Medicinrådet

Health Economic Analysis and Extrapolation

Guideline

Version 1.0

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1. Introduction

The applicant must base the health economic analysis on a health economic model comparing the effects and costs of the new treatment (intervention) and the current standard of care (comparator(s)) in Danish clinical practice. The model must be implemented in Excel.

The health economic model is based on a series of assumptions regarding the patients' disease and treatment pathway in Danish clinical practice, as well as a range of inputs in the form of study data, external sources, and other assumptions.

1.1 Type of Analysis

The applicant must submit a cost-utility analysis reporting differences in QALYs and costs between the intervention and the comparator(s) as an incremental cost-effectiveness ratio (ICER).

If the new treatment and the current standard of care are equivalent across all relevant clinical outcomes (including health-related quality of life) and safety, the applicant may instead submit a cost-minimisation analysis.

2. Reference-case assumptions

2.1 Perspective

The applicant must apply a limited societal perspective. This entails including only treatment-related effects and costs, including drug costs, hospital costs, and patient costs, see Table 1. For the estimation of individual cost components, reference is made to the Danish Medicines Council's guideline on cost calculations. For the estimation of health-related quality of life reference is made to the Danish Medicines Council's guideline on health-related quality of life.

Table 1. The Danish Medicines Council's definition of a limited societal perspective

Limited societal perspective
Include
Health effects measured as quality-adjusted life years (QALYs).
Drug costs related to treatment and, when relevant, subsequent treatment.
Hospital costs, including costs related to administration, disease management, treatment monitoring, and management of adverse events.
Patient costs, including costs related to patient time and transport.
Consider
Other relevant costs of particular importance for the treatment, e.g., costs covered by public health insurance, municipal costs, or costs related to caregivers' time.
Do not include
Indirect effects or costs not directly related to the treatment in question, e.g., productivity loss.

2.2 Time Horizon, Cycle Length, and Half-Cycle Correction

Based on the relevant disease and treatment pathway, the applicant must describe and justify the choice of time horizon, cycle length, and the use of half-cycle correction.

The time horizon must be sufficiently long to capture all important differences in effects and costs between the intervention and the comparator(s). This implies that extending the time horizon should not substantially affect the results of the analysis. It must always be possible to adjust the time horizon in the health economic model.

The cycle length must reflect the disease and treatment pathway such that effects and costs occur at time points that are representative of the actual pathway, for example in relation to administration frequency.

The applicant must apply half-cycle correction to account for the fact that costs and effects typically accrue continuously throughout a model cycle rather than at the beginning of a cycle. Half-cycle correction must be applied when the cycle length exceeds one week. However, half-cycle correction must not be applied to drug and administration costs for one-off treatments or drugs administered or dispensed on day 1 of a model cycle.

2.3 Discounting

The applicant must discount both costs and QALY gains to present value using a fixed annual discount rate corresponding to the social discount rate set by the Ministry of

Finance. The applicable discount rate can be found at www.fm.dk. The rate for 0–35 years (3.5% as of 2025) must be applied for both costs and effects over the entire model time horizon from week 53 onwards.

Box 1. Rationale for discounting

Discounting implies that future costs and effects are valued less than present costs and effects. This enables consistent comparison of different disease and treatment pathways, even when costs and effects occur at different points in time.

The use of discounting is supported by theoretical and empirical studies demonstrating that both society and individuals value future costs and effects less than present cost and effects. The appropriate rate of discounting depends on whether it is viewed from a societal or an individual perspective (Gyrd-Hansen & Søgaard, 1998). On the cost side, the theoretical and empirical arguments for discounting are grounded in a societal perspective, whereas on the effect side the arguments can be viewed from both societal and individual perspectives.

Costs are discounted because financial resources can be invested and accrue interest until they are needed. Consequently, a smaller amount set aside today can cover a future cost. Discounting also reflects the opportunity cost of using resources today, as resources invested today are no longer available for other potentially more cost-effective interventions.

Effects are discounted because a health benefit received today is perceived as more valuable than the same benefit received in the future (time preference). This is partly due to greater uncertainty, as short-term benefits are considered more certain from both societal and individual perspectives, and partly due to diminishing marginal utility of health gains (Gyrd-Hansen & Søgaard, 1998). Diminishing marginal utility of health gains means that each additional life year gained yields less utility than the previous one.

