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Methodology

Reflecting Parameter Uncertainty in Addition to Variability in Constrained Healthcare Resource Discrete Event Simulations: Worth Going the Extra Mile or a Road to Nowhere?

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A B S T R A C T

Objectives: Probabilistic sensitivity analysis (PSA) has been shown to reduce bias in outcomes of health economic models. However, only 1 existing study has been identified that incorporates PSA within a resource-constrained discrete event simulation (DES) model. This article aims to assess whether it is feasible and appropriate to use PSA to characterize parameter uncertainty in DES models that are primarily constructed to explore the impact of constrained resources.

Methods: PSA is incorporated into a new case study of an Emergency Department DES. Structured expert elicitation is used to derive the variability and uncertainty input distributions associated with length of time taken to complete key activities within the Emergency Department. Potential challenges of implementation and analysis are explored.

Results: The results of a trial of the model, which used the best estimates of the elicited means and variability around the time taken to complete activities, provided a reasonable fit to the data for length of time within the Emergency Department. However, there was substantial and skewed uncertainty around the activity times estimated from the elicitation exercise. This led to patients taking almost 3 weeks to leave the Emergency Department in some PSA runs, which would not occur in practice.

Conclusions: Structured expert elicitation can be used to derive plausible estimates of activity times and their variability, but experts' uncertainty can be substantial. For parameters that have an impact on interactions within a resource-constrained simulation model, PSA can lead to implausible model outputs; hence, other methods may be needed.

Keywords: discrete event simulation, probabilistic sensitivity analysis, uncertainty analysis.

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Introduction

Modeling Approaches to Inform Decisions Regarding Cost-Effectiveness of Health Interventions and Policies

Many healthcare systems face budget constraints; therefore, difficult decisions must be made regarding funding of interventions and services. Decision analytic models are commonly used to determine costs and outcomes of competing interventions/services to inform policy decisions. There are different types of models that can be used to determine cost-effectiveness.[1] Markov models are commonly used in health technology assessment. These simulate cohorts of patients through a series of health states with associated outcomes. Patients' history is not explicitly modeled, although it is possible to specify a series of tunnel states to reflect previous events that patients experience. Microsimulation models can be used to incorporate individual-level heterogeneity more easily, including previous procedures and events experienced by patients.[2] Therefore, each individual is assigned a set of characteristics, which will determine their modeled outcomes.

Discrete event simulation (DES) is a type of microsimulation which models the sequence of key events within a system by estimating each time to the next event.[2] DES models do not require that events occur at fixed points in time, as with cohort type models. Instead, movements between health states are determined by events that can occur at varying times. Within DES models, individuals can be given different characteristics to determine their pathway through the model.[2] Limited resources such as staffing levels and healthcare service capacity can be incorporated into the model such that patients can only be assessed or treated if the resource is available. Patient arrival times will also affect capacity of the system. DES models are useful when there are interactions between individuals and their environment, where queues may build up because of resource constraints (such as the closure of a hospital wing[3]), or when there is substantial heterogeneity, which affects patient pathways (such as patient histories and comorbidities[4]). However, the greater flexibility offered by DES must be traded off with the additional computational time and modeling expertise required.[5]

Defining Uncertainty, Variability, and Heterogeneity

In estimating the parameters required to establish cost-effectiveness or optimum service design, uncertainty is often pervasive.[6] Epistemic uncertainty (otherwise known as parameter or second order uncertainty) pertains from the evidence used to populate these models, including estimation of treatment effects and health-related quality of life. As others have described,[7] failure to reflect uncertainty in estimating costs and outcomes of competing interventions, can lead to biased results and potentially incorrect reimbursement/commissioning decisions, with associated health losses and costs incurred. Further data collection can, potentially, reduce this epistemic uncertainty.

