PRM52

Minimum run-time requirements to reduce Monte Carlo error in stochastic simulations

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Objective

- In HEOR the role of probabilistic sensitivity analysis (PSA) is to assess the uncertainty of model predictions with respect to the underlying parameter uncertainty.
- However, in Monte Carlo simulation parameter uncertainty coincides with and cannot be distinguished from random noise (Monte Carlo error (MCE)).
- The minimum criteria for PSA should be therefore to reduce MCE to such an extent that a meaningful assessment of parameter uncertainty is possible.
- The objective of this study was to quantify the minimum run time requirements to reduce MCE to acceptable levels and to present a feasible approach to distinguish the remaining degree of MCE from outcome variability attributable to parameter uncertainty.

Methods

- A established and validated computer simulation model, the IMS CORE Diabetes Model (CDM)[1], was used to compare outcome variability of bootstrap simulations, each performed with 1,000 iterations, but with varying numbers of generated patients ranging from 500 to 100,000.
- Model projections were performed evaluating the cost effectiveness of two hypothetical interventions with a difference in glycohemoglobin (HbA1c) of 0.5%-points and a difference in body weight of 2 Kg.
- Each simulation was performed in three ways:
  - I. No parameter sampling
  - II. Parameters were sampled around 5% of mean values (intending to represent variability for standard error (SE) input)
  - III. Parameters were sampled around 25% of mean values (intending to represent variability for standard deviation (SD) input)
- The degree of Monte Carlo error was determined according to the relationship of the confidence sizes of the non sampling analyses versus sampled analyses (Figure 1).
- In the modeling analyses, minimum run time requirements were considered to be reached when the ICER (per QALE) confidence ranges of non sampling analysis (representing stochastic uncertainty) decreased **steadily** and **consistently** below 50% of confidence size obtained in PSA (representing both stochastic and parameter uncertainty).
- Upon fulfillment of this criteria, the degree of MCE still contained in the confidence ranges (including both, stochastic- and parameter uncertainty) was estimated from ratings obtained from an theoretical exercise that was conducted in MS Excel (Figure 4) (attempting to replicate the conditions in PSA).
- The theoretical exercise compared the variability of 10,000 samples from two random distributions A and B to the variability of the joint distribution (A+B).
  - → Distribution A with static mean of 50 and SD of 5 (representing parameter uncertainty)
  - → Distribution B with static mean of 0 and decreasing SD from 10 to 0 (representing decreasing level of stochastic uncertainty).
  - → Joint distribution = distribution A + distribution B

Results

- ICER confidence ranges in non PSA runs demonstrated an irregular pattern (increased or maintained stable) with increasing patient number until 10,000 patients were included (Figure 2).
- The 50% threshold criteria (ICER confidence size from non PSA <= 50% of PSA confidence size) was reached at 10,000 and 50,000 included patients for SD and SE based PSA, respectively (Figure 3).
- For these patient numbers, 36.6% and 45.0% of overall outcome variability were found to be attributable to stochastic uncertainty (MCE) for SD and SE based PSA.
- The theoretical exercise demonstrated that when stochastic variability decreased below 50% of overall (joint) variability, 85% of overall variability was attributable to parameter uncertainty (Figure 4).
- More precise estimates were obtained from a functional relationship found between the percentage of parameter- and stochastic uncertainty from overall (joint) outcome variability (Figure 5).
- This relationship demonstrated that for SD based PSA with 10,000 included patients (where 36.6% of joint variability were due to random noise) 93.3% of the observed confidence size was attributable to parameter uncertainty.
- The corresponding percentage for SE based PSA with 50,000 included patients (where 36.6% of joint variability were due to random noise) was measured as 88.9% (Figure 5).

Figure 1. Relationship of confidence sizes of non parameter sampling – vs. sampling analyses in deterministic and stochastic models