For both costs and effects, the discount rate also reflects systematic risk at the societal level (Ministry of Finance, n.d.). Systematic risks may include economic recession, which alters societal priorities due to tighter public budgets and higher requirements for treatment effectiveness, as well as changes in the prevalence of comorbidity and rapid technological development that may reduce the value of certain treatments.

Discounting and treatment-specific uncertainty

The rationale for discounting is general and applies across all treatments and diseases. Treatment-specific uncertainties related to, for example, effect size, safety profile, or treatment duration are not, and must not be, reflected in the discount rate. Instead, these uncertainties must be analyzed separately using scenarios and sensitivity analyses, see the Danish Medicines Council's guideline on uncertainty and sensitivity analyses in health economic evaluations.

Differential or declining discounting

The Danish Medicines Council applies the same discount rate to both costs and effects. Some countries apply differential discount rates, discounting effects at a lower rate than costs. A key argument for a lower discount rate for effects is that the societal value of health may increase over time, as increased wealth could lead to a greater willingness to pay for health. If future health benefits are valued more highly than present benefits, this may justify a lower discount rate for effects than for costs (Attema et al., 2018). However, this argument assumes that health will receive relatively greater priority as society becomes wealthier, which is currently uncertain in a Danish context. For a more detailed review of the theoretical and empirical arguments for and against differential discounting of costs and effects, see Attema et al., 2018.

In broader societal economic analyses (e.g., analyses of climate policies), the Ministry of Finance recommends using a declining discount rate over time, such that effects occurring far in the future are assigned greater weight (Danish Ministry of Finance, 2021). A declining discount rate is partly justified by the need to account for the welfare of future generations. However, this argument cannot be transferred to economic evaluations of medicines. Based on the current evidence, the Danish Medicines Council finds insufficient justification for applying a declining discount rate in health economic evaluations of medicines, see Attema et al., 2018; O'Mahony et al., 2015.

2.4 Adjustments

2.4.1 Age adjustment of utility values

The increased morbidity and functional impairment generally associated with ageing result in a decline in the population's overall health-related quality of life with age. The applicant must therefore apply age adjustment of utility values in the health economic model, in accordance with the Danish Medicines Council's guideline on health-related quality of life. For this purpose, the Danish Medicines Council's standard sheet for age adjustment must be used in the Excel model. The adjustment must be based on the patients' expected starting age.

2.4.2 Adjustment for background mortality

The applicant must adjust the modelled mortality to ensure that background mortality (i.e., mortality in a Danish general population matched by age and sex) does not exceed the estimated mortality at any point in time.

For this purpose, the Danish Medicines Council's standard background mortality sheet must be used in the Excel model. The adjustment must be based on the patients' expected starting age and sex distribution.

It must always be clearly described how the model has adjusted for background mortality, including the scale applied (e.g., hazard scale or probability scale).

3. Choice of Model and Model Structure

3.1 Model Type

The choice of model depends on the available data (data maturity and relevant outcomes) and the complexity of the disease and treatment pathway. Commonly used models include (semi-)Markov models and partitioned survival models.

The applicant must justify the choice of model, including its advantages and limitations as well as the assumptions underlying the choice, for example if the model assumes dependency between certain clinical outcomes.

3.2 Model Structure

The applicant must submit a model in which the model structure (health states and possible transitions between states) reflects the disease and treatment pathway for the treatment arms in Danish clinical practice, and where the model structure is not unnecessarily complex. The applicant must describe and provide a graphical illustration of the model structure, including the health states incorporated in the model and the possible patient transitions between these health states.

4. Extrapolation of Patient Transitions

To estimate differences in treatment-related effects and costs between the intervention and the comparator(s) in the health economic analysis, it is often necessary to extrapolate the disease and treatment pathways beyond the observation period in the clinical studies.

The Danish Medicines Council's requirements for extrapolation using parametric extrapolation models and transition probabilities are set out in Sections 4.1 to 4.3. The choice of extrapolation model must be based on an overall assessment of internal and external validity, see Section 4.4.

