (when simulating one patient at a time)



The simulation can be processed once for the intervention arm and then once for the control arm (serial processing) or it can be processed in parallel by putting the same patient (i.e. one sampled to have the same characteristics and time-to-event samples) through both the intervention and control arms concurrently. The use of common random numbers to allow alternative configurations, in this case treatments, to be compared "under similar experimental conditions" is a popular variance reduction technique which can be used to decrease the number of patients that need to be sampled.[25] In bespoke simulation packages, the random number streams can be controlled to ensure that the same patient characteristics and pathways through the model are sampled each time, allowing serial processing of the intervention and control arms. When using a generic programming language, the same can be achieved either by processing the patients in parallel or by manually controlling the random number streams to ensure that the same patient attributes are sampled for intervention and control.

4.2. IMPLEMENTING A DES IN A GENERIC PROGRAMMING LANGUAGE

Code is provided in Appendices A and B demonstrating how to implement the example osteoporosis model in Visual Basic (as a Microsoft Excel module) and R respectively. (Accompanying files can also be downloaded from the DSU website, www.nicedsu.org.uk). Figure 1 can be used as a guide to determine the key steps that need to be included in the simulation code. However, ultimately the programmer is responsible for determining the most efficient way to implement the simulation within the chosen programming language and this will depend on the specifics of the individual model.

4.2.1. Visual Basic DES

In the Visual Basic code, the event list is processed by working sequentially through each of the time-to-event samples for the various event types and;

1. comparing each value against the previous to determine if the next event type occurs earlier than the previous one in the list
2. updating the time-to-next event to the lower value for that pair of events
3. updating the router variable to record the event type with the lower time-to-event as the next event type

4. repeating steps 1 to 3 until all event types have been considered such that the time-to-next event and router have been set to the right values for the earliest event predicted from the list of time-to-event data

[NB: This logic for setting the next event is similar to that implemented within the SIMUL8 example model described below and is suitable in models where patients do no interact and individuals can be evaluated one at a time. More complex logic would be needed to process the event list in models where there are multiple entities being processed simultaneously]

The next event is then processed, at which time the costs and QALYs since the previous event are accrued and the time-to-last event variable is updated. The event list may also be updated when the event is processed. For example, when the first vertebral fracture occurs, the time to next vertebral fracture is updated to allow a second vertebral fracture to occur. When calculating the time to events that are assumed not to occur e.g. second hip fracture or third vertebral fracture, the time-to-event for that event type is set to a large number which is greater than the time horizon to prevent those events recurring. When fatal events occur, time-to-last event is again set to a large number, greater than then time horizon, and this is used as a flag to end the simulation.

In our Visual Basic code we have included a time horizon variable and logic which ensures that if death does not occur before the time horizon, the relevant costs and QALYs are accrued from the previous event to the time horizon. This was done to allow comparisons to be made between our example individual patient-level state-transition model (see section 4.4) and this DES implemented in Visual Basic. It is not generally necessary to specify an explicit time horizon for a DES as each patient can be simulated until death, but a time horizon can be specified either by using logic similar to ours or by specifying 'time horizon reached' as an additional event type. Most bespoke packages have a built-in function to end the simulation after a particular amount of time has elapsed.

In our example Visual Basic code we process the control and intervention arm in series. We generate and store arrays of random numbers to ensure that the patients being simulated are identical for each treatment strategy.

In additional to the core model outputs (costs and QALYs), we have added other tracker variables which record patient-level and cohort-level outcomes in order to facilitate model validation and debugging. These additional variables can be added to a watch window to allow the programmer to see how they change in real time when stepping through the model. Alternatively, the watch window can be used to specify conditions which stop the simulation in order to detect model errors (e.g. stop when current utility >1). In addition, we have added a debugging mode to the simulation. When the debugging flag is switched to TRUE, the simulation stores patient-level results in an array. This slows the model down, but only when the debugging mode is switched on, allowing fast cohort-level results to be generated once the programmer is satisfied that the model is behaving as expected.

The example Visual Basic model described above and provided in Appendix A is intended to demonstrate the basic workings of a DES to people who are familiar with using Visual Basic to automate PSA. This is a straightforward approach, but it has the disadvantage that, as models become more complex, the coding may become cumbersome and/or difficult to follow. An alternative is to adopt an object-orientated approach to implementation, taking advantage of Visual Basic's class-module and user-defined function capabilities to define entities (simulated patients) as objects with properties and methods. This is likely to lead to a model that is more transparent and more readily amenable to alteration and extension; however, it will also usually entail a slightly longer run-time. A version of the Visual Basic model implemented in this way is provided on the DSU website (www.nicedsu.org.uk).

4.2.2. DES in R

In the example R code the time-to event data is handled using a list structure and the list is sorted in order of occurrence using a standard R function (order[]). The event list is then processed with events being removed from the list until the list is empty. In our example, we have used two different elements in the list to handle the first and second vertebral fractures. This avoids the need to update this element of the list when the first vertebral fracture event occurs and then re-sort the list. However, if we were modelling a situation where an unlimited number of similar events could occur e.g. diabetic hypoglycaemia episodes in a type 1 diabetes model, it would be more efficient to simply update the event list each time a hypoglycaemic episode occurs to add the time to the next episode and re-sort the list.

In our example R code the event list for the intervention arm is generated after the event list for the control arm and the two groups are processed concurrently (i.e. in parallel). This avoids the need to generate and store random number arrays to ensure that similar conditions occur for each intervention. We have however set the random number seed to ensure that the results are replicable from one run to the next as this is helpful when debugging and validating a model.

Where possible, we have used functions to implement identical processes in the intervention and control arms. For example, the same functions are used to calculate costs and QALYs across the two treatment strategies with only the function inputs differing according to whether the treatment or control arm is being processed. This minimises the opportunity for errors to be introduced by making changes to one part of the code for the intervention arm, but failing to make similar changes to the equivalent control arm code, which is a risk when running both arms concurrently.

As with the Visual Basic example, we have added code to facilitate debugging and validation. In this case a debugging mode outputs the event list and the accrued costs and QALYs at the time of each event. Patient-level results are also saved to an array and output to a '.CSV' file for validation purposes.

4.3. IMPLEMENTING A DES IN TREEAGE PRO

Here we provide a brief description of how to implement a DES within TreeAge Pro. The 2014 version of TreeAge introduced new functionality which simplified creation of time-to-event models and provides the capability to graphically model both Markov and DES sub-trees that are part of a larger decision tree. The example model is available from the DSU website (www.nicedsu.org.uk) and its structure is shown in Figure 2.