Aleatory uncertainty (otherwise known as variability or stochastic or first order uncertainty) refers to the fact that a set of individuals can possess the same characteristics, but alternative events and outcomes still occur for these individuals.[8] These alternative events can include arrivals and completion of activities within the system, and variability in these events may be due to variability within the system, such as resource availability. This variability (eg, lots of patients arriving at similar times, staff being absent in a nonuniform way, some patients taking a long time to be treated) leads to queues building up in the system, which affects outcomes. Ignoring this variability may assume that the system runs perfectly, with no buildup of queues; an unlikely assumption in many healthcare systems. The key distinction here between variability and uncertainty is that, no matter how much more information is obtained, variability cannot be reduced, which is not the case with uncertainty.

Similarly, heterogeneity (variability that can be explained by alternative characteristics) is another source of uncertainty that cannot be reduced. Heterogeneity is key in determining outcomes for resource-constrained DES, and this may also be true for some pharmacoeconomic models. However, in addition to heterogeneity in individuals' characteristics, in models of healthcare systems, there may also be heterogeneity between local systems. It may be important to understand and model this to be able to generalize the model results, for example, to >1 hospital department. Thus, it may be necessary to develop several DES models with alternative structures because they are inherently different.

Characterizing Uncertainty in Health Economic Models

Methods to reflect epistemic uncertainty have developed in recent years and many healthcare decision makers require the use of probabilistic sensitivity analysis (PSA), in addition to univariate sensitivity analysis, as part of their appraisal processes.[9] PSA involves representing the uncertainty in the input parameters via an appropriate distribution and sampling from these distributions over multiple model runs to propagate the uncertainty through to the model outcomes.[6] For many model types, the use of PSA is relatively straightforward to implement, and results can be generated in a timely manner. For more complex models, PSA may be a computationally expensive and time-consuming task.[10]

Epistemic uncertainty will also be present in DES models. For instance, the time to event data used to populate some of the relationships between elements of the model may be subject to uncertainty. This is because not all possible events have been observed for all patients relevant to the decision (censoring). Some of the parameters may also be estimated from external sources, including the use of expert opinion, for example, the time taken to complete activities. The extent to which this certainty (or uncertainty) drives decisions will depend on the consequences of making the wrong decision. However, PSA is not typically incorporated within resource-constrained simulation models of healthcare systems.

Within a typical health economic model, patients are often simulated over a lifetime to reflect all differences between the intervention(s) and current care. Yet, recommendations about the use of a healthcare intervention need to be made before lifetime outcomes can be collected. Thus, it is usually not possible to validate the long-term outcomes using existing data, unless patients are very close to end of life.

Characterizing Uncertainty in Resource-constrained DES Models

Karnon et al[11] published the findings of an ISPOR task force on best practices in DES modeling. This report covers resource-constrained modeling and also recommends the use of PSA in DES models, which implies that the combination should be suitable in principle. However, a formal literature search to identify any existing studies which have incorporated PSA within a resource-constrained simulation identified only 1 case study[12,13] (see Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.09.003 for full search strategy). Within this case study, the system modeled was a triaging process and subsequent treatment in orthopedic care, in which the type of staff member undertaking triage was altered to assess the impact on subsequent treatment and outcomes. The results produced seemed reasonable; however, the authors did not discuss the results of the PSA specifically in the context of the resource-constrained version of the model. This dearth of PSA application within DES models could simply be a result of the different disciplinary origins of the methods, rather than the underlying characteristics of the methodologies.

However, when modeling a healthcare system such as a hospital department, the goal of the model is to first reflect the current system over a relatively short period. The model is then used to predict the impact on outcomes for alternative policy options. In situations which the model does not reflect current practice, the modeler can discuss this with clinicians and review the evidence available, thus improving its validity. Therefore, in cases for which there is greater availability of existing data to validate the model, the level of uncertainty around the model structure and parameters may be considered to be lower and less impactful than variability and heterogeneity.