4.1 Extrapolation Using Parametric Extrapolation Models

The applicant may extrapolate time-to-event data beyond the observation period using parametric extrapolation models. Time-to-event data refer to data in which time to a given event constitutes the outcome, and where the time of treatment allocation (randomisation time in an RCT) typically reflects the starting point (time 0). Examples include 'time to disease recurrence' and 'time to death'. The most recent prespecified data cut must always be used for extrapolation of time-to-event-data. Data must not be excluded in order to obtain a better statistical fit (Latimer, 2013). As a general rule, the extrapolation model should be applied across the entire time horizon of the health economic model, rather than only beyond the observation period. This ensures that uncertainty across the full time horizon is adequately reflected (e.g., in the PSA). If extrapolated data provide a poor fit to the observed data, the applicant must submit extrapolation models using a piecewise approach (e.g., combinations of several parametric models). See below regarding the use of more flexible models.

The applicant may use different methods to extrapolate time-to-event data, including the seven standard parametric models (exponential, Weibull, log-logistic, log-normal, gamma, Gompertz, generalised gamma) or more flexible models (e.g., spline models or mixture cure models). Flexible models must be used if the standard parametric models do not adequately fit the clinical data or do not yield clinically plausible extrapolations. This may, for example, be relevant in the presence of long-term survivors or where treatment response is delayed or declines abruptly. When more flexible models are used, they must always be presented as a supplement to the seven standard parametric models. The sensitivity of modelling assumptions must be thoroughly explored in sensitivity analyses (e.g., through alternative knot placements or varying the number of knots in spline models). The Danish Medicines Council's assessment of flexible models aligns with the technical guideline developed by NICE (Rutherford et al., 2020).

The applicant must describe the key assumptions underlying the choice of parametric extrapolation model based on the decision tree shown in Figure 1. As a general rule, treatment arms should be modelled separately (independently). Any deviation from separate modelling must be justified based on clinical plausibility and supported by graphical assessment, e.g., hazard plots, log-cumulative hazard plots, (Schoenfeld) residual plots, and quantile-quantile plots, see Figure 1. Statistical tests (e.g., tests of proportionality) cannot alone justify modelling the treatment arms with a joint extrapolation model.

Log-cumulative hazard plots and residual plots must likewise be used to justify the use of flexible models, for example in the presence of structural changes.