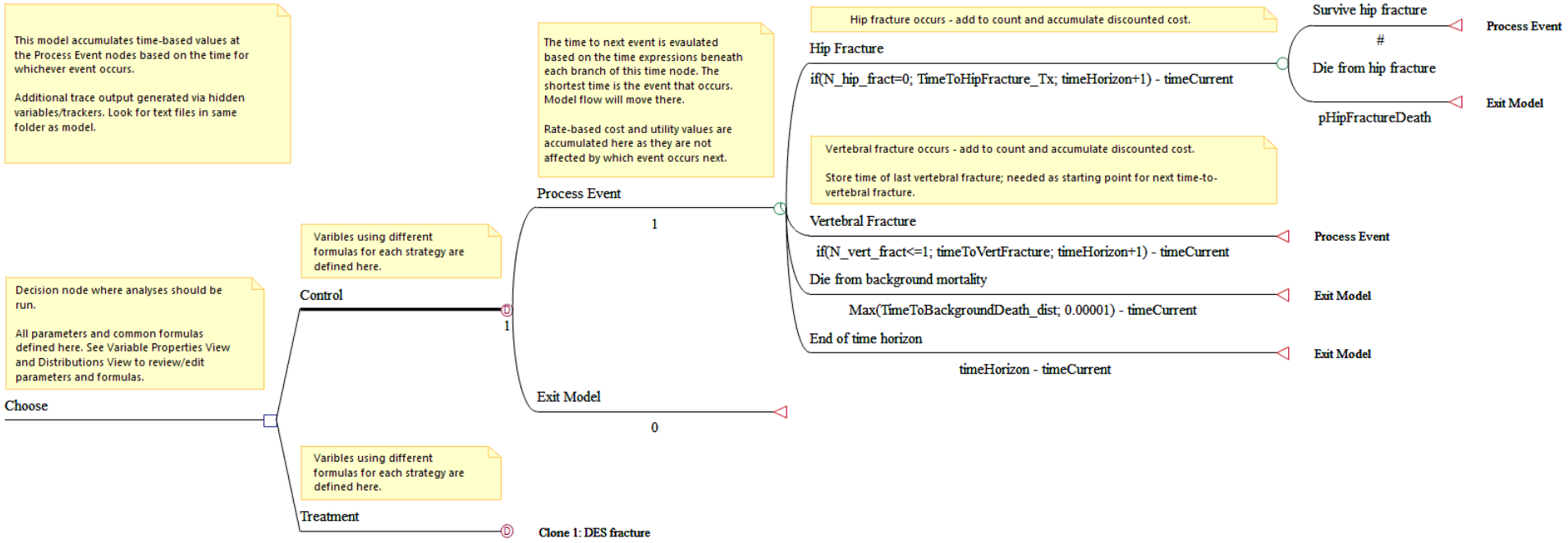
In broad terms, the steps needed to set-up the example model for DES simulation are as follows:

1. Starting with a default decision node, add branches for each treatment strategy (Control and Intervention) and add DES nodes at the end of each branch.
2. Define distributions for time-to-event attributes e.g. Weibull for time to hip fracture

3. Define variables and set starting values at the root decision node (e.g. set time-to-event attributes equal to time-to-event distributions, set starting utility, set patient history of fractures, utility multipliers, costs, discount rates)
4. Select the Control DES node as the master and set the time horizon of the simulation.
5. Downstream from this node, create at least one Time node for processing events and one Terminal node to Exit the model.
6. Add branches from the Time node to represent different events: hip fracture, vertebral fracture and death.
7. Add a sub-tree to the hip fracture event to capture the risk of concurrent death
8. Route the patient back to the Processing Event node or to Exit Model node.
9. Add an event to capture the end of the time horizon, routing to Exit Model node.
10. Add tracker variables to count occurrences of fractures.
11. Set costs and utilities that will be accumulated at selected nodes (apply appropriate discounting conversions if required).
12. Add logic to control adjustment to time-to-event by type of treatment and to control maximum allowed number of fractures.
13. Identify and adjust any distributions that need to be resampled at selected nodes (e.g. time to vertebral fracture should be resampled after the first one has occurred).
14. Make the Treatment DES node a clone of the Control node and define variables that pass treatment specific values to this sub-tree.
15. Run the model in Microsimulation mode (Menu options: Analysis > Monte Carlo Simulation > Trials (Microsimulation)…)

Further information about building and validating DES models can be found in TreeAge Pro's built-in help documentation.

Figure 2: Structure for DES implemented in TreeAge Pro



4.4. DES IN A BESPOKE SIMULATION PACKAGE (SIMUL8)

Here we provide a brief description of how to implement a DES within a bespoke simulation package. The benefits of using a bespoke package include;

- graphical representations of the simulation
- easy debugging and validation
- quick and easy development of new models
- random number control
- easy sampling of time-to-event variables from commonly used distributions e.g. Weibull, exponential

There are several bespoke simulation packages that can be used to implement a DES and we have chosen to use SIMUL8 purely because this is the package which the authors have access to and with which the authors are most familiar. Figure 3 gives a graphical representation of the example DES model implemented within the bespoke modelling package SIMUL8.

In broad terms, the steps needed to set up the example DES simulation in SIMUL8 are as follows;

1. Set up a work-entry point which feeds the required number of patients into the simulation
2. Define distributions for time-to-event attributes e.g. Weibull for time to hip fracture
3. Define attributes and set starting values (e.g. set time-to-event attributes equal to time-to-event distributions, set starting utility, set patient history of fractures)
4. Add variables to information store (e.g. utility multipliers, costs, discount rates)
5. Add visual logic to the work-entry point to set the patient's route (which work-station they go to next) according to the next event
6. Create a work-station to process each of the event types; hip fracture, vertebral fracture and death
7. Add visual logic to the work-stations which;
    a. Calculates costs and QALYs accrued since the last event (discounted and undiscounted) and add these to totals so far.
    b. Updates attributes to record the event that has happened (e.g. Utility, patient's fracture history, set time of last event equal to time of this event)

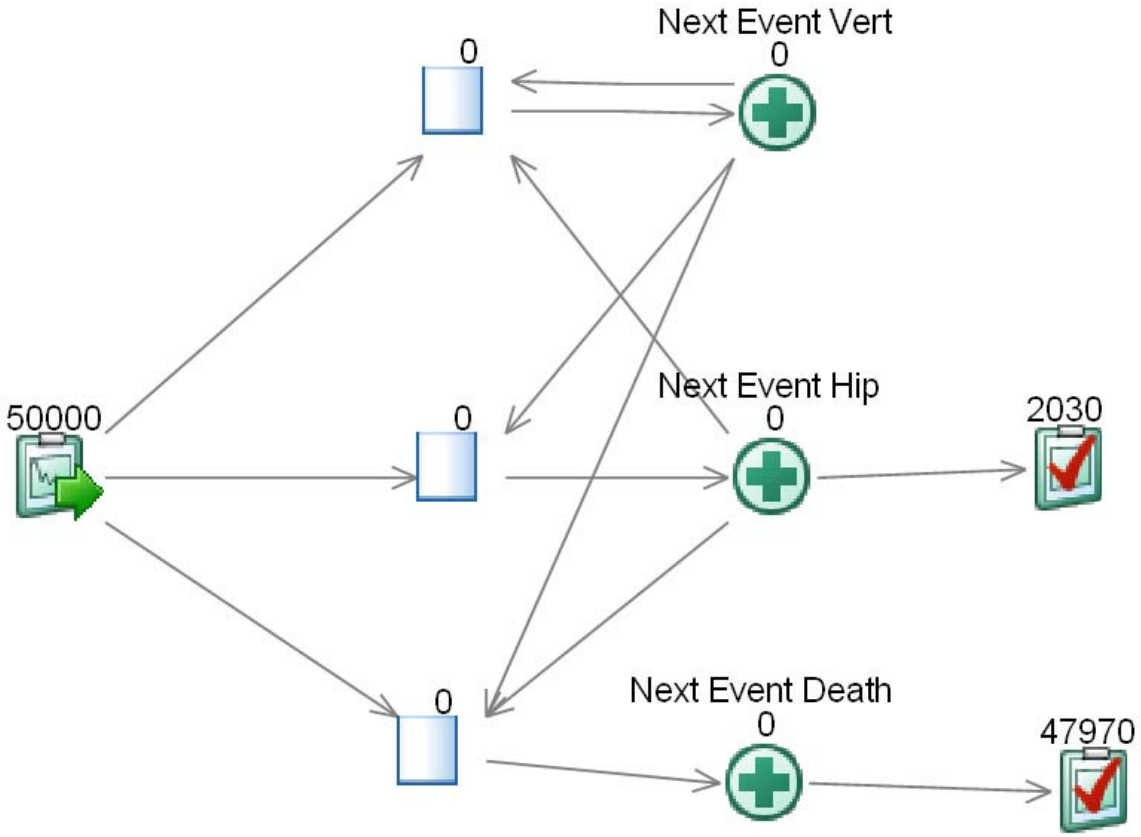
c. Updates event list to reflect changes needed following this event e.g. prevent further hip fractures after first hip fracture, sample time to second vertebral fracture after first vertebral fracture
d. Sets the patient's route out to the appropriate work-station according to the next event or alternatively route them to a work-exit point if exit condition met (e.g. death due to hip fracture)