This article therefore explores whether it is feasible and appropriate to use methodology typically used in health economic models to characterize parameter uncertainty, in addition to variability, in those models that are primarily constructed to explore the impact of constrained resources. A new case study is used to demonstrate potential challenges with conducting PSA in resource-constrained DES. The structured expert elicitation used to derive plausible estimates of resource-related parameters, including the uncertainty and variability, is described. Finally, a discussion is provided on the key challenges for characterizing decision uncertainty in resource-constrained DES models and priorities for further research.

Methods of a Case Study Incorporating PSA within a Resource-constrained DES of an Emergency Department

To demonstrate the complexity and challenges in implementing PSA within a resource-constrained DES model, we updated a simulation model of the Emergency Department (ED), undertaking such analyses. Details about this model and results are provided within Squires et al.[14] In brief, this model was designed to assess the impact of reducing low-acuity attenders within the ED on waiting times. There is evidence that crowding and longer waiting times are associated with worse patient outcomes including morbidity and mortality.[15] This version of the model did not estimate the impact of alternative interventions on quality-adjusted life-years, but cost per minute saved in the system was estimated. Options that were tested within the model were for low-acuity attenders to be dealt with within other parts of the National Health Service (NHS111 or general practice [GP] surgeries) instead of the ED or to be sent to a colocated GP, which consisted of a reception and standard GP appointment. The model includes reception, triage, clinical evaluation, investigations, treatments, and discharge. Resource constraints within the model are staff and cubicles, based on expert clinical input. A questionnaire was sent to the hospital to complete the number of cubicles and each staff type over the course of a week.

Individual-level data from the CUREd database[16] were available to parameterize interarrival times and the investigations and treatments patients received. The model utilized 1 year of data from the Northern General Hospital in Sheffield, which included 117 238 patients. However, the data set included insufficient detail about the time taken to undertake the investigations and treatments within the ED. This was important because each activity was dependent upon relevant staff and cubicles being available for patients so that the impact of reducing low-acuity attenders upon length of stay in the ED could be assessed. More staff time and cubicles would be available for treating higher acuity patients if there were fewer low-acuity attenders, potentially leading to reduced length of stay. In the absence of any published data about the time taken to complete investigations and treatments within the ED, these parameters were elicited from clinicians within the ED.

Structured Expert Elicitation

A structured expert elicitation process was used to improve accountability and transparency, using reference methods to design and implement the task.[17] The full elicitation protocol is presented in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.09.003. In summary, the elicitation exercise was designed to capture experts' uncertainty about the mean time taken for each activity and about the variance (variability between patients), using methods previously developed by Alhussain and Oakley (2020).[18] For example, elicitation questions for taking a blood test are as follows:

Question 1 (mean): *"How long, on average, does it take to take a blood test?"*

Question 2 (variance): *"If a blood test takes, on average, 8 minutes, what proportion of blood tests take up to 7 minutes?"*

Quantities presented in question 2 (7 and 8 minutes) were based on experts' previous responses (see the elicitation protocol in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2023.09.003 for details).

The elicitation was conducted using a web application coded in R, Shiny.[19] The app included background information about the project, training, and the elicitation questions, as well as contact details of the researchers for any questions/problems. The total number of activities in the elicitation exercise was 23, but experts only expressed beliefs about activities they performed regularly. Experts' uncertainty about the mean (question 1 above) was elicited using a histogram (Chips and Bins method), shown to work well for experts not trained in probabilities and statistics.[17] Uncertainty around the variance (question 2 above) was elicited by asking for a range of proportions, as advised by Alhussain and Oakley (2020),[18] to minimize the burden on experts.

Seven experts agreed to take part in the exercise (2 ED consultants, 1 middle grade doctor, 1 senior nurse, 2 junior nurses, 1 research nurse). Experience level ranged from <1 year working within the ED to >20 years. Responses from 4 experts who terminated the task before answering all questions were included in the analysis. Experts were individually asked to express their beliefs. These were then aggregated using linear opinion pooling. First, a probability distribution was fitted to each expert's beliefs from the histogram, and then these were pooled, assuming that each expert contributed equally to the group overall distribution used within the DES model. These were validated by another clinician.

