Medicinrådet

Health-Related Quality of Life

Guideline

Version 1.0

Tabel of Contents

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1. Evidence Hierarchy for Health-Related Quality of Life

To ensure consistent comparison of health-related quality of life and QALY effects across the Danish Medicines Council's recommendations, all submissions must include data on health-related quality of life measured using the generic instrument EQ-5D-5L. Utility values applied in the health economic analysis must be based on EQ-5D-5L using Danish preference weights. Other generic and/or disease-specific instruments may be included as supplementary instruments if EQ-5D-5L is considered insufficient to capture changes in health-related quality of life for the disease in question (Finch et al., 2018; Payakachat et al., 2015).

If EQ-5D-5L data have not been collected in the clinical study that informs the clinical effect and safety, it may, in some cases, be necessary to report health-related quality of life measured using other validated instruments or to convert (map) these data to EQ-5D-5L. If no health-related quality of life data have been collected in the study, data identified through a systematic literature search for external evidence may be used.

The Danish Medicines Council's assessment of instruments used to collect health-related quality of life data is described in the evidence hierarchy presented in Figure 1. The ordering reflects the Danish Medicines Council's preferred choice of instrument. Deviations from the use of EQ-5D-5L data collected directly in the clinical study informing clinical effect and safety are always considered to be associated with increased uncertainty.

The use of vignettes, direct valuation of own health (e.g., using time trade-off methods), or the use of instruments from proxy diseases is considered to be associated with very high uncertainty and may only be applied when the other methods listed in Figure 1 are not feasible. These methods are therefore not described further in the this document. Instead, reference is made to the technical document by NICE (Brazier & Rowen, 2011).

Data on caregivers' health-related quality of life may be submitted as supplementary evidence and must likewise be described and documented in accordance with the requirements set out in in this document.

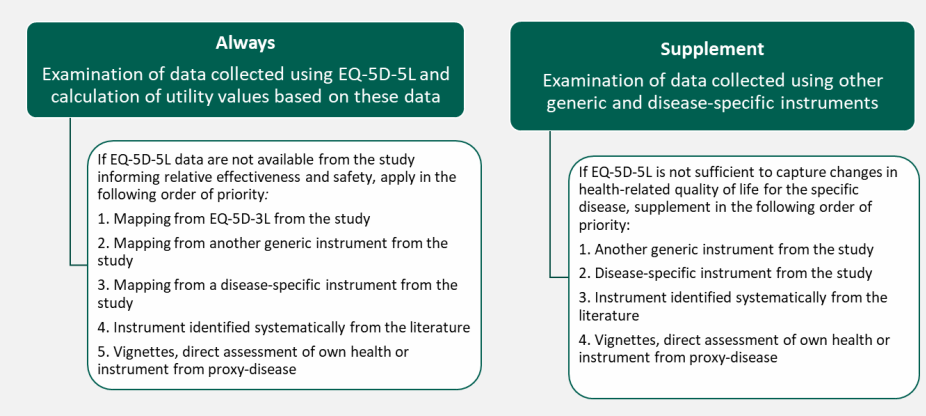

Figure 1 Hierarchy of preferred sources for health-related quality of life data (adapted from (Dawoud et al., 2022; NOMA, 2024))

2. Instruments

The Danish Medicines Council's guideline regarding the description of instruments is based on the CONSORT-PRO reporting standards (Calvert et al., 2013).

The same documentation standards apply to all included instruments, regardless of whether the instrument was used in the same study that informs clinical effect and safety or originates from another source. These documentation standards also apply to instruments whose primary purpose is to form the basis for the estimation of utility values.

2.1 Instrument and Study Design

If instruments other than EQ-5D are used, the applicant must describe and justify the choice of instrument, including, but not limited to:

- the clinical rationale for selecting the instrument
- the instrument's validity, reliability, and sensitivity in relation to the patient population.

Regardless of the instrument used, the applicant must describe the study design and potential sources of bias, including, but not limited to, whether:

- the study design or the selected instrument introduced a risk of bias
- the population contributing data on health-related quality of life differs from the population contributing to other clinical endpoints. If so, the differences between the populations must be presented in a table, and the implications for the assessment must be described.