8. Add visual logic for end of run which converts total costs and QALYs to average per simulated patient

The full documentation for the SIMUL8 implementation of our example DES model is provided in Appendix C and the accompanying model can be downloaded from the DSU website (www.nicedsu.org.uk). When reviewing this SIMUL8 model, please note that we have set up the DES to step through the events for each patient as efficiently as possible using the visual logic to accumulate outcomes according to the time elapsed between events rather than holding entities in queues while time elapses on the simulation clock. In our example model, the maximum clock time we have specified is sufficient to ensure that all patients will have died before the maximum clock time is reached. The time frame of the analysis is therefore the lifetime of the population. If results were required for a specific time frame, then it would be necessary to add 'time horizon reached' as an additional event and to set up an additional work station to calculate the costs and QALYs accrued from the patient's most recent event to the end of the time horizon.

Figure 3: Graphical representation of example model in SIMUL8

Work-entry point **Queues** **Work-station** **Work-exit points**



4.5. TECHNIQUES REQUIRED TO IMPLEMENT A DES

4.5.1. Sampling from a distribution

Commercial simulation packages should provide a reasonable choice of statistical distributions for sampling parameters. The following are useful distributions;

- Uniform
- Normal
- Lognormal
- Gamma
- Beta
- Triangular
- Exponential
- Weibull

The normal, lognormal, gamma, beta and triangular distributions are commonly used within cohort models to characterise parameter uncertainty within PSA, although the triangular distribution has historically been over used given its properties.[11,26] However, the main drivers of patient-level variation within a DES are the time-to-event data which are sampled for each patient to give each one a unique pathway through the model. Two related distributions that are commonly used to sample time-to-event data are the exponential and Weibull distributions.

The exponential distribution can be used to sample the time-to-event when the hazard of an event occurring is constant over time. This is analogous to a Markov state-transition model with two states (e.g. alive and dead) where the probability of an event occurring is constant over time e.g. a 2% risk of death per annum. The survival function gives the likelihood of surviving up to a particular time which is equivalent to the predicted population of the 'alive' state for that point in time when the starting population is one. Table 1 shows the survival function for an exponential with a mean time-to-event of β which is often described as the scale parameter. The rate is given by the reciprocal of the scale parameter ($1/\beta$). When using a generic programming language to implement a DES, the time-to-event can be sampled as shown in Table 1, provided that a function is available to compute the natural logarithm and to provide a uniformly distributed sampled bounded by 0 and 1.

The Weibull distribution can be used when the hazard of an event occurring is either decreasing or increasing over time. Its form is similar to that of an exponential, but it includes a shape parameter which determines whether the hazard is increasing (shape>1) or decreasing (shape <1). Setting the Weibull parameter's shape parameter to 1 gives an exponential distribution. The survival function and the method for calculating samples from the Weibull distribution are given in Table 1.

Table 1: Survival functions

Distribution	Survival function	Sample	Notes
Exponential (β)	$S(t) = e^{\frac{-t}{\beta}}$	$-\beta ln(U)$	β = scale
Weibull (α, β);	$S(t) = e^{-(\frac{t}{\beta})^{\alpha}}$	$\beta[-ln(U)]^{\frac{1}{\alpha}}$	α=shape, β =scale

Where *U* is a uniformly distributed random number between 0 and *ln(U)* is the natural logarithm of *U*

Other continuous distributions which may be used to sample time-to-event are the gamma, lognormal, Gompertz, and log-logistic. Further details on how to sampled from these and other relevant distributions can be found in standard simulation texts.[25]

When choosing a distribution to describe a particular model parameter, consideration should be given to both how well the distribution fits the empirical data and whether the hazard functions underlying the distributions are clinically plausible. For example, the exponential distribution assumes that the hazard of an event occurring is constant over time which is unlikely to be true when modelling human survival.

4.5.2. Sampling time to death from national life-table data

In a DES it is important to reflect the fact that patients will have different paths through the model due to stochastic variability even if there is no patient heterogeneity or parameter uncertainty included in the model. So in the case of life-expectancy, there should be variation in the time to death for individual patients in the population even if their starting age is the same and their mean life-expectancy is known precisely. The interim life-tables for England and Wales includes data on the number dying between each birthday (e.g. between age 50 and age 51) for a starting birth cohort of 100,000, which is referred to as d_x in the tables. This

provides an empirical frequency distribution for age at death which can be used to sample time to death for a particular starting age. Alternatively, a parametric survival model (e.g. Weibull, Gompertz) can be fitted to the predicted number of survivors, given by the l_x data in the tables, and samples can be taken from that parametric survival model.

4.5.3. Calculating discount rates for costs and QALYs accrued over an extended time period

For costs accrued at a single time point, such as the costs of fracture in our example, the standard discounting formula can be applied:

Equation 1: $Discounted\ cost = \frac{C_t}{(1+DR)^t}$,

where C_t is the cost accrued at time t and DR is the annual discount rate (e.g. 3.5%).

However, within the discrete event framework, the costs and QALYs accrued since the last event are calculated when the next event occurs. If these costs and QALYs have been accrued at a constant rate between times a and b, then the discounted value can be calculated as follows;

Equation 2: $Discounted\ cost = V_{ab} \frac{(e^{[b(-IDR)]} - e^{[a(-IDR)]})}{(-IDR)}$

Where V_{ab} is the value accrued at a constant rate from time a to b and IDR is the instantaneous equivalent of the annual discount rate (DR) given by,

Equation 3: $IDR = \ln(1 + DR)$.

This formula can be derived by considering that the discount factor, as a continuous function of time, is essentially an exponential distribution which can be integrated to give the area under the curve from the time since the last event to the time of the current event. If time is measured in years, then the first term in equation 2 (V_{ab}) would be the cost per annum for cost calculations or the utility value for QALY calculations. Note that this formula results in an error if it is evaluated for a discount rate of zero, so it is advisable to have one variable tracking discounted outcomes and another variable tracking undiscounted outcomes rather than setting the discount rate to zero and re-running the model to obtain undiscounted values.

4.5.4. Estimating acceleration factors from hazard ratios when time to event data follow a Weibull distribution

In a DES framework the clinical outcomes which could be modified by effective interventions are likely to be specified in terms of the time to various events. In our example model the clinical outcomes affected by intervention are the time to hip fracture and the time to first vertebral fracture and we have assumed that the effect of the intervention is to double the time to event for each of these fracture outcomes. This is consistent with an accelerated time failure model with an acceleration factor of 2. This factor can be conveniently applied directly to the sampled comparator arm time to event data to give the corresponding time to event sample for the intervention arm. However, not all clinical trials which report time to event outcomes will use an accelerated time failure model to analyse the intervention effect. Instead it is common for them to use a proportional hazards model to analyse the impact of the intervention on time to event outcomes, in which the hazard ratio (H_r) between treatment and control is assumed to be constant throughout the time frame of the analysis. In the special case where it can be assumed that the time to event data for both intervention and control follow a Weibull distribution with a common α parameter (or an exponential distribution as this is a special case of the Weibull distribution), it is possible to convert between a proportional hazards model with hazard ratio, H_r and an accelerated time failure model with acceleration factor, γ, as follows;

Equation 4: $$Acceleration\ factor, \gamma = e^{-\ln(H_r)/\alpha}$$

It is also possible to sample the time to event for the treatment arm directly by including the hazard ratio in the formulae to estimate the random variate from Table 1 as shown in Eq 5, where α and β are the parameters for the comparator arm survival curve.