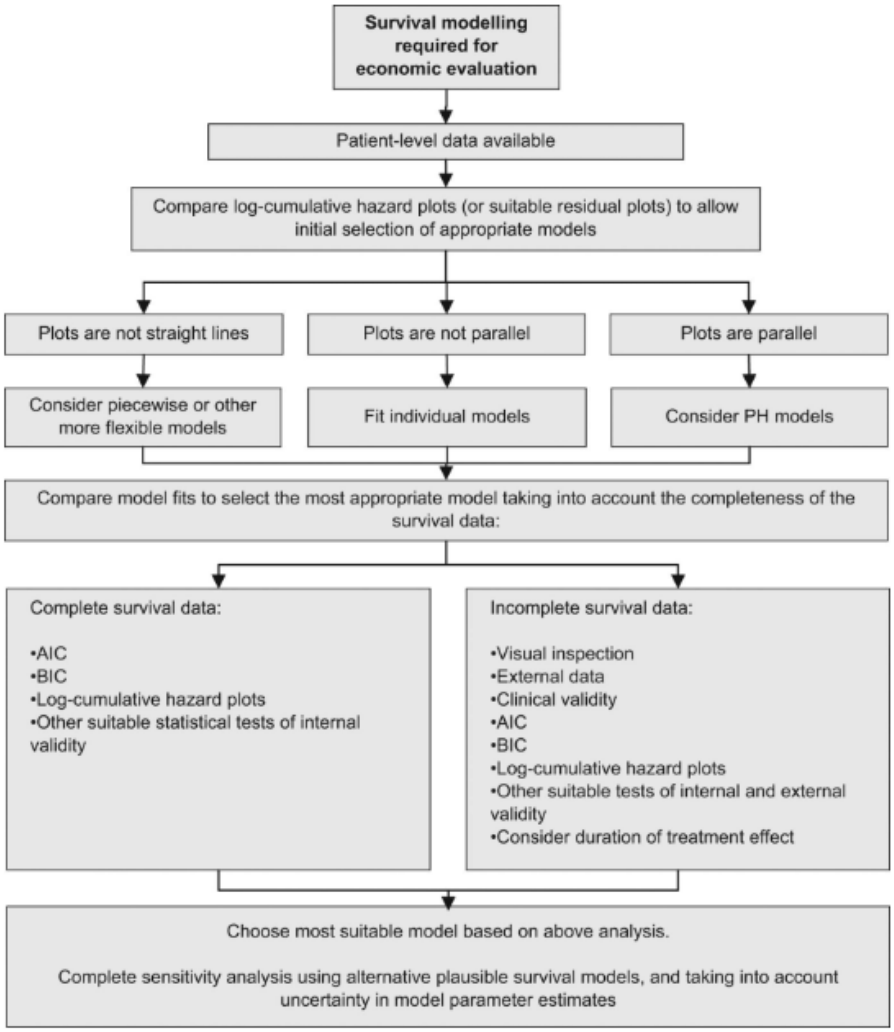

Figure 1 Decision tree for selecting survival extrapolation models (Latimer, 2013)

4.2 Extrapolation Using Transition Probabilities

The selection of transition probabilities must be based on evidence that is relevant and representative of the target population and the disease and treatment pathway in Danish clinical practice. The chosen transition probabilities must be clinically plausible and ensure internal consistency over time, meaning that patient transitions must remain logical and clinically plausible both over time and across treatment arms.

The applicant must demonstrate that each transition probability is:

- **representative** of the population and of the disease and treatment pathway in the relevant health state. This includes a thorough description of similarities and differences in patient populations and study designs when multiple data sources are used.

- **relevant**, meaning that transition probabilities must be identified through a systematic or focused literature search. It must also be stated whether other relevant transition probabilities exist in the literature that could inform the same transition. See also the Danish Medicines Council's guideline on literature.

The applicant must justify the clinical plausibility of each transition probability, for example by explaining why a transition probability:

- can be assumed to be either constant or time-dependent.
- is assumed to be either identical or different from that of the other treatment arm.

The choice of transition probabilities must be based on an overall assessment of internal and external validity, see Section 4.4.

It must be clearly described how transition probabilities have been derived from clinical data, including whether time-to-event data using parametric models has been applied to estimate transition probabilities for certain patient transitions.

4.3 Other Assumptions Related to the Extrapolation of Patient Transitions

4.3.1 Use of surrogate outcomes and structural relationships between outcomes

The applicant must describe whether surrogate outcomes have been used in the health economic analysis, including the underlying structural assumptions regarding the relationship between the surrogate outcome(s) and the clinical outcome(s) of primary interest.

The applicant must assess whether modelling the clinical outcome(s) of primary interest via the surrogate outcome(s) is clinically plausible and, if possible, support this assessment with relevant evidence.

The applicant must also describe whether any clinical outcomes or surrogate outcomes are associated with substantial uncertainty, as this will be reflected in the modelling of the primary clinical outcome. If evidence on the clinical outcome of primary interest exists, the applicant must include a sensitivity analysis exploring the uncertainty surrounding the relationship between the surrogate outcome and the primary clinical outcome. This is best addressed by including a health economic analysis in which the primary outcome is modelled both directly and indirectly through the surrogate outcome.

4.3.2 Curative potential

If the introduction of a new drug is considered to have curative potential, the applicant may incorporate assumptions regarding cure in the health economic analysis. The assumptions must be thoroughly described and justified with respect to clinical plausibility (e.g., demonstrating long-term plateaus in Kaplan-Meier curves). It must always be possible for the Danish Medicines Council to modify cure assumptions within

the health economic model (e.g., the time point of cure and/or the proportion cured), such that the cure assumption can both be varied and omitted.

4.3.3 Duration of treatment effect (treatment waning)

If the applicant includes assumptions regarding the duration of treatment effects, these assumptions must be thoroughly described. The applicant must also include sensitivity analyses exploring the sensitivity of the results to the assumptions regarding duration of treatment effect. In addition, it must be possible for the Danish Medicines Council to adjust the assumed duration of treatment effect within the health economic model.

