Medicinrådet

Uncertainty and sensitivity analyses

Guideline

Version 1.0

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Language: English
Format: PDF
Published by the Danish Medicines Council February 19th 2026

1. Uncertainty

How the company should address uncertainties in the health economic analysis will depend on the specific treatment, patient population, and the available data.

The company must always thoroughly address – and when possible – analyze uncertainties in the health economic analysis using sensitivity analyses, see Section 2.

In addressing uncertainties, the company must describe the key drivers of uncertainty, such as study design, choice of model structure and/or specific parameters. The company must also describe the potential impact of these uncertainties on the validity of the results of the health economic analysis.

1.1 Types of Uncertainty

Health economic analysis is based on interdisciplinary methodology, and different terminology exists in the literature to describe uncertainties. The Danish Medicines Council distinguishes between parameter uncertainty and structural uncertainty (model uncertainty). Parameter uncertainty relates to parameter precision (standard errors), whereas structural uncertainty relates to the assumptions built into the health economic model. Structural uncertainties can arise from the clinical evidence base (e.g., limitations in the transferability of clinical effectiveness data) as well as from modelling choices (e.g., the selection of a model structure that does not reflect the disease and treatment pathway).

Other types of uncertainty

Heterogeneity, stochastic uncertainty, and methodological uncertainty are theoretically defined as the third, fourth, and fifth types of uncertainty in health economic analysis (Briggs et al., 2012).

Stochastic variation (identical individuals may experience different effects of the same treatment due to random variation) and **heterogeneity** (different individuals may experience different effects due to systematic variation) are underlying sources of parameter uncertainty and may also cause structural uncertainty. For example, very early data with few events may lead to structural uncertainty regarding the choice of extrapolation model and parameter uncertainty in the form of wide confidence intervals. Parameter uncertainty and some structural uncertainties can be reduced by larger datasets and/or longer follow-up.

Although parts of the literature clearly distinguish between structural uncertainty and heterogeneity (Bojke et al., 2006; Briggs et al., 2012), the Danish Medicines Council considers that heterogeneity in practice may contribute to structural uncertainty in the model. For example, if the model is based on subgroups with different comparators or uses weighted averages across subpopulations. In cases where the population is heterogeneous, but the data and the model support conducting a

cost-effectiveness analysis at the subgroup level, heterogeneity will often not be a significant source of uncertainty.

Methodological uncertainty refers to uncertainty associated with the set of methods underlying the health economic analysis, such as the choice of perspective, discount rate etc. (Briggs, 2000; Briggs et al., 2012). Methodological uncertainty is expected to be minimized in submissions to the Danish Medicines Council, as the company's analysis should generally follow the Danish Medicines Council's methodological guidelines.

1.2 Choice of Base-Case or Scenarios

In cases of substantial uncertainty regarding the choice of the base-case analysis, companys are encouraged to report the results for two or more equally plausible scenarios rather than a single base-case. When reporting scenarios, sensitivity analyses must be conducted for each scenario, see example in the text box below. The Danish Medicines Council is aware that definitions of scenarios and sensitivity analyses vary across HTA organizations, please refer to the Danish Medicines Council's definitions in Table 1.

Example of distinction between base-case, scenarios, and sensitivity analyses

There is substantial uncertainty about the choice of parametric distribution used for the extrapolation of survival, as it cannot be determined whether a Weibull distribution or a log-normal distribution is more accurate. Two scenarios are therefore presented, as both distributions are equally plausible. Since both scenarios are still uncertain, a sensitivity analyses (deterministic and probabilistic sensitivity analyses) are conducted and presented for each scenario.

Table 1. The Danish Medicines Council's definitions of differences between base-case, scenarios, and sensitivity analyses

Term	Definition
Base-case	A base-case may be used when one analysis is more plausible than all other alternatives.
Scenarios	Scenarios consist of two or more equally plausible analyses. Avoid presenting multiple scenarios that address the same uncertainty (e.g., several survival extrapolations curves that are very closely aligned and would not lead to any substantial difference in results).