Equation 5: $$Weibull\ time\ to\ event\ sample = \beta \left[\frac{-ln(U)}{H_r}\right]^{\frac{1}{\alpha}}$$

If it cannot be assumed that both the intervention and control arm data follow a Weibull distribution and that the hazard ratio is constant (i.e the α parameter is common across both arms), then an alternative method must be used to apply the efficacy evidence within the DES model. For example, it may be necessary to fit separate time to event curves to the data from each arm, allowing β and α parameters to be specified separately for each treatment arm. For further details on fitting survival curves to patient-level data see TSD 14.[27,28]

4.6. PATIENT-LEVEL STATE-TRANSITION FRAMEWORK

In a patient-level state-transition framework, the model is constructed in a similar manner to a cohort state-transition model, but random numbers are used to determine exactly which transition is made each cycle based on the probabilities defined in the transition matrix. This is in contrast to the cohort state-transition model where a proportion of the cohort experiences the event. Provided that the appropriate non-Markovian assumptions are applied to the transition matrix, our simple example model can be implemented using four health states;

- No fracture this cycle
- Hip fracture this cycle
- Vertebral fracture this cycle
- Dead

Patients move to the hip fracture and vertebral fracture health states for a single cycle when these events occur. They then return to the 'no fracture this cycle' health state. They can occupy the hip fracture health state once and the vertebral fracture health state up to twice. They occupy the 'no fracture this cycle' health state for all other cycles until they die. They can therefore make return transitions to this state up to three times (once after each possible fracture). Re-using health states in this manner avoids the numerous duplicate health states required to capture all the possible combinations of patient fracture history. It is this simplicity that makes patient-level state-transition models attractive compared to cohort-level state-transition model in situations where future events are dependent on previous events.

Each cycle, the probability of each transition in the matrix is compared with a random number to determine if that particular transition occurs that cycle. When the random number is less than the probability, the transition element is set to 1 to indicate that the transition occurs. However, each row of the transition matrix must sum to one, just as it must for a cohort-level state-transition model. So if more than one transition in a row is sampled to occur a rule must be set up to determine which of the possible transitions is acted on. In our example spreadsheet model, we have assumed that deaths have precedence over hip fractures and hip fractures have precedence over vertebral fractures. This bias towards the more extreme event ensures that rarer but potentially more dangerous events are not ignored within the model, but this means that the model is likely to favour treatments which prevent the more severe events over those that prevent the less severe events. The bias that this generates within the cost-effectiveness estimates can be minimised by reducing the cycle length, as this

lowers the probability that two events are sampled to occur within a single cycle, although as discussed earlier reducing the cycle length may also make the model large and slow to evaluate over long time-horizons. Using a DES modelling approach avoids the potential bias associated with using a discrete time approach as the exact timing of each event is sampled, and then processed in order of occurrence, allowing multiple events to occur within a short period of time without additional computational expense.

As the health states themselves do not track the patient's history of previous fracture, future events are made dependent on previous events through the transition matrix. This is possible as the path of each patient is simulated individually and therefore their exact history is tracked through their occupation of health states in earlier cycles. In a cohort-level Markov state-transition model it is not possible to distinguish between patients according to anything other than their current health state. So in our example, patients entering the vertebral fracture state from the 'no fracture this cycle' state cannot be dealt with differently according to whether this is their first or second vertebral fracture or whether they have previously had a hip fracture. Therefore, the transition matrix for a cohort-level Markov state-transition model cannot be made dependent on the patient's history without defining separate health states to capture all the various histories that could result in a patient occupying that particular state. In our example patient-level state-transition model, the transition matrix refers back to the health state occupation of all previous cycles to determine whether there has been a previous vertebral or hip fracture. It cannot therefore be referred to as a 'Markov' model as the Markovian assumption no longer holds.

The transition matrix may also need to be made dependent on the current time or the time since previous events have occurred. As the survival distributions for avoiding either a hip or vertebral fracture are considered to follow a Weibull distribution, the probability of making a transition during a single cycle is not constant over time. For the first hip and vertebral fractures occurring, the transition probabilities are dependent on the time since the start of the simulation. For the second vertebral fracture the transition probability is dependent on the time since the first vertebral fracture, so this also needs to be tracked by the model based on the model's record of when the vertebral fracture state was previously occupied. The utility values for each of the states are also dependent on the patient's state occupation history as the current utility value is simply updated with a multiplier for each new event. Furthermore, in the case of vertebral fractures a different utility value must be applied according to whether

this is the first or second vertebral fracture, and in the case of hip fractures the utility must be set to zero for fatal hip fractures.

The costs in our example model are more easily calculated as these depend only on the current health state occupation with one exception. The treatment costs need to stop being applied at the time of death but when patients die as a result of a hip fracture they do not move to the death state until the following cycle as it is necessary to record their transition through the hip fracture state in order to apply hip fracture costs. Therefore, the cost of the treatment has been set to zero for fatal hip fractures, but the full costs of the fracture itself are applied. Similarly, the estimate of life-years has been calculated based on the time spent in health states with utility >0 as this correctly captures fatal hip fractures at the time of hip fracture rather than at the next cycle when the patient moves to the death state.

In order to create fracture risks in our state-transition model example which are equivalent to those in our DES example, we need to calculate the probability of patients experiencing an event during a single cycle length. When the likelihood of remaining free of a particular event is defined as following a Weibull distribution (as for hip and vertebral fractures in our example model), the likelihood of experiencing a transition during the period from t_1 to t_2 can be calculated as;

Equation 6: $P(t_1, t_2) = 1 - exp[(\frac{t_1}{\beta})^{\alpha} - (\frac{t_2}{\beta})^{\alpha}]$

Therefore transition probabilities can be calculated for the comparator arm using the relevant α and β parameters for the comparator arm, but the relative impact of treatment on fracture risks still needs to be captured in the intervention arm.

In our DES example model, the time to hip and first vertebral fracture is doubled for intervention compared to control. Doubling the time to fracture for intervention compared to control is analogous to a scenario where the time at risk of fracture moves at half the pace for the intervention arm. This is equivalent to saying that the probability of experiencing fracture events in the comparator arm between time t_1 and t_2 is equivalent to the probability of experiencing those fracture events in the treatment arm between times $2t_1$ and $2t_2$ .This can be described as an accelerated time failure (ATF) model with an acceleration factor of 2.

Transition probabilities for the intervention arm can be calculated directly by applying such a time-transformation to the formula used within the comparator arm.

However, when implementing a state-transition model it is more usual to apply efficacy data that is reported using either hazard ratios or relative risks. It can be shown that an accelerated time failure model for a Weibull survival distribution is equivalent to a proportional hazards model with the following hazard ratio for intervention versus control;

Equation 7: $Hazard\ Ratio, H_r = e^{-\alpha ln\gamma}$

where γ is the acceleration factor i.e. 2 in this case.

In our example model, the time to hip and vertebral fractures are sampled from Weibull distributions with shape parameters of 4 and 2 respectively. Therefore the ATF model with an acceleration factor of 2 is equivalent to a proportional hazards model with a Hazard Ratio of 0.0625 and 0.25 for hip and vertebral fractures respectively.

The hazard ratio cannot be applied to the scale parameter directly as the hazard is a function of both shape and scale. However it is possible to make a relatively simple change to the transition probability calculation when using an alternative parameterization for the Weibull function. In this alternative parameterization the survival function is defined as

Equation 8: $S(t) = e^{-\lambda t^{\alpha}}$,

where λ is defined as follows;

Equation 9: $\lambda = \beta^{-\alpha}$.