4.4 Internal and External Validity

The applicant must support the assessment of internal and external validity of the extrapolated patient transitions with appropriate figures in both the submission and the Excel model:

- One stacked area chart showing the proportion of patients in each health state over time for each treatment arm (i.e. Markov traces), as well as a tabulated summary of time spent in each health state. The Danish Medicines Council's standard sheet for presentation of results must be used for this purpose and inserted as the first sheet in the Excel model. The figures must be described in the submission dossier, and the plausibility of time spent in each health state must be assessed.
- For extrapolation using parametric extrapolation models, the Excel model must include:
    - one figure per treatment arm showing the extrapolated time-to-event data for all tested models examined together with the observed data (including confidence intervals for Kaplan-Meier data), adjusted for background mortality and any other assumptions (e.g., cure assumptions).
    - one figure including both treatment arms showing only the selected extrapolation models for the intervention and comparator(s), adjusted for background mortality and any other assumptions (e.g., cure assumptions), alongside the observed data.
    - tables presenting relevant annual rates (e.g. 1-, 3-, 5-, and 10-year rates) for all tested extrapolation models for each outcome. The rates must be adjusted for background mortality and any other assumptions (e.g., cure assumptions).

4.4.1 Internal validity

4.4.1.1 Internal validity when extrapolating using parametric extrapolation models

Assessment of internal validity involves evaluating whether the extrapolated data adequately fit the observed data from the clinical study. This includes a comparison of

models using the statistical measures Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), as well as an assessment of visual fit, both on the *probability scale* (e.g., Kaplan-Meier estimate compared with the extrapolation model) and on the *hazard scale* (e.g., smoothed estimated hazard compared with the parametric hazard function).

4.4.1.2 Internal validity when extrapolating using transition probabilities

Assessment of internal validity involves evaluating whether all transition probabilities are relevant, representative, and clinically plausible. See the reporting requirements for transition probabilities in Section 4.2. If possible, observed data must be compared with modelled data over the study period.

4.4.2 External validity

In the assessment of external validity, the applicant must focus on the clinical plausibility of the extrapolated patient transitions, including whether they are comparable with evidence from external sources. External evidence may include clinical studies, databases, or expert opinion.

The applicant must investigate whether data are available from other studies with comparable patient populations and/or from national or international registries with longer follow-up than the clinical study or studies underlying the extrapolations. If external evidence that may inform the choice of extrapolation is identified, these data must be presented in the submission dossier together with a description of their validity, including the comparability between the external evidence and the clinical study or studies underlying the extrapolations (e.g., study design, patient characteristics, subsequent treatments). External data will most often be available for the comparator(s). For the intervention, external validation may, for example, consist of data from early-phase clinical trials (phase I/II) with longer follow-up, expert opinion, evidence from drugs with the same mechanism of action, or evidence from studies of the same drug in other indications.

5. Requirements for the Excel Model

The applicant must include the Danish Medicines Council's standard sheets as the first sheets in the Excel model and link them to the relevant sheets in the health economic model. The Excel file must be certified in accordance with the Danish Medicines Council's checklist for formal requirements.

The health economic model must be fully manipulable and traceable. This means that all inputs must be editable and that all cell assumptions and dependencies are traceable. Accordingly, the model must not contain hidden sheets, hidden cells, or links to external files.

The model must be dynamic, such that all results, figures, and inputs for sensitivity analyses, etc., are automatically updated when a input parameter is changed. The model must also include a set of dynamic figures, see Section 4.4.

The model must be intuitive and user-friendly and should preferably include sheets in which all key inputs can be easily modified.

Model inputs must be fully adapted to Danish clinical practice, and all inputs must be referenced within the Excel model itself. The applicant must remove all content form the model that is not relevant to the submission to the Danish Medicines Council.

The applicant must conduct a thorough validation of the submitted model to ensure that all calculations and parameter estimates are correct.

Macros must be used only to perform sensitivity analyses, as a broader use of macros reduces the transparency of the model's calculations.

The Danish Medicines Council's assessment of health economic models generally draws on the model validation tool developed by the Canadian Agency for Drugs and Technologies in Health (CADTH) (Coyle et al., 2024)The applicant is therefore encouraged to follow the specifications in this tool alongside the Danish Medicines Council's guideline.

6. References

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7. Version log

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Medicinrådet

The Secretariat of the Danish Medicines Council
The Danish Medicines Council, Dampfærgevej 27-29, 3rd floor
2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk