

# A Comparison of Modelling Techniques: Patient Simulation vs Markov Modelling in Ophthalmology



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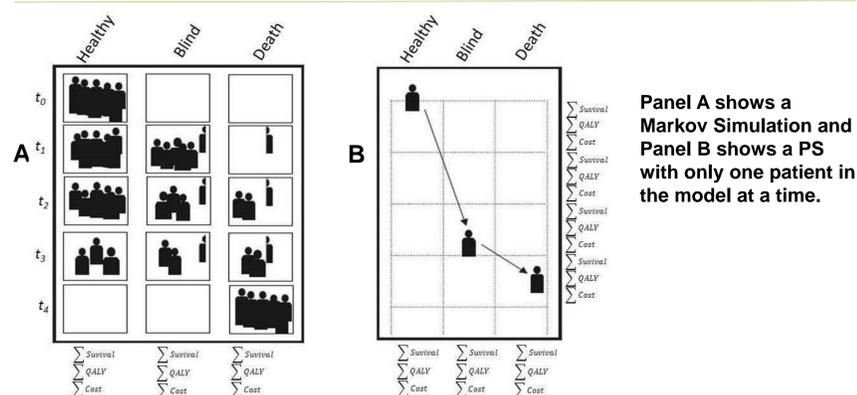
## Background and Objectives

Cost-effectiveness analysis is used to evaluate healthcare system performance, by indicating interventions yielding the highest value for money; maximising health given restrained resources. Economic models are a flexible way of estimating cost-effectiveness over long time horizons; something not possible in trial based cost-effectiveness evaluations, and are the primary means of estimating cost-effectiveness for new drug interventions. There are a number of approaches to economic modelling. The optimal approach depends on the nature of the problem being modelled and therefore needs to be assessed on an individual basis. It is therefore important that the choice of modelling approach is given careful consideration and properly justified; often a criticism of models submitted for Technology Appraisal<sup>1</sup>.

The majority of economic models utilise Markov structure. In brief Markov models follow cohorts of patients across distinct sets of mutually exclusive health states. Health states are evaluated at regular intervals to determine the proportion of patients in each state per cycle. Patients move into different states according to predefined transition probabilities. Transition matrices define the flow of patients (and the associated costs and utilities) through the models states per-unit-time.

An alternative to Markov models is patient-simulation (PS) models. In a PS model individuals move through the model one at a time; rather than as a cohort. This allows individuals to be tracked through the model and means it is possible to reflect a patient's history (e.g. time since last event) and provide a more realistic picture of a patient's treatment pathway. Furthermore, PS models enhance the granularity of the results, better representing the comparative clinical evidence, since this is often diluted depending on the number of Markov states used. Patient simulation models build a patient population by repeating the simulation numerous times; estimates of cost-effectiveness are generated from estimated mean cost and benefits for the sample population. Figure 1 depicts Markov and PS models.

**Figure 1: Diagrammatic representation of Markov and patient simulation models**



Ophthalmology presents an interesting area to explore the choice of model as many aspects of an eye diseases lend themselves to a patient-level simulation, most notably the ability to model two eyes. Despite the potential advantages of a PS approach all recent HTA submissions to NICE have used Markov approach, but have effectively been one-eye models, attracting criticism from NICE.

The aim of this study is to compare the use of Markov and PS models in the context of a degenerative ophthalmological condition. A basic analysis was developed using both a Markov and PS using the same input parameters in each model. Due to the differences in the two model structures, it was necessary to transform some inputs to fit with each model structure. The PS was developed further to include aspects of the disease which could not be modelled robustly with a Markov model, and to demonstrate the impact of each of these aspects on the results.

## Methods

To avoid extrapolation of the results of these models to specific drugs, the parameter inputs do not reflect any interventions in particular, but were based on published literature to ensure internal validity. The model was driven by visual acuity (VA) score, as measured by ETDRS. In the Markov model, health states were defined as bands of 10 letters. A individual patient dataset was simulated, which contained VA in the study eye at three-monthly follow-up points for two years. From this dataset, a set of eight unique transition matrices for the Markov model and mean change in VA were calculated for two comparator options, for the study eye. It was not possible to explicitly model two eyes in the Markov model, since it would be necessary to make assumptions about the behaviour of the fellow. Drug A was assumed to be more effective than Drug B.