The transition probability in the comparator arm can now be written as;

Equation 10: $P(t_{1,}t_2) = 1 - exp[\lambda {t_1}^{\alpha} - \lambda {t_2}^{\alpha}]$

with the transition probability in the treatment arm given by;

Equation 11: $P(t_{1,}t_2) = 1 - exp[(H_r\lambda){t_1}^{\alpha} - (H_r\lambda){t_2}^{\alpha}]$

where H_r is the hazard ratio for treatment versus control.

All of the above can be implemented within either a bespoke modelling package such as TreeAge, or within a generic modelling environment such as Microsoft Excel or R. TreeAge includes an option for conducting stochastic patient-level simulations and tracker variables can be set up to record the patient's previous events in order to make the transition probabilities dependent on patient history. Programming a patient-level state-transition model within Microsoft Excel requires great care as the logic required to specify the transition matrices may be complex and difficult to check for errors. Whilst a patient-level state-transition structure may require more complex logic, it may still be easier to construct and validate than an equivalent Markov cohort-level state-transition structure given the number of health states required to capture all the possible patient histories in order to maintain the Markov assumption. Our example model may be implemented with a reasonable number of distinct health states, but if the number of fracture types was increased from 2 to 4, then the number of health states would quickly become unmanageable for a cohort-level Markov model, particularly if the number of repeat fractures was not restricted to one or two per fracture type.

4.6.1. Practical difficulties of implementing a patient-level state-transition model within a spreadsheet package.

- A rule of precedence must be set to process events when more than one is sampled to occur within a single cycle (this introduces a bias which is minimised, but not eliminated, by lowering the cycle length).
- Time-dependent transition matrices may need to be specified if constant hazards cannot be assumed. Care should be taken to ensure that it is the time since the person became at risk that is used to calculate the transition probability rather than time since the start of simulation (e.g. risk of second vertebral fracture applies from time of first vertebral fracture)
- Transition matrices may have to incorporate many logical statements if they need to be dependent on both the occurrence of previous events and the time since those previous events.
- Care must be taken to specify exactly the time period being referenced within each formula to avoid circular references, as the current state occupation at time t_2 is dependent on the transition matrix from time t_1 to t_2, which itself is dependent on state occupation up to time t_1.
- The spreadsheet can become large and difficult to work with if a large number of health states or time cycles are needed or if a large number of therapies are to be compared using duplicate structures.
- Controlling the random number stream to achieve identical results for each model run and/or to apply common random numbers across different interventions becomes more difficult as the number of health states, time cycles and interventions increases due to the need to store and access a large number of random number samples.

4.6.2. Implementing a patient-level state-transition model in TreeAge Pro

Here we provide a brief description of how to implement a state-transition model using patient-level simulation in TreeAge Pro. The example model is available from the DSU website (www.nicedsu.org.uk) and the model structure is shown in

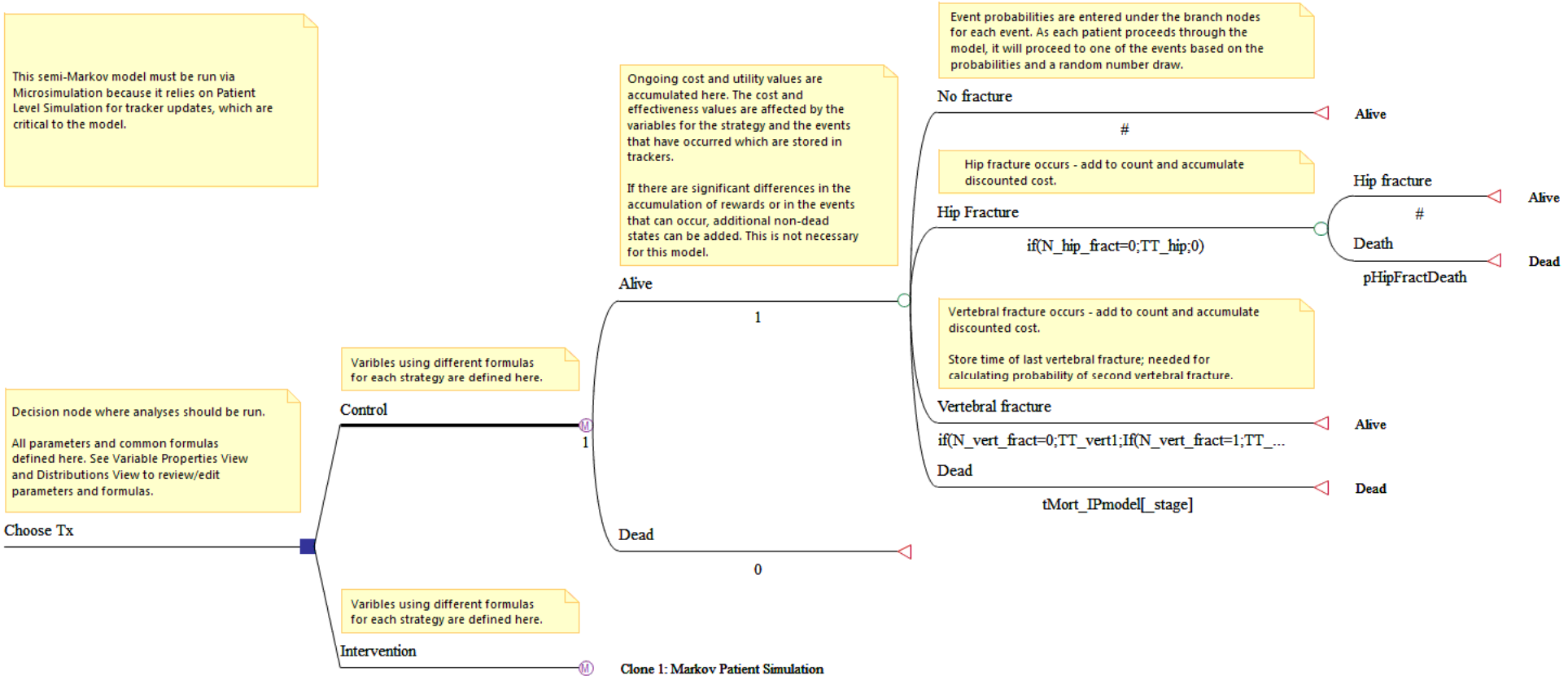
Figure 4.

In broad terms, the steps needed to set up the example model for individual patient simulation are as follows:

1. Starting with a default decision node, add branches for each treatment strategy (control and intervention) and add Markov nodes at the end of each branch.
2. Define all model parameters and common formulae at the root decision node.
3. Define treatment specific formulas at each strategy node (the Markov nodes) and set the number of cycles.
4. At the control treatment branch, create health states for 'alive' and 'dead' using chance nodes.
5. Create branches for the 'alive' state for all possible events which can occur, i.e. no fracture, hip fracture, vertebral fracture and death.
6. Add a sub-tree for hip fractures to capture the risk of concurrent death.
7. For each event branch, direct the patients back to the appropriate health state ('alive' or 'dead') via the terminal nodes.
8. Add tracker variables to count occurrences of fractures.
9. Enter appropriate formulae for probabilities, costs and utilities (apply appropriate discounting conversions if required).
10. Use the common event structure from the control treatment branch to clone any additional treatment strategies, including the intervention node.
11. Run the model in Microsimulation mode (Menu options: Analysis > Monte Carlo Simulation > Trials (Microsimulation)…)

Further information about building and validating DES models can be found in TreeAge Pro's built in help documentation.