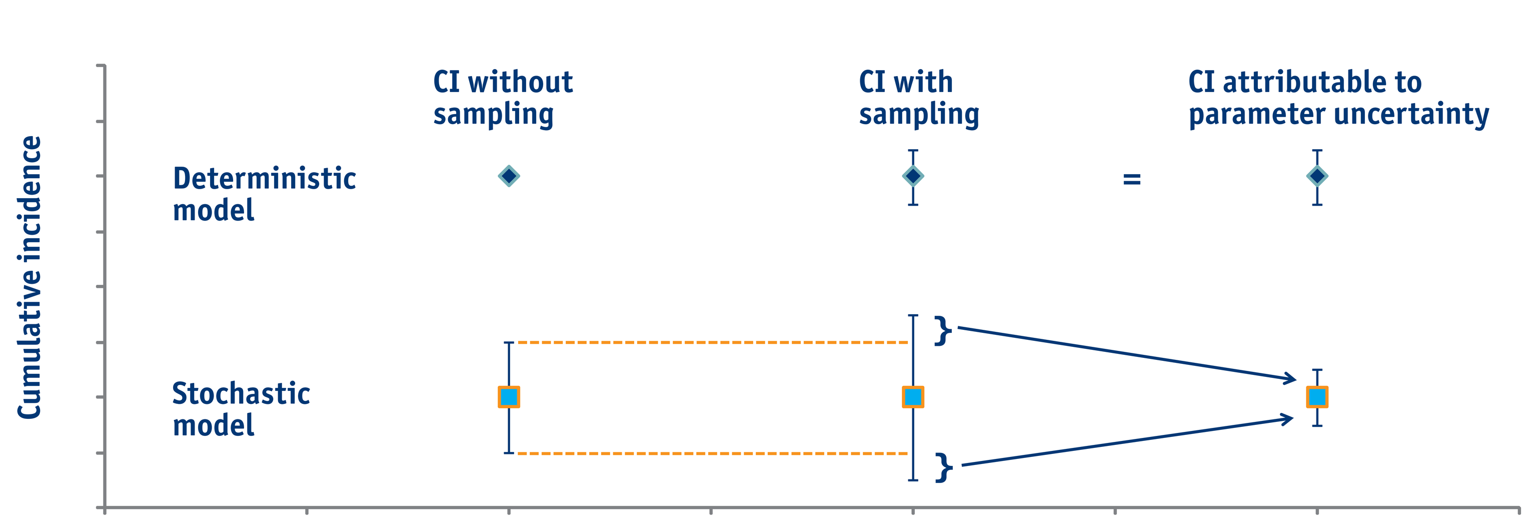


Figure 2. ICER confidence ranges across included patients

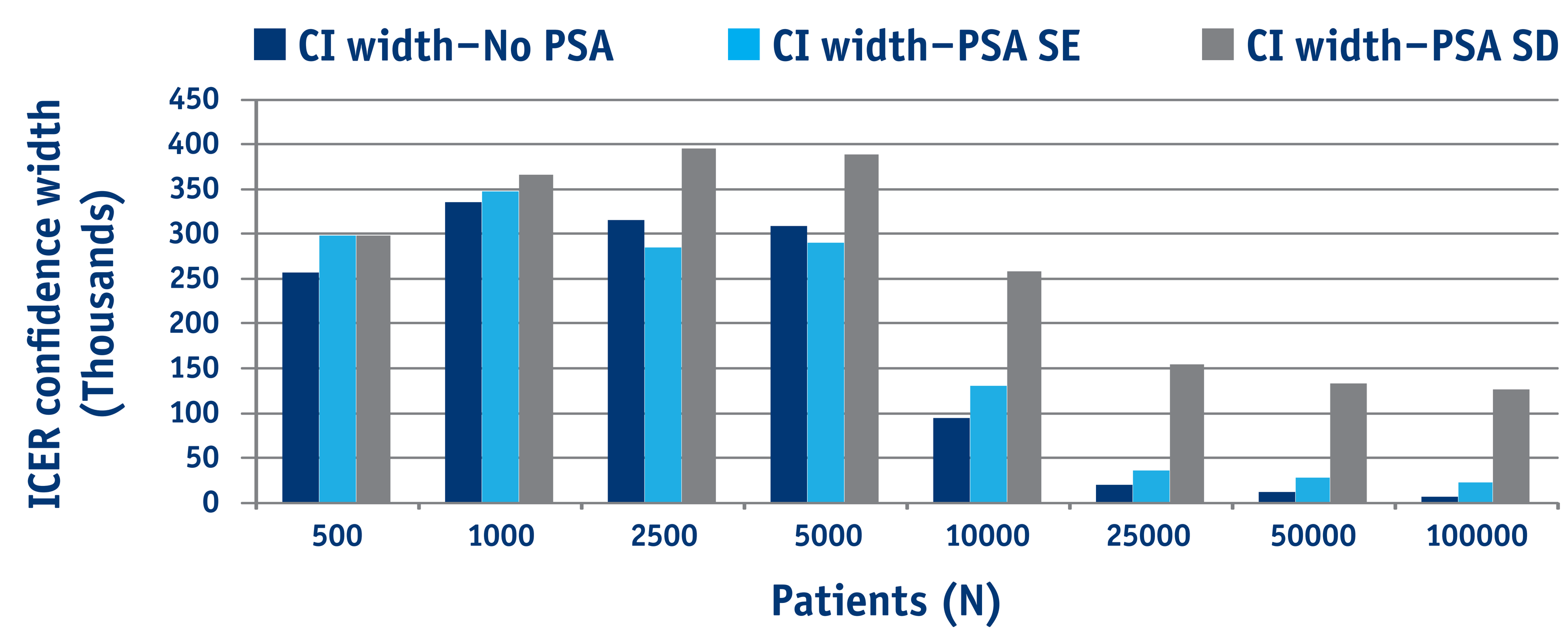


Figure 3. % MCE contained in PSA confidence ranges (ICER)

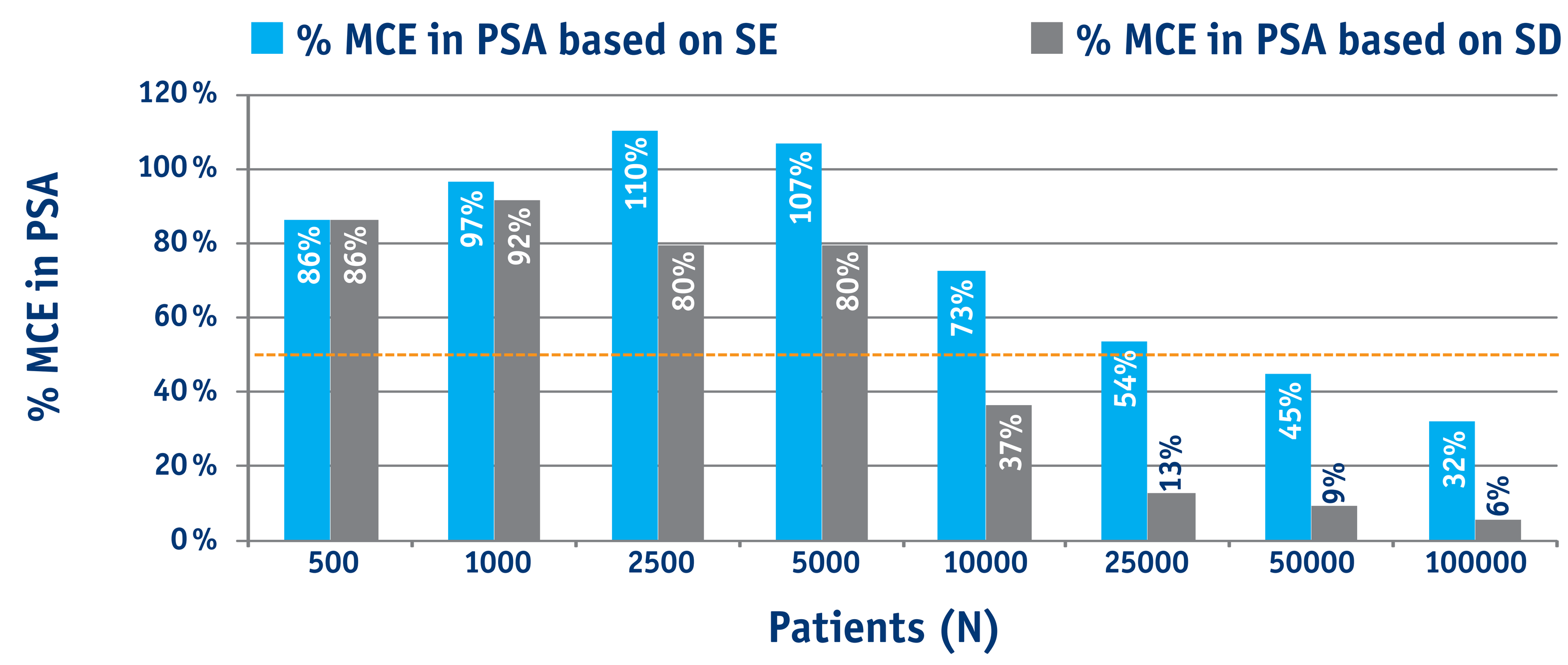


Figure 4. Relationship of two overlaying distributions (due to random noise and parameter uncertainty) to the joint distribution

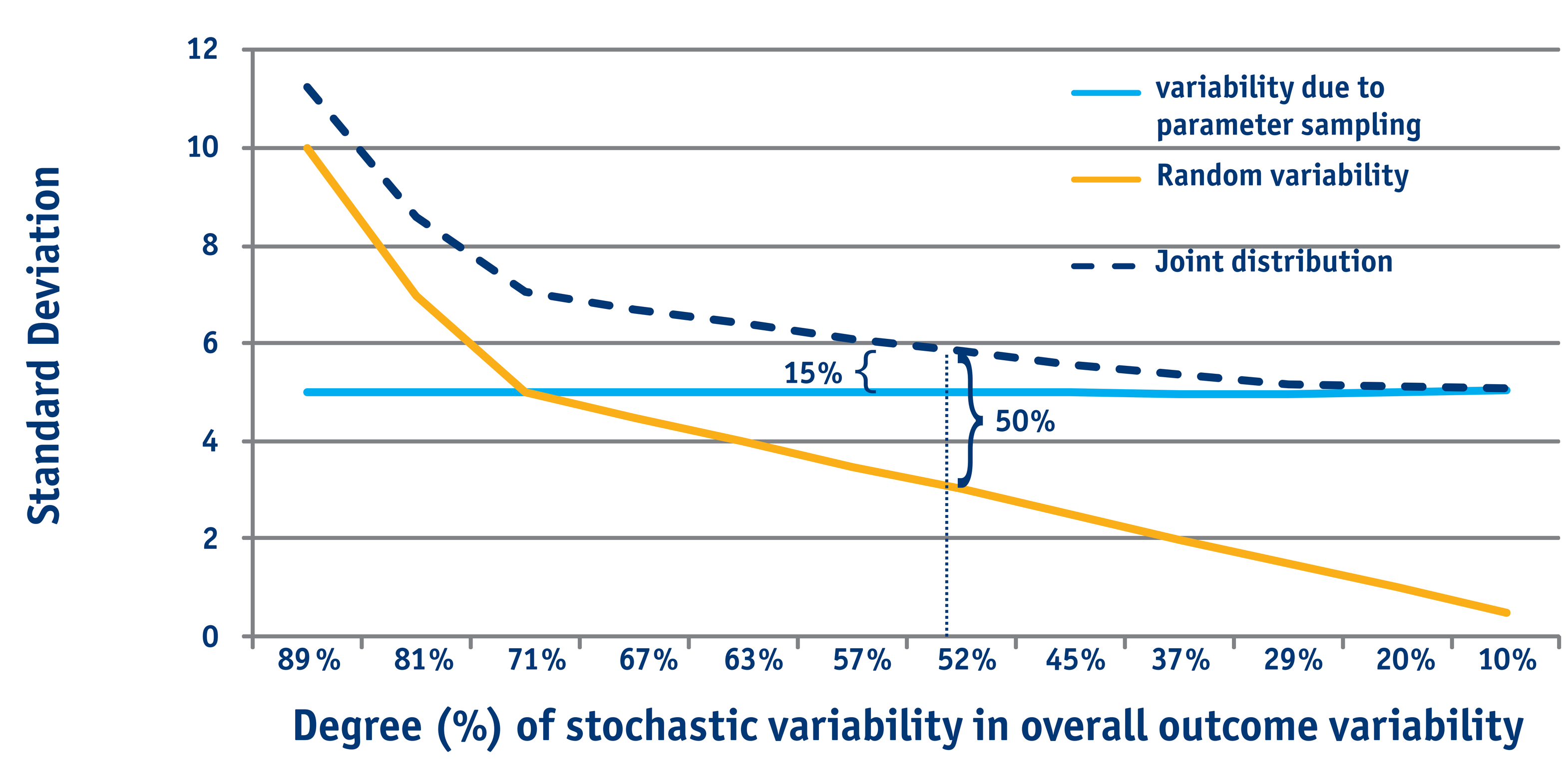
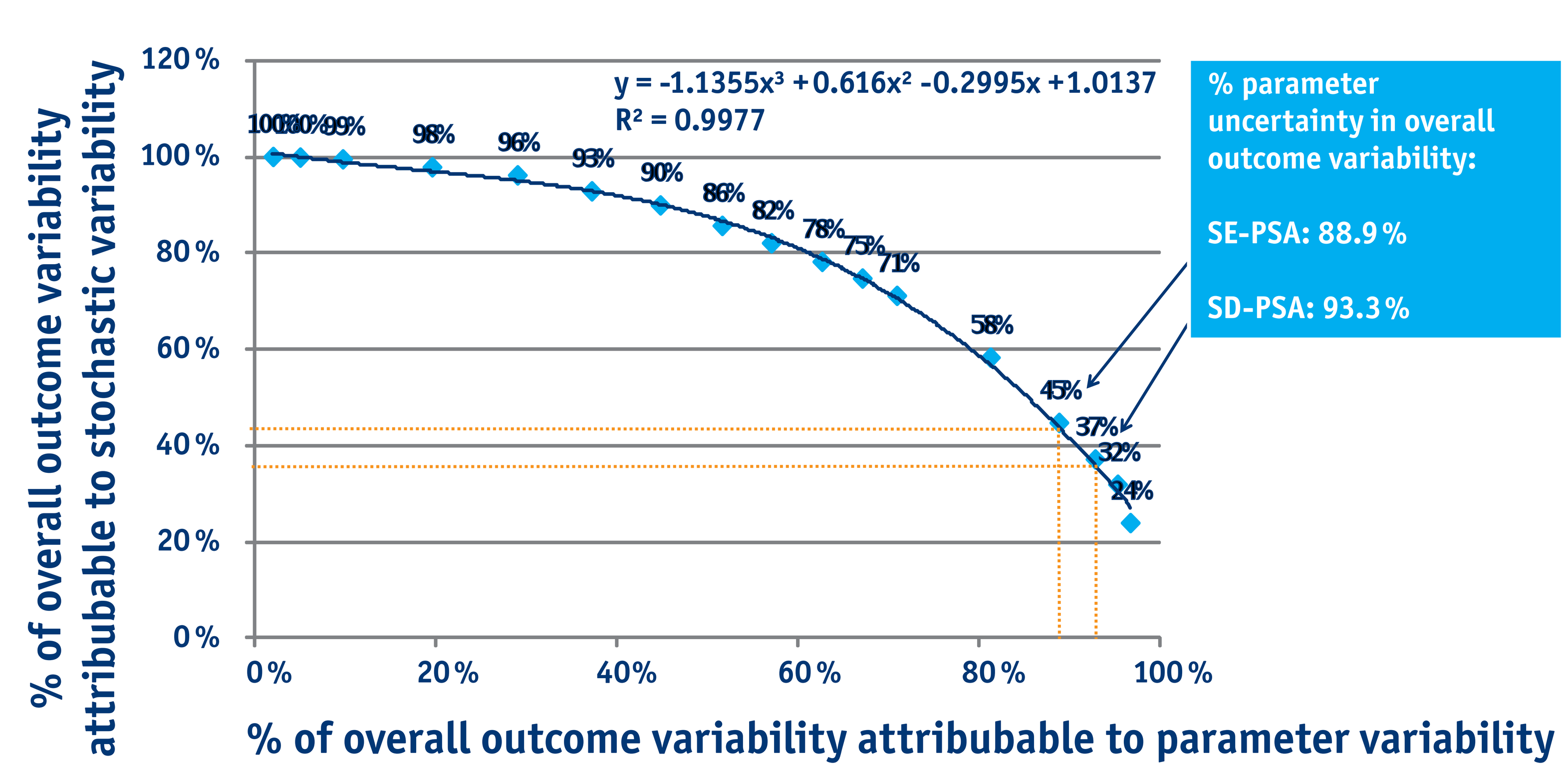


Figure 5. Functional relationship found between the percentage of parameter- and stochastic uncertainty from overall (joint) outcome variability



Conclusions

- Run time requirements to reduce Monte Carlo error are lower whenever the uncertainty of included parameters is increased.
- For the selected degrees of parameter input variability 10,000 patients (based on SD) and 50,000 patients (based on SE) simulated in 1,000 bootstrap iterations were found to be sufficient to reduce MCE to the degree that allows meaningful assessment of parameter uncertainty.
- For this run time, less than 15% of the presented output variability is attributable to random noise and the remaining 85% represent parameter uncertainty.
- This analysis demonstrated a feasible approach to precisely estimate the degree of parameter uncertainty in stochastic simulations.

References

1. Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, Lammert M, Spinas GA. The CORE Diabetes Model: projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. Curr Med Res Opin. 2004; 20:S5-S26.