2.2 Data Collection

The applicant must describe the data collection process, including, but not limited to:

- The data cut and the median follow-up time. The applicant must also state whether additional health-related quality of life data are expected at future planned data cuts.
- The timing of data collection and its relevance in relation to treatment frequency, adverse events and disease progression.
- Any reasons for differences in response rates across treatment arms (e.g., differences in adverse event profiles) and the implications thereof, including potential sources of bias. See also Section 3.3.1.2 regarding missing data. If response rates differ, the applicant must report any differences in characteristics between respondents and non-respondents at relevant time points.

2.3 Mapping

If EQ-5D-5L data were not collected in the clinical study informing clinical effect and safety, it may in some cases be possible to apply mapping from another instrument to approximate EQ-5D-5L. However, this requires that a suitable mapping algorithm is available for the relevant patient population.

The Danish Medicines Council always prefers the use of validated mapping algorithms. When assessing the validity of a mapping algorithm, the Danish Medicines Council refers to the HERC database of mapping studies, available at: http://www.herc.ox.ac.uk/downloads/herc-database-of-mapping-studies. The use of double mapping is generally discouraged.

The use of mapping must be thoroughly described, including:

- Whether a validated algorithm is used and whether it is based on indirect or direct mapping.
- If a validated mapping algorithm is used:
    - The purpose of the original mapping study must be described, and the study design and patient characteristics on which the mapping is based must be presented in detail and compared with the patient population included in the submission.
- If a validated mapping algorithm is not used:
    - Briefly describe the methods used to select the patient population, recruit patients, and collect data in the mapping study, including the number of patients and any censored patients.
    - Describe the statistical methods applied in the mapping study, including the choice of statistical tests and statistical models.
    - Present the results of the tested statistical models and justify the selection of the model used to estimate the final mapping algorithm.

Particular focus should be placed on measures of precision, such as root mean square error (RMSE), mean square error (MSE), or mean absolute error (MAE).

2.4 External Sources

If instruments based on other sources than the study informing clinical efficect and safety are used, such sources must be identified through a systematic literature search.

If multiple sources and instruments are used to report health-related quality of life, they must be based on comparable studies with comparable study populations. As part of the documentation of comparability, information must be provided on study design, inclusion and exclusion criteria, data collection methods, etc. If differences exist across the selected sources, the applicant must justify and document why the external sources are appropriate despite such differences.

If vignettes, direct valuation of own health (e.g., using time trade-off methods), or instruments developed for a proxy disease are used, additional methodological considerations apply. For a detailed discussion, reference is made to the technical document prepared by NICE regarding the use of these methods (Brazier & Rowen, 2011).

3. Health State Utility Values

3.1 General Information

If multiple sources and/or instruments are used to estimate utility values, the use of utility values derived from different study populations and/or different instruments and preference weights across health states should, to the extent possible, be avoided. See also section 2.4.

3.2 Preference Weights

For the valuation of health states derived from the descriptive EQ-5D-5L system, the applicant must use EQ-5D-5L preference weights based on the general Danish population (Jensen et al., 2021). If direct mapping between utility values is applied, see Section 2.3.

3.3 Calculation of Utility Values

3.3.1 Regression Model

When selecting the model, it must be taken into account that patient-level responses are typically correlated over time. The use of mixed-effects models for repeated measures (MMRM) is therefore recommended.

The specification of the regression model should depend both on the structure of the health economic model (i.e., disease progression) and on the mechanisms underlying changes in health-related quality of life (e.g., differences between treatment arms and the reasons for such differences). The applicant must therefore describe (preferably supported by literature) the mechanisms driving changes in health-related quality of life in each treatment arm, how the variables included in the regression model (e.g., health states or time to death) reflect disease progression, and whether there is uncertainty regarding the choice of regression model such that alternative regression models should be explored in sensitivity analyses.

Models fitted on the same dataset may be compared using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Models that are both fitted to the same dataset and nested may be compared using likelihood ratio tests.

The applicant's description of the regression model must, overall, address the following elements:

- **Choice of regression model**
  I. Description of the data basis, including the study population, instrument, and preference weights.
  II. Reporting of sample size and response rate at each measurement time point.
  III. Description of data quality, including potential sources of bias and the handling of missing data, see Section 3.3.1.2.
  IV. Description of all underlying assumptions related to the choice of regression model.
- **Choice of explanatory variables**
  I. Presentation of the regression equations and the rationale for including explanatory variables, including linkage to the model structure and the underlying mechanisms driving differences and changes in health-related quality of life across treatment arms and over time.
  II. Definition of all included explanatory variables, including their parameterisation (e.g., categories, linear terms, polynomials, or other transformations).
  III. Presentation of any model simplification procedures, including the testing hierarchy and associated p-values or AIC/BIC.
- **Presentation of the final model**

I. Presentation of parameter estimates, standard errors, and confidence intervals.
II. Presentation of the calculated utility values and corresponding confidence intervals, as well as the method used for their estimation. If the calculated utility value is based on more than one parameter estimate (e.g., a linear combination), any potential correlation between the relevant parameter estimates must be considered.

- **Validation of the final model**
  I. Reporting of the results of goodness-of-fit assessments and evaluation of model assumptions.
  II. Discussion of the plausibility of the results, including contextualisation with relevant literature and/or data.
- **Uncertainty and sensitivity analyses**
  I. Reporting of how uncertainty has been addressed.
  II. Discussion and examination of the model's limitations.
  III. Presentation of relevant sensitivity analyses.

The elements outlined above are inspired by the recommendations of Kearns et al. (2013).

3.3.1.1 Adjustment for differences in patient characteristics

In some cases, it may be relevant to adjust for patient characteristics. The regression equations must clearly specify which adjustments have been included in the regression model. The applicant should be aware of the risk of double counting, for example when adjusting for age and adverse events.

If the gender distribution in the study differs from that observed in Danish clinical practice, the Danish Medicines Council recommends incorporating any differences in utility values between men and women into the health economic model. For further details, see, for example, Ara et al. (2017).

All adjustments must be justified, and the sensitivity of the results to these adjustments should be assessed by presenting regression results both with and without the adjustments.

3.3.1.2 Missing data

Missing data constitute a fundamental challenge in the analysis of health-related quality of life data, whether arising from study design, data collection procedures, disease progression, or the nature of the treatment. If patients' health-related quality of life is correlated with dropout or non-response, missing data will be informative and may introduce bias. For example, if patients with very poor health-related quality of life are also those who fail to complete the questionnaire.

Missing data can be categorised as dropout (i.e., patients who withdraw from the study, for example due to death or adverse events) and non-response at a given measurement time point. Both dropout and non-response reduce the number of available

observations, making it more difficult to detect statistically significant differences and thereby reducing statistical power. In addition, bias may arise if the data are missing-not-at-random (MNAR) or if they are missing-at-random (MAR) but are analysed without appropriately accounting for missing data.

The applicant must justify and discuss the missing data assumption underlying the analysis of health-related quality of life data:

- **Missing-completely-at-random (MCAR):** The missing values occur completely at random, and a complete-case analysis would be unbiased. MCAR is a very strong assumption and often unrealistic.

- **Missing-at-random (MAR):** The missing values are not random but can be explained by observed data (e.g., if men are less likely to complete the questionnaire). This assumption cannot be proven but may in some cases be rejected. If the MAR assumption holds, a MMRM will provide unbiased estimates for longitudinal data. Single-value imputation methods (e.g., last observation carried forward) are not recommended due to a high risk of bias and underestimation of uncertainty. Multiple imputation may also be applied under the MAR assumption.

- **Missing-not-at-random (MNAR):** The missing responses cannot be explained based on observed data. For example, patients with poor health-related quality of life may be less likely to complete the questionnaire. Sensitivity analyses may be conducted under alternative assumptions regarding the missing values.

In assessing the applicant's handling of missing data, the Danish Medicines Council considers, among other aspects, the following elements, which are adapted from recommendations of Mukherjee et al. (2023):

- **Has the applicant conducted a descriptive analysis of missing data and reported the reasons for missing data?**
    I. Reporting of response rates.
    II. Registration of informative dropout, i.e., if dropout is due to poor health, adverse events, or death. The reason for dropout must be reported.
    III. Reporting of associations between missing data and baseline variables, as well as between missing data and outcome variables.
- **Has the applicant described how missing data were handled? Was it handled adequately?**
    I. Is the underlying assumption regarding the missing data mechanism realistic?
    II. Given the missing data assumption, has an appropriate statistical model been applied?
- **Has the applicant assessed the impact of the missing data assumption on the results of the analysis?**
    I. How do the results change under an MNAR assumption, for example when using pattern-mixture models or simple sensitivity analyses?

3.4 Adjustment of Utility Values

3.4.1 Adverse Events

If reductions in health-related quality of life associated with adverse events are not expected to be captured in the applied utility values, it may be appropriate to incorporate decrements in health-related quality of life within specific health states (i.e., disutilities). The applicant must describe how disutilities are estimated and incorporated into the model, and the relevance of any external sources used must be thoroughly justified. If disutilities are estimated using regression models, reference is made to the guideline set out in Section 3.3.1.

3.4.2 Age Adjustment

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.

In the health economic model, age adjustment must be applied using a multiplicative approach, whereby the utility values used in the model are weighted by an adjustment index based on age-specific population norms from the Danish general population. The adjustment index is currently derived from Danish EQ-5D-3L population norms, as Danish EQ-5D-5L population norms stratified by age and based on a sufficiently large number of responses in each age group have not yet been published.

The applicant must use the EQ-5D-3L population norms presented in Table 1, which are based on EQ-5D-3L responses from 21,384 adults (Region Nord, 2017) and EQ-5D-3L preference weights (Wittrup-Jensen et al., 2009). The Danish Medicines Council's standard sheets for age adjustment must be used in the Excel model. The adjustment must be based on the patients' expected starting age, see example in Table 2.

Table 1. Basis for age adjustment: Index calculated based on population norms using starting age of 18 years as reference.

Age	Population norm	Age adjustment index (with starting age of 18 years)
0-29*	0.871	1 (reference)
30-39	0.848	0.848 / 0.871 = 0.974
40-49	0.834	0.834 / 0.871 = 0.958
50-69	0.818	0.818 / 0.871 = 0.939
70-79	0.813	0.813 / 0.871 = 0.933
80+	0.721	0.721 / 0.871 = 0.828

*For ages *0-17 years, the population norm is assumed to be identical to that of ages 18-29 due to lack of data for this age group.*

Table 2. Example of age adjustment with a starting age of 48 years in the health economic model

Age	Utility value from study	Population norm (from Table 1)	Age adjustment index (starting age 48 years)	Age-adjusted utility value
48	0.78	0.834	1 (reference)	0.78 (= 0.78 x 1)
49	0.78	0.834	1	0.78 (= 0.78 x 1)
50	0.78	0.818	0.981 (=0.818 / 0.834)	0.77 (= 0.78 x 0.981)
51	0.78	0.818	0.981	0.77
52	0.78	0.818	0.981	0.77
…	0.78	0.818	0.981	0.77
…	0.78	0.818	0.981	0.77
70	0.78	0.813	0.975	0.76
71	0.78	0.813	0.975	0.76
…	0.78	0.813	0.975	0.76
…	0.78	0.813	0.975	0.76
80	0.78	0.721	0.865	0.67

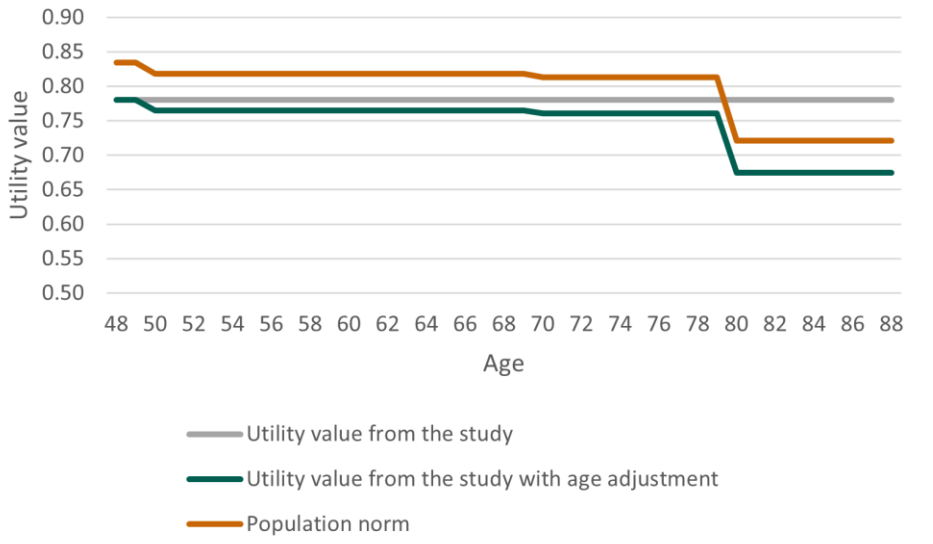

Figure 2. Example of age adjustment with a starting age of 48 years in the health economic model

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5. Version Log

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