The drugs were assumed to be effective at maintaining VA for two years, after which vision in the study eye was assumed to decline gradually, derived from Wong (2008)<sup>2</sup>. In the Markov model decline in VA was converted to a probability of deteriorating by five letters (equivalent to a deterioration by one health state) by assuming that vision loss was normally distributed. It was assumed that patients would not improve in VA but may remain in the same health state, and that vision loss was gradual so patients would not deteriorate by more than one health state per cycle.

To estimate quality of life in each model, a real world dataset was obtained from Czoski-Murray (2009)<sup>3</sup>, a study that used contact lenses to simulate the effect of visual impairment. For the Markov model, the mean utility associated with both the BSE and the WSE for each health state was estimated. Since the fellow eye was not modelled explicitly, the model assumed that in each health state, a certain proportion of patients would be treated in their BSE. A regression analysis was undertaken for the simulation, which used two methods to estimate the utility from visual acuity: one as a function of the visual acuity in both eyes and assuming no correlation between eyes (comparable to the approach in the Markov model), and the second assuming a correlation.

## Methods cont.

The key costs considered in the analysis included drug costs, drug administration costs and monitoring costs. Costs were also applied as patients entered the blindness health state (>35 letters). Blindness costs consisted of ongoing costs that are incurred throughout the time in that health state. An additional cost was applied the first time a patient entered this health state. Since the Markov model cannot record patient history, the model assumed that patients newly entering this health state were doing so for the first time. Discontinuation could not be incorporated into the Markov model as it is assumed that cessation of active therapy results in a loss of effectiveness. Similarly, the development of bilateral disease further in the model timeline could not be modelled.

## Results

Table 1 presents the resulting cost-effectiveness estimates for the Markov model and a number of variants of the simulation model. The results are generated assuming a lifetime time horizon. Results for the PS models were generated from 50,000 iterations of the model. The simulation model in which no bilateral disease is assumed and no discontinuation of treatment is possible provides the most similar results to the Markov model. The difference is, however, quite large suggesting that the modelling approach taken impacts on the ICER obtained, despite similar assumptions being made. Cost estimates were similar in both models for Drug A; however, the Markov model provided higher cost estimates for Drug B and lower QALY estimates for both drugs.

More sophisticated versions of the simulation model, in which assumptions about bilateral disease and discontinuation of treatment are relaxed, increase the difference between the results from each model. The ICER estimated in these versions of the simulation models is higher than that obtained in the Markov model; however, with the introduction of bilateral disease Drug A is dominant over Drug B. The inclusion of bilateral disease in the model has a large impact on both overall costs (specifically for treating blindness) and on total QALYs gained.

**Table 1: Model results**

Model	Inc. costs	Inc. QALYs	ICER
Markov model	£4,022	1.097	£3,668
Basic simulation	£6,616	0.832	£7,955
Simulation with utility Model II	£6,560	0.716	£9,165
Simulation with discontinuation	£6,545	0.703	£9,309
Simulation with bilateral disease	-£143	0.941	Dominant

## Conclusions

Patient simulation models are better able to represent the course of a degenerative ophthalmological disease, incorporating explicitly and efficiently all relevant aspects without the need for mutually exclusive branches or states with few restrictions. A PS may also be a better choice of model structure for eye diseases due to less onerous data requirements. Often the modeller does not have access to patient-level trial data, making it a challenge to produce transition matrices from evidence available in the literature. Data inputs for PS models are more likely to be reported consistently in the literature and are more easily calculated from published trial data. In a Markov model it is necessary to find data that corresponds to the health state VA bands in the model, or as was carried in the Bayer NICE STA<sup>4</sup> submission carry out a statistical analysis using artificially imposed dichotomous outcomes which contain substantially less evidence than the continuous data set.

The simplifying assumptions necessary to implement a Markov approach in this disease area do not appear to be neutral in terms the ICER estimate obtained. There are significant differences between the results of the models; however, it was not possible in this study to determine which model reflects the real-world scenario more accurately. The lack of external validity to determine the models predictive power remains a limitation of the study, and is a possible area of future research.

## References

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