Updating of the Model

The results of the elicitation exercise were used directly in the simulation model, such that for every individual within a model run, the time taken to complete the activities were sampled from a distribution of the variability between individuals. The model was run 12 times with these same distributions with different random number seeds to allow for stochastic variation and to account for the variation in interarrival times over the course of a year. The parameters of the distributions were then updated, with new values sampled from the distributions of uncertainty around the mean parameters provided by the clinicians, and the model was run again 12 times. This was repeated for 100 PSA runs, to begin to assess the outcomes of the model. Additional PSA runs could have been undertaken in subsequent analyses.

Results

Structured Expert Elicitation

For the elicitation exercise, 3 experts completed the task in full (1 ED consultant, 1 junior nurse, and 1 research nurse). However, no priors were obtained for 4 tasks (time to interpret scan results, time to provide continuous positive airways pressure/nasal intermittent positive pressure ventilation/bag valve mask, time to insert an arterial line, and time for active rewarming). This indicated that none of the experts would normally perform that task in the ED. In part 1, about uncertainty for the mean parameter, the number of experts who responded was between 1 and 6. In part 2, about variability, the number of experts that responded was between 0 and 3 (as some experts only completed part 1). In the absence of any other data, an "other" category was included for those treatments for which we had no elicited data, which utilized the average time taken of the elicited treatments.

Table 1 shows the summary of aggregate priors for each task, including the mean of experts' aggregate mean, uncertainty in the aggregate mean, and variability around the mean (conditional on values in column 2). The shortest tasks included taking patient observations (~6 minutes) and interpreting them (~2 minutes), receiving a urine test result (~8 minutes), and provision of supplemental oxygen. The longest activities included getting results for blood test (~96 minutes), x-rays (~50 minutes) and scans (~90 minutes), and resuscitation (~57 minutes).

The tapering of answers to the questions toward the end of the elicitation exercise suggested that the number of parameters that can reasonably be elicited in this way is limited (in the region of 10-15 parameters). The outputs of the elicitation exercise were generally found to be reasonable in terms of the predicted means and variability but with some having larger tails than expected. The uncertainty distributions generated from the elicitation exercise gave large ranges of mean activity times.

Table 1. Summary of results for the aggregate priors.

Task	Mean time to perform the task (min)	Uncertainty in the mean (95% CI in minutes)	Variability conditional on the mean in column 2 (95% CI in min)
Q1: Time to take a blood test	12.8	1.4-36.2	9.6-16.4
Q2: Time to get blood test results	96.2	34.2-189.6	62.5-137
Q3: Time to receive x-ray results	50	7.5-132.1	43.9-56.5
Q4: Time to perform an ECG	13.6	0.4-49.9	7.4-21.7
Q5: Time to get scan results	89.1	25.8-190.9	60.2-123.6
Q6: Time to obtain patient observations	6.4	1.2-15.9	0-31.6
Q7: Time to interpret patient observations	2.1	0.1-6.8	0-8.1
Q8: Time to receive urine test results	7.6	0.2-28.2	3-14.3
Q9: Time for a doctor to evaluate a patient	21.2	1.7-64.6	15.4-27.9
Q10: Time for a nurse to evaluate a patient	15.5	7.3-26.5	5.6-30.3
Q11: Time to undertake a postinvestigation/ treatment evaluation of the patient	13	0.4-46.4	9.4-17.2
Q12: Time to remove a foreign body	14.6	1.8-40.5	7.2-24.6
Q13: Time to undertake lavage/ emesis/ charcoal/ eye irrigation	15.1	9.8-21.6	NA
Q14: Time to insert a urinary catheter	19.9	5-44.9	NA
Q15: Time required for defibrillation	19.4	1.5-59.6	13-27.1
Q16: Time required for resuscitation	56.7	7.8-153.1	17-120
Q17: Time to undertaking a minor surgery	22.8	10.7-39.5	10.5-39.9
Q18: Epistaxis control	28.4	1.3-96.1	NA
Q19: Time required for provision of supplemental oxygen	5.1	1.5-10.7	NA

Note. NA because no variability was input during the elicitation exercise.
NA indicates not available; Q, question.