Figure 4: Structure of patient-level state-transition model implemented in TreeAge Pro



5. GOOD MODELLING PRACTICE FOR PATIENT-LEVEL SIMULATIONS

This section provides a summary of issues thought to be of value to general readers. More advanced readers are referred to standard simulation text books such as Pidd, Law and Banks and colleagues.[18,25,29]

5.1. STRUCTURING A PATIENT-LEVEL SIMULATION

In typical pharmaceutical evaluation models, where patients are assumed to be independent, the computational time required is approximately proportional to the number of patients, However, where patients are competing for resources and held in queues until resources become free the computational time can increase dramatically with the number of patients in models. Therefore it is good practice to not hold entities in queues unless absolutely necessary.

To illustrate these points, a simple model was constructed in SIMUL8 where entities were forced to wait in queues until a single event occurred (the timing of which was assuming to be normally distributed with an average of 10 units and a standard deviation of 2.5). Once the event occurred a cumulative total of event times was updated and the entity exited the model. The running time took less than ten seconds to evaluate 10,000 entities; four minutes to evaluate 50,000 entities and in excess of four hours to evaluate 300,000 entities. These values demonstrate the non-proportional increase in time as patient numbers increase.

A replicate model was constructed with entities not held in queues but instead the running total was increased by the estimated time to event and the entity exiting the model immediately such that only one entity was in the model at any point in time. The replicate model processed 300,000 in three seconds demonstrating the efficiency of not holding entities within queues in the final analysis model. However, it is often beneficial to construct models with queues for debugging purposes or for walking through models with clinical experts and then to remove these when processing results.

5.2. ESTABLISHING THE NUMBER OF INDIVIDUAL PATIENTS TO SIMULATE

In patient-level models there is sampling error due to the variability in the simulated experiences between patients. This uncertainty is often referred to as first-order uncertainty, and can be decreased by simulating an increased number of individual patients; however, this will result in a greater computational time requirement. In contrast, the marginal effect of each patient on the average costs and QALYs is expected to decrease as the number of patients previously simulated increases. For example, the change in average costs is likely to be less when sampling the one millionth patient compared with the one hundredth patient.

As the computational requirements are at least proportionate to the number of patients but there is a decrease in the marginal information provided by patients, it is clear that there will be a point at which the increased accuracy associated with running one additional patient would not be considered sufficient to justify the additional computational time required. To the authors' knowledge there is no widely-used algorithm within the discipline of health economics to determine the optimal number of patients to simulate. O'Hagan and colleagues have detailed a method that uses an analysis of variance approach to determine the appropriate number of patients and number of samples from the parameter uncertainty which can reduce the computational time required.[30] However, this method requires initial runs for calibration and is often not necessary for models which have a relatively quick computational time.

Outside the confines of health economics, published papers have explicitly estimated the costs of sampling compared with the value of additional information; interested readers are referred to Chick and Frazier, and Chick and Gans and the references contained therein.[31,32]

Typically the number of patients to sample is left to the discretion of the modeller. However, it would be expected that all modellers justify the number of patients selected. Methods of justification can include a graphical representation of the costs, QALYs and the cost per QALY gained and determining at what number of patients the estimated error in the results appear acceptable. Examples of such a diagram depicting the incremental costs, incremental QALYs and the cost per QALY gained using the simple osteoporosis model is provided in Figure 5 to 7. Each figure includes error bars to show the uncertainty in the mean estimate, calculated using the standard error for incremental costs and QALYs and by jackknifing for

the cost per QALY gained, which is discussed in more detail in section 5.3. As expected, the length of the error bars decrease as the number of patients simulated increases.

Figure 5: A plot of incremental costs in relation to the number of patients simulated.

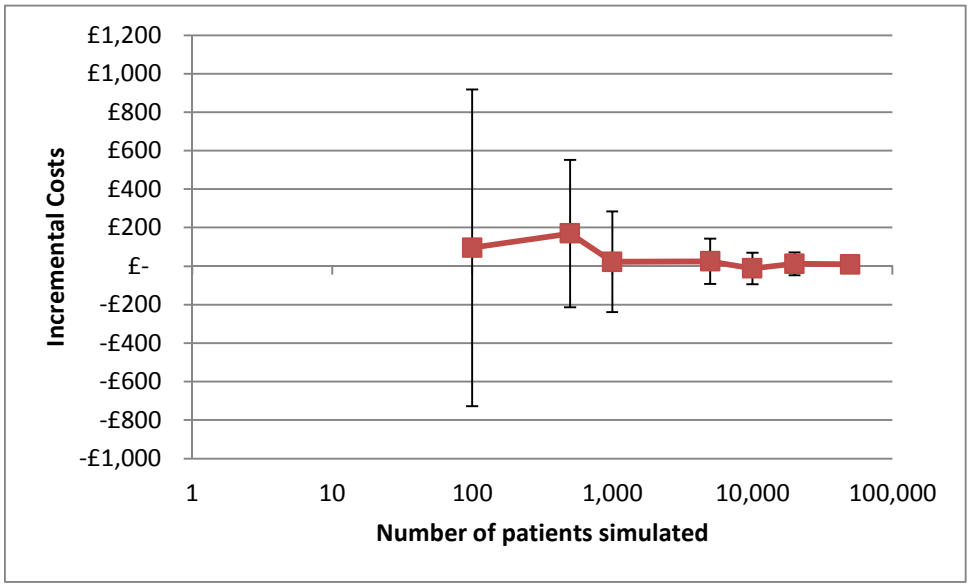


Figure 6: A plot of incremental QALYs gained in relation to the number of patients simulated.

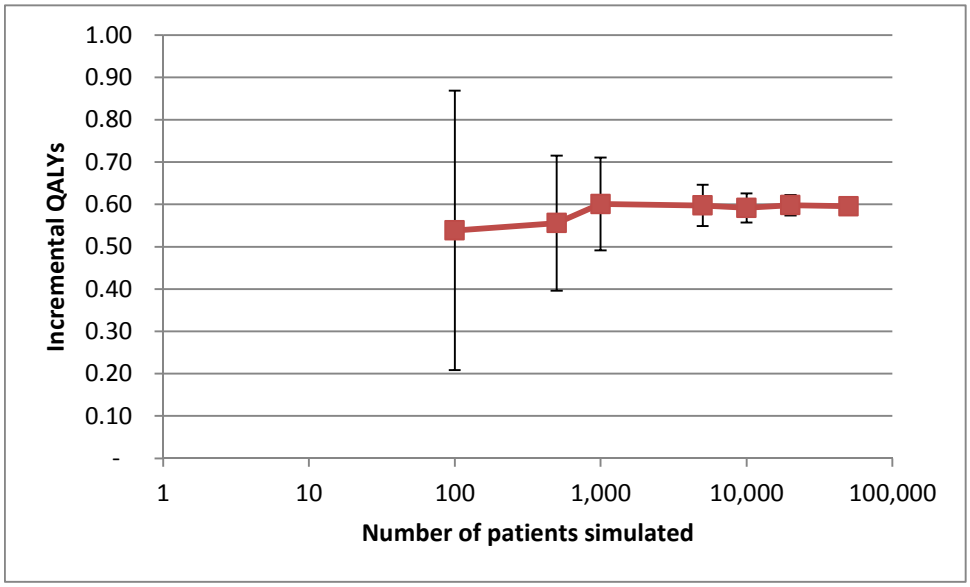
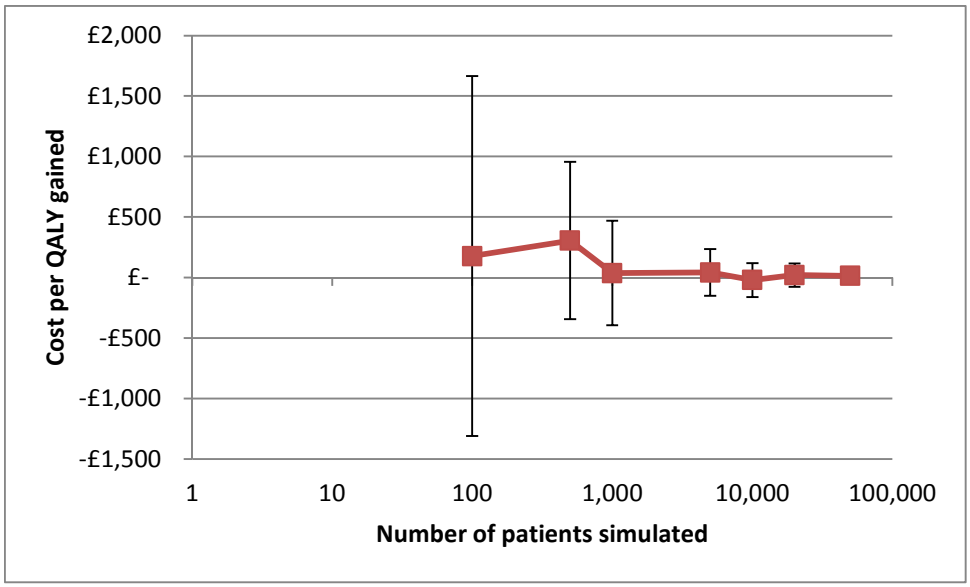