Sensitivity analyses	Sensitivity analyses are used to analyze the impact of uncertainties. Sensitivity analyses must not be more or equally plausible than the base-case (or scenarios).

2. Sensitivity Analyses

2.1 Probabilistic Sensitivity Analyses

To assess overall parameter uncertainty, the company must present a PSA for the base-case (or each scenario).

In cost-utility analyses, the results of the PSA must be illustrated as a scatter plot of incremental costs versus incremental QALYs and as a cost-effectiveness acceptability curve (CEAC). In cost-minimization analyses, the PSA must be illustrated as a histogram of incremental costs.

All input parameters associated with uncertainty must be included, while input parameters assumed not to be associated with uncertainty must be excluded. Parameters to include typically consist of resource-use frequencies, utility values, parameter estimates from extrapolation models, and hazard ratios (HRs) assuming constant HR in extrapolation. Parameters to exclude include discount rates, all drug prices, and unit costs, since these are not considered uncertain.

Companys must select plausible probability distributions for sampling uncertain parameters, see Table 2. If a parameter is not empirically estimated, companys must explain how uncertainty around the estimate is handled. A parameter cannot be excluded simply because it lacks empirical estimation or the evidence behind the choice of distribution is weak (Briggs et al., 2012).

In cases of substantial uncertainty regarding a single parameter (e.g., the effect on overall survival (OS)), a univariate PSA can be conducted and presented, in which only the HR for OR is varied while all other parameters are held constant.

Table 2. Commonly used distributions in probabilistic analysis

Type and logical constraint	Parameter	Distribution
All parameters without constraints and with an assumed symmetric distribution	E.g. age and weight	Normal
Categorical variables, transition probabilities	E.g. state distribution or transition probabilities	Dirichlet

Type and logical constraint	Parameter	Distribution
$0 \leq \theta \leq 1$	E.g. proportions and utility values (not applicable for scenarios with categorical variables such as state)	Beta
Ratios $\theta > 0$	Odds/hazard ratio/risk ratio	Log-normal
	log(hazard ratio)/log(odds ratio)/log(risk ratio)	Normal
$\theta \geq 0$	E.g. time measures such as treatment duration and duration of adverse events	Gamma Log-normal

2.1.1 Technical Requirements for Implementing PSA in Excel

If parameters are correlated, these must be described and addressed in the PSA. The method used to address correlated parameters must also be described.

The company must always use the Danish Medicines Council's two standard PSA sheets in the Excel model (input and output). This entails:

- That the "PSA input" sheet is linked to all relevant input parameters.
- That parameters can easily be activated and deactivated via a drop-down list.
- That the choice of distributions can easily be modified via a drop-down list.
- That the output for each iteration is shown in the "PSA output" sheet at both an aggregated (e.g., QALYs per health state, cost category, ect.) and at the parameter level.

The company may also use the PSA output sheet to identify parameters with substantial uncertainty for further univariate PSA, deterministic sensitivity analysis, or debugging.

2.2 Deterministic Sensitivity Analyses

The company must present deterministic sensitivity analyses in a table format to illustrate how sensitive the results are to key structural assumptions (e.g., the choice of extrapolation model for survival) and to the parameters associated with the greatest uncertainty in the health economic analysis (e.g., HR).

The company must conduct the deterministic sensitivity analyses by varying one, two, or multiple parameters simultaneously.

3. References

Bojke, L., Claxton, K., Palmer, S., & Sculpher, M. (2006). *Defining and Characterising Structural Uncertainty in Decision Analytic Models*.

Briggs, A. H. (2000). *Handling Uncertainty in Cost-Effectiveness Models*.

Briggs, A. H., Weinstein, M. C., Fenwick, E. A. L., Karnon, J., Sculpher, M. J., & Paltiel, A. D. (2012). Model parameter estimation and uncertainty analysis: A report of the ISPOR-SMDM modeling good research practices task force working group-6. *Medical Decision Making*, *32*(5), 722–732. https://doi.org/10.1177/0272989X12458348

4. Version log

Version	Date	Revision
1.0	February 19th 2026	Approved and published.

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