Updating of the Model

The results of one trial of the model, which used the best estimates of the means and variability around the time taken to complete each activity, provided a reasonable fit to the data for length of time within the ED. The results of the PSA in comparison are shown in Figure 1. The PSA model runs led to an expected average time in the system of over 3 days, which is far in excess of both the non-PSA model runs and the length of stay taken from the data set. The PSA results had very wide interquartile ranges, with some runs having an average time in the system of almost 3 weeks. These results were implausible.

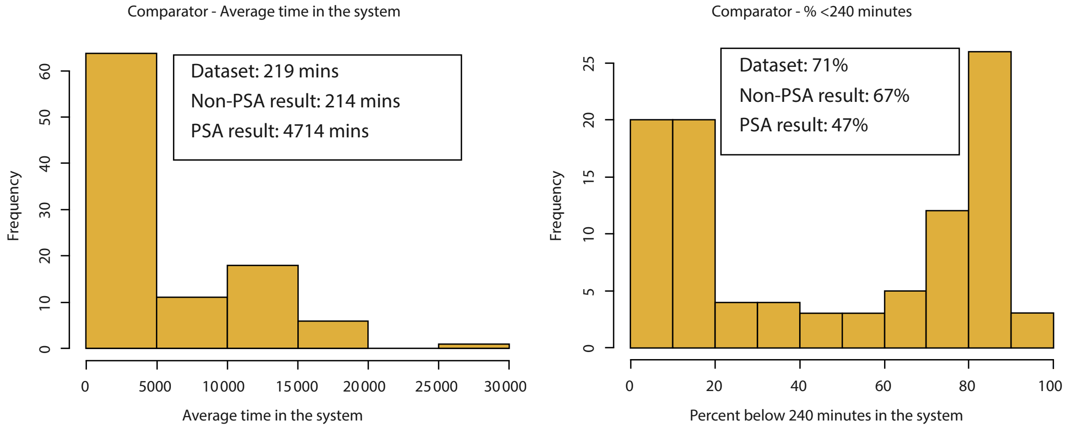
The model was found to be very sensitive to small changes in the parameters around time taken to complete activities, such that slightly increasing some of the times would lead to substantial queue build ups, which led to much longer average length of stay.

Discussion

Undertaking PSA within cost-effectiveness models has been shown to reduce bias in expected results.[7] However, there is a dearth of evidence around incorporating PSA within a resource-constrained model. Within the broader literature, it has also been demonstrated that ignoring uncertainty in input parameters can lead to poor model estimates.[20] This can be made worse by running more simulations, which reduces the confidence intervals around the results. Our case study explored the appropriateness and feasibility of using methodology for quantifying parametric uncertainty in health economic models in a DES model with resource constraints. These methods assume that uncertainty in model outputs can be quantified by propagating uncertainty in each parameter though the model.

Within standard health economic models, provided that the ranges of uncertainty around the parameters are plausible (eg,

Figure 1. Results of the PSA exercise.



PSA indicates probabilistic sensitivity analysis.

costs that are not negative), then the uncertainty in the model inputs are simply propagated into the model outputs. However, our case study suggests that for resource-constrained DES models this is not the case. Our results show that the PSA inputs can substantially alter the model outputs in cases which there are interactions within a simulation model. The resulting uncertainty in model outputs was considered implausible when validated against existing data, although the uncertainty around the model inputs was plausible, whilst highly uncertain and skewed. Therefore, this highlights the need for further research into methods for quantifying parametric uncertainty in DES models with constrained resources.