Figure 7: A plot of cost per QALY gained in relation to the number of patients simulated.



The actual number of patients to simulate may be dependent on the running time. For the example shown in Figure 5, if the model has a short running time then running 100,000 patients may be appropriate, but if computational time was a constraint it could be argued that running 5000 patients per simulation would provide relatively accurate results (95% confidence interval on the cost per QALY gained of less than £400) with a reduction of 80% in the computational time required. This reduction would allow for more extensive sensitivity and subgroup analysis to be conducted within the timeframe available.

An important consideration when determining the required number of patients is the level of similarity between the interventions being compared. If there are clear differences in terms of the efficacy and/or costs of the intervention then the number of patients required may be fewer than if two similar treatments are compared.

An alternative approach, or one that can be complimentary to the graphical method, is to re-run analyses multiple times having decided on a candidate number of patients and to compare results across the multiple runs for consistency. If the data are too inconsistent then a further analysis with a greater number of patients would be required. It is noted that different random number streams should be used for each run to avoid identical results being generated.

Care should be taken to determine whether the sample size required to achieve acceptably accurate results varies depending on the random number stream used. This can be done by

altering the seed number used to initialise the random number stream and re-running the results. The sample size chosen should be sufficient to ensure that comparable results are achieved regardless of the chosen seed.[16] If the results are found to vary significantly when selecting a different random number stream then the model should be checked to see whether there are any unintended correlations between samples that are supposed to vary independently. Coordination of random number streams between interventions can provide a more rapid estimation of the desired outputs and can be achieved in bespoke DES packages. Law *et al.* provide details on the use of common random numbers and several other variance reduction techniques, which may be of interest if the level of precision required cannot be efficiently obtained by increasing the number of patients sampled.[25]

Limitations associated with the random number in Microsoft Excel have been documented of which modellers should be aware.[33] In a problem observed by the authors, a model had shown relative stability of results at a given number of individual patients. However, when a further strategy was added to the decision problem the results changed substantially. It was identified that the problem was due to autocorrelation between random numbers within Microsoft Excel. The experience of each patient was simulated under all strategies before progressing to the next hypothetical patient; as such adding an additional strategy caused a different distribution of the values within the chosen random numbers stream. The impact of the autocorrelation problem was minimised by evaluating the results for all simulated patients for a strategy before evaluating the next strategy.

5.3. CONDUCTING PROBABILISTIC SENSITIVITY ANALYSIS

Probabilistic sensitivity analysis is recommended as it produces a more accurate assessment of the expected cost-effectiveness of interventions when the model is non-linear.[4] This enables the uncertainty associated with parameters to be simultaneously reflected in the results of the model. In non-linear decision models, probabilistic methods provide the best estimates of mean costs and outcomes.[1] The National Institute for Health and Care Excellence advocates their use stating that 'Probabilistic sensitivity analysis is preferred' […. to a deterministic analysis using means or most-likely values].

Conducting PSA within a patient-level model is no different to conducting it within a cohort-level model. Samples for the parameter estimates are drawn from appropriate distributions,

taking into account any correlations between parameters, and then the model is evaluated at each of these PSA configurations. The only difference is that in a patient-level model, the model evaluation step involves estimating the average outcomes across a large number of simulated individuals, whereas the cohort-level model can be evaluated analytically. As such this section applies equally to both patient-level and cohort-level models.

Historically there has been little justification of the number of PSA configurations evaluated in submissions received by NICE and the number undertaken is typically a round number (for example 1000) and has been left to the discretion of the modeller. However, approaches do exist to provide an indication of whether the number that has been run is likely to be sufficient. A simple approach denoted 'jackknifing' was proposed by Iglehart[34] and is summarised in Law.[25] The jackknife approach allows a confidence interval to be estimated for the mean incremental cost-effectiveness ratio (ICER) and is not affected by the statistical bias that is associated with classical estimates of a non-linear function (such as cost per QALY) that is a ratio of two model outputs. Using this approach the robustness of the decision can be evaluated. For example, if the 95% confidence interval (CI) for the mean cost per QALY was wide and crossed one of the commonly reported thresholds then it is an indication that further PSA configuration may be required to produce a more definitive ICER. In contrast, if the 95% CI was narrow and confined to one side of commonly reported thresholds, for example £20,000 to £30,000 per QALY gained in the context of NICE, then this is an indication that sufficient PSA configurations have been undertaken. An example of the jackknife used within a health technology assessment setting is provided in Stevenson *et al*.[15] For further information on stochastic versus parameter uncertainty in disciplines other than health economics readers are directed to Zouaoui and Wilson[35], Ng and Chick[36], and Barton and colleagues[37] and included references.

In rare occasions where the running time of the model is so large that PSA cannot be run within the timescales of a project then mathematical approximations of the output may be required in order to facilitate PSA. An example of such techniques is provided in Stevenson et al.[38]

5.4. THE RELATIVE IMPORTANCE OF FIRST- AND SECOND- ORDER UNCERTAINTY

A result provided by O'Hagan and colleagues[30] is that for patient-level simulations without patient interaction, if the only objective of PSAs was to estimate the mean cost, effectiveness or net benefit then the optimal number of patients to run per sample (for a given computational resource) would be one patient, whilst running as many configurations from parameter uncertainty as possible. However, this would not provide data on the uncertainty in the output. Nevertheless, this would imply that where there is a choice between either reducing the number of individual patients simulated or reducing the number of configurations drawn from parameter uncertainty, then the former is the most appropriate option, although a reasonable number of patients should be maintained if outputs such as cost-effectiveness acceptability curves are required.

Strong *et al.*[39] have recently described a nonparameteric regression method for estimating partial expected value of perfect information (pEVPI) from the PSA output. This eliminates the need to run a 2-level nested Monte Carlo Simulation to estimate the pEVPI, thus substantially reducing the computational effort required to obtain pEVPI estimates from either cohort-level models or patient-level simulations. Furthermore, in the case of patient-level simulations, Strong et *al.*'s method treats any residual variability in the net benefit due to non-convergence of a patient-level simulation as noise in the regression, which is averaged out, allowing a small patient sample size to be used to inform the pEVPI analysis without causing any upward bias in the pEVPI estimate. Therefore, the choice to use a patient-level simulation should not preclude analysts from conducting either PSA or pEVPI analysis.