For some parameters, such as costs and utilities, the existing methodology is likely appropriate, but for parameters that affect interactions within a simulation model, such as duration of activities, alternative methods may be needed. This may depend upon the level of data available to inform model inputs. Within the case study, no data were available around the activity durations; hence, elicitation was used to inform both the variation and uncertainty in these input parameters. Alternative approaches do exist for representing uncertainty in model inputs, including bootstrapping, delta methods, metamodeling, and robust-optimisation.[20] Their use in DES of resource-constrained healthcare systems could be explored within future research. However, most of these approaches depend on substantial data to quantify the uncertainty. In situations which there are limited data for informing model inputs, but data exist for validation of model outcomes, an option may be to use the data to estimate uncertainty in model parameters. Bayesian calibration can be used to capture uncertainty using probability distributions which is consistent with PSA[21] and the priors can be informed by elicitation, however, this is computationally expensive and is not typically used in resource constrained models. This could be explored within further research.

This article focuses upon the incorporation of parameter uncertainty within resource-constrained DES models; however methodological uncertainty and structural uncertainty are also relevant considerations for health economic models.[9] Methodological uncertainty relates to decisions about the methods used, such as measuring and valuing outcomes, or which discount rate is appropriate. This is often dealt with via the use of a reference case, which leads to consistency between analyses, although uncertainty remains. Within resource-constrained models, the decision maker is often a local decision maker, and the methodological decisions will be dependent on their needs. It will be equally important for the modeler to be aware of and test the impacts of key methodological uncertainties within resource-constrained models as for standard health economic models.

Structural uncertainty relates to whether all relevant relationships between parameters are captured appropriately within the model. This can be dealt with prospectively by considering the process through which decisions are made about the conceptualization, structuring, and implementation of the model. For example, within the ED case study, time was spent observing the hospital and consulting with clinicians to understand the current process within the ED. A validation exercise was undertaken with clinicians to ensure that the structural assumptions were representative of the current system. Any remaining structural uncertainties can be explored using scenario analyses. Where structural variations were found to exist between hospitals, these could be implemented within alternative simulations to capture local heterogeneity.

Reducing structural uncertainties prospectively tends to be easier for a resource-constrained system because the system is usually observable, and decision makers in these contexts generally do not want to make predictions far into the future, as for a health economic model. It is important to note, however, that the behavior of people within the system may adapt to the current circumstances; hence, policies can have unintended consequences on the system by affecting individuals' behaviors. Thus, there may be additional structural uncertainties when exploring the impacts of policy changes, which should be explored. In addition, the ED in our case study was found to be a complex system in which clinical decision making includes many nuances that are challenging to capture within a model. For example, within our model, 1 treatment was always completed before another was begun by the same staff member, whereas within the real system, staff may move between patients before treatment is complete.

Within such complex systems in which there are interactions between individuals and their environment, small changes in model inputs can lead to large and unexpected impacts on outcomes because of the structural assumptions within the model; therefore, it should be a priority to explore this structural uncertainty, both prospectively and retrospectively.

Conclusion

Structured expert elicitation can be used to derive plausible estimates of resource-related parameters and their variability, but experts' uncertainty can be substantial, limiting their suitability for use in this context. For some parameters, such as costs and utilities, the existing PSA methodology is likely appropriate, but for parameters that have an impact on interactions within a resource-constrained simulation model, PSA can substantially alter and lead to implausible model outputs; hence, other methods may be needed. Further research could develop methods for quantifying parametric uncertainty in resource-constrained DES models, including the use of calibration, and provide guidance on when these are worthwhile, given a potentially low impact of parametric uncertainty compared with structural uncertainties within these models. Further research is also required about methods of elicitation for informing uncertain parameters within such models.

Author Disclosures

Links to the individual disclosure forms provided by the authors are available here.

Supplemental Material

Supplementary data associated with this article can be found in the online version at Appendix https://doi.org/10.1016/j.jval.2023.09.003.

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