5.5. TRANSPARENT REPORTING OF PATIENT-LEVEL SIMULATIONS

The clear presentation of the intended and actual structure of a simulation is essential in ensuring that model users understand the strengths and limitations of the model and the evidence upon which the model has been structured and parameterised. It is important to report not only the structure of the final model and its assumptions, but also why those assumptions should be considered necessary and appropriate. Existing guidelines, for example the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement may provide a useful structure for reporting models.[40]

In addition to existing reporting standards, the reader should note that TSD 13[41] presents a detailed exposition of methods for developing and reporting two key classes of conceptual model:

1. Problem-oriented conceptual models. These conceptual models are associated with developing, sharing and testing one's understanding of the decision problem and the system in which that problem exists. Problem-oriented models do not involve making assertions about how the model will be developed. The two key forms of problem-oriented conceptual model are:
    a. Disease Logic Models which set out in visual and textual formats, the model developer's conceptual understanding of the key disease-specific factors and how the disease process operates, and;
    b. Service Pathways Models which set out the model developer's understanding of the way in which disease services are organised and delivered.
2. Design-oriented models. These conceptual models are associated with designing, specifying and justifying the model and its structure given the evidence that is anticipated to be available. Design-oriented models are thus more reflective of the interrelationships between the disease and service pathways and the necessary simplifications and abstractions required in order to synthesise evidence to reflect such interrelationships.

In separating out these two types of conceptual model development, the model developer and model user is able to compare and contrast between the conceptual model types in order to argue and justify simplifications and abstractions in the final model. TSD 13 provides detailed advice on what to consider and how to formulate these conceptual models.[41]

5.6. VALIDATING PATIENT-LEVEL SIMULATIONS

Health policy decisions must be relevant, evidence-based and transparent. Decision-analytic modelling is well placed to support this process however the usefulness of the results of cost-effectiveness analyses in informing decisions are hinged on the credibility of the model from which they are drawn. The presence (and identification of) errors in mathematical decision models or simulation exercises may reduce the credibility and usefulness of such models. Errors can be introduced at any point in the model development process, from understanding the decision problem to using the model to inform decision-making. Errors which are

identified may reduce the decision-makers' trust in the model, whilst errors which are not identified may unintentionally lead to suboptimal decisions. The processes and techniques employed to validate and verify patient-level simulations, or indeed any type of model, therefore represent an important part of the model development process. Broadly speaking, model verification relates to whether the model behaves as intended (is the model right?), whilst the broader concept of model validation, which subsumes model verification, relates to whether the model can be considered fit for purpose (is it the right model?).[42,43]

In the absence of a standardised set of guidelines for model checking, and given the fact that all models are unique, setting out a comprehensive and exhaustive guide to checking simulation models is difficult, if not impossible. It is further important to recognise that model validation and verification involves more than simply resolving programming or technical errors; it extends to problems in identifying and addressing "softer" aspects of the decision problem relating to the definition of the decision problem and setting out the conceptual basis which will underlie the hard implemented software model. The definition of what constitutes an error (and what does not) is not always clear. As a consequence, certain problems in models may be deemed to represent unequivocal errors (e.g. failure to adhere to the laws of probability), whilst the acceptability of other matters of judgement must be interpreted subjectively.

The avoidance and identification of errors are highly relevant aspects of ensuring that a model is behaving as intended and that confidence can be placed in the model's results. The distinction between error avoidance and identification is however somewhat hazy, but is probably best considered in terms of the occurrence and timing of the error. An effective error avoidance strategy may prevent an error from being introduced in the first place, or may result in the early identification and resolution of the error prior to the model's completion and use. Error identification may occur whilst the model is being developed or after it has been considered to be completed. Ideally, error avoidance should reduce the need for, and limit the adverse consequences of, error identification.

Several software packages include functionality that can assist the modeller and reviewer to identify potential sources of errors in the model by validating the model against a selection of potential issues. For example, TreeAge Pro has functions which can help identify missing or incorrectly defined nodes, probabilities, pay-offs and jump states or variables, distributions

and tables that have been defined but are not used. SIMUL8 Professional offers a suite of debugging tools to aid the identification of model errors. Similarly, later versions of Microsoft Excel offer formulae auditing and error checking functions.

An ability to control the random number streams used by the simulation to ensure that results are replicable from one run to the next is extremely useful when debugging patient-level simulations as any unexpected behaviour will be reproduced at the same point in each run making it easier for the modeler to detect when that behaviour has been eliminated. Model implementations which do not allow the random number streams to be controlled in this way should be avoided for this reason.

A recent Health Technology Assessment (HTA) report by Chilcott *et al.*[44] highlighted a number of different processes and techniques to avoid and identify errors in HTA models. These relate not only to the implementation of the model but more widely to the overall model development process. An amended version of this list, adapted to a simulation context, is presented in Table 2. This list should be considered as a starting point rather than a definitive comprehensive guide. Further general guidance on model transparency and validation is available from the ISPOR-SMDM Modeling Good Research Practices Task Force.[45]

Table 2: Avoiding / identifying errors in patient-level simulations

Suggested activities for avoiding errors within patient-level simulations
*Ensuring mutual understanding between modeller and problem-owners**
• Ensure mutual understanding of the problem situation, the decision-makers' objectives and the clinical intent of relevant interventions across the system • Develop explicit conceptual models* of the disease logic and service pathways in conjunction with clinical experts who practice within the disease service • Iterative negotiation and communication between the modeller and the decision-maker concerning what is required of the model and what can be achieved (subject to time, expertise, expense)
Checking face validity of the model
• Establish ongoing long-term involvement with stakeholders who know about the disease and its treatment • Undertake peer review of conceptual models* • Discuss data sources with clinicians • Step through simulation model pathways with clinical experts • Ask clinicians to provide feedback on whether the model results meet their pre-determined expectations (note – deviations may indicate either an error or that the prior expectation was incorrect) • Compare interim or final model results against pre-determined expectations (from previous models, from skeleton/back of the envelope model)
Transparency of methodology and assumptions
• Produce written and diagrammatic descriptions of conceptual models* • Explicit agreement of problem-oriented conceptual models prior to developing design-oriented conceptual model* • Development of written design-oriented conceptual model plus consultation • Transparent and iterative comparison of design-oriented conceptual model with problem-oriented conceptual model
Housekeeping techniques
• Use of a standard model layout • Consistent use of programming logic to route patients to the next event • Use of separate referenceable model parameters worksheet / input file within

simulation package / programming language

- Use of identifiers which distinguish between patient attributes (i.e. labels or tracker variables), distributions and global simulation variables e.g. "utility_patient", "utility_dist", "QALYs_global"

Suggested activities for error checking within patient-level simulations

Model testing

- Compare the mean of the parameter samples generated by the model against the point estimate for that parameter.
- Use graphical methods to examine distributions, functions etc.
- Output patient-level information on intermediate and final outcomes and apply logical tests to check for unintended behaviour (e.g. check time of death≤life expectancy)
- Check data used in the model against source material
- Check the integrity of all pre-model analysis including the ability of the model to predict the data used to inform it
- Construct mock-ups in Microsoft Excel for portions of the simulation that are difficult to assess
- Annotate all model logic to aid stepping through the code
- Test model logic by stepping through the experience of individual patients
- Insert dummy states and examine throughput using specific patient labels or global numbers
- Record interim outputs (e.g. numbers of patients and time to events) within the logic that processes events to check model flows and event times are as intended
- Check model results against expectations (and ensure that unexpected results can be explained)
- Compare deterministic results with PSA

Model peer review

- Internal peer review by modeller responsible for building model
- Internal peer review by modeller not involved in developing the model
- External peer review by clinical experts and methodologists
- Check model input values against source material

** For further details on formal conceptual modelling approaches, the reader should refer to TSD13 .*[41]

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