Behandlingsrådet

Alfred Nobels Vej
27, 9220 Aalborg Ø,
Denmark
+ 45 70 21 08 00
kontakt@behandlingsraadet.dk
www.behandlingsraadet.dk

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Technical annex. Health economic modelling

Objective

This technical annex aims to support the preparation of applications to the Danish Health Technology Council with respect to enquiries regarding the use of health technology, including medical devices, but also other types diagnostic devices, as well as treatments, rehabilitation, prevention, and types of organisation and collaboration in the provision of healthcare services. In the following, 'health technology' is used as an umbrella term for all of these.

This technical annex concerns health economic modelling, including modelling in relation to the preparation of cost-utility analyses. In collaboration with the Danish Health Technology Council secretariat, the expert committee may set specific requirements in the evaluation design for the economic analysis to be carried out in the application. These requirements can relate to use of a health economic model, and if so, which type of model is to be used, as well as possible model specifications. Another requirement could be to use quality-adjusted life years as outcome measure, which would entail that the applicant should perform a cost-utility analysis, which, in turn, often entails applying health economic modelling. If the applicant has to use a health economic model to prepare the economic analysis in the application, this must be on the basis of the approaches described in this annex.

The design of the economic analysis will always reflect the health technology under examination, including its core outcome and the context in which it is to be used. The analysis design will never be more comprehensive than the expert committee considers necessary.

The approaches and methods set out in this technical annex should be considered as guidelines, and therefore it is recommended that they be applied as the basis for drafting applications to the Danish Health Technology Council. However, the Danish Health Technology Council is aware that there may be situations in which it makes sense to deviate from the recommendations in this document. In such cases, the applicant should account for the reasons.
For further information on health economic modelling, see other texts [1–4]. See also the Danish Health Technology Council's process guide and methods guide for further information on applications to the Danish Health Technology Council. The Danish Health Technology Council's methods guide is subject to regular updating, so make sure to check out www.behandlingsraadet.dk for any recent updates. If there are further queries about specific areas, these may be clarified in dialogue with the Danish Health Technology Council secretariat after publication of the evaluation design.

1. Preparation and documentation of health economic models

Applicants may draw up and submit models in Microsoft® Excel or Treeage® software when submitting applications to the Danish Health Technology Council. Models submitted to the Danish Health Technology Council should not be locked or contain hidden elements. All input in the model must be fully editable, and in the event of changes, the model must automatically update all the results, sensitivity analyses, etc. Applicants should name model inputs meaningfully such that an outsider can identify what they represent. Data in the form used in the model should be stated in the application or an annex to the application, so that it is possible to trace its origin. Applicants should remove all content that is irrelevant for the application to the Danish Health Technology Council.

Use of international models may be accepted if they reflect a Danish context or are adapted to a Danish context with regard to clinical practice, patient characteristics, health effects, cost statements, discounting, etc. See Technical annex. Cost statement for considerations regarding cost statements in this respect. If international models are used, in an annex to the application (Annex 10.5), the applicant should document how the model has been adapted to Danish conditions and which sources have been in the process.

1.1. Model description

In connection with the model description (section 8.2.4.2 in the application template), the applicant should indicate significant assumptions concerning the model design and the reasons for these based on current evidence. Where relevant and possible, the applicant should include knowledge from the systematic literature search (see PICO, the Danish Health Technology Council's methods guideline) when designing the health economic model.

The model structure should be in accordance with the description of the clinical disease or treatment pathway described in section 3 of the application template, as well as the description of the organisation within which the intervention and comparator(s) are expected to be used (described in section 7.3 of the application template) and how they influence the organisation. The applicant should describe how adverse effects and late complications that may arise from using the health technology in Danish clinical practice have been included in the model. This includes how these have been managed, e.g. with respect to monitoring, follow-up, derived resource consumption and total costs etc. If relevant safety data has not been included in the economic analysis, the applicant should explain why. For more complex models, it may be advisable for the applicant to explain the model flow in Annex 10.5.

The applicant may have to base the structure and flow of the model on assumptions for which the applicant has no evidence. In this connection, the applicant should describe the assumptions and state sources, if such exist, that support these assumptions.

In connection with the description of the health economic model, applicants should state any limitations in the model with regard to the clinical disease pattern that it is to reflect (see section 3 of the application template). If the model reflects a significantly different disease pattern or organisation of the treatment than is likely in Danish practice, the applicant should account for the most important differences.

2. Management of clinical data

2.1. Use of epidemiological data

Where possible, the applicant should base the analysis on Danish epidemiological data, e.g. with regard to background risks of complications with the disease (such as mortality, etc.). The Danish Health Technology Council recommends that the applicant base the economic analysis on clinical, patient-relevant endpoints such as relapse, blood clots, death, etc., unless the expert committee indicates otherwise in the evaluation design.

If there is no Danish epidemiological data, the applicant may use data on other populations. This can happen if these populations are likely to be representative of the Danish population with regard to the prevalence of the disease and other characteristics likely to be significant for the disease and treatment pathway in focus. If no epidemiological data exist that is likely to be representative of the Danish population, the control arm from a randomised controlled study can be used, for example. If Danish epidemiological data is not used, the applicant should account for why the data used is likely to be representative of the Danish patient population and/or the treatment pathway in the Danish organisation.

There may be situations in which there are several sources for the same data input. The applicant may have to make a choice, for example between a source of high-quality information and a source of information that is assessed to be (more) relevant in the Danish treatment context (studies with high internal and external validity, respectively). In this situation, the applicant should describe in the application the advantages and disadvantages of the different sources of information, and justify the final choice of information source.

2.2. Use of data from clinical trials

If the applicant uses comparative data from clinical trials in the health economic model, the Danish Health Technology Council recommends that the estimates be included in the form of hazard ratios (or, alternatively, relative risks) based on Danish epidemiological data (see section 2.1 in the application template).

The applicant should use intention-to-treat data whenever possible.

Hazard ratio and relative risk

Hazard ratio is used for data in the form of rates, while relative risk is used for probabilities. If it is necessary to transform data to reflect another cycle length than that which is available via data, relative risks should only be used in relation to their original observation periods and they should be applied to data on probabilities before the probabilities are transformed (e.g. a relative risk observed over a 5-year period can only be compared with a “background risk” that also covers a 5-year period). Alternatively, the relative risk can be transformed to reflect the cycle length applied.

2.3. Data extrapolation

If data is extrapolated beyond the observation period of the data available, the applicant should describe the assumptions made for the extrapolation.

For example, this may include whether a difference in the incidence of late complications between the intervention and its comparator(s) is expected to remain constant, increase or fall beyond the observed period[2,3]. The applicant should also give reasons if the assumptions concerning the data on the health technology under examination are different from the assumptions for its comparator(s). When extrapolating clinical time-to-event data, the applicant should present graphs of the observed data and Kaplan-Meier plots with the extrapolated adjusted curves, as well as any external data that the applicant

has used to validate the extrapolation. This may include epidemiological data. The curves should be illustrated in the application. In connection with the explanation for the assumptions regarding extrapolation, the applicant should also state the software used for the extrapolation. If it has been relevant to extrapolate time-to-event data, the applicant should present a summary of the approach applied in the application (section
8.2.5.6). This should include the choice of methodology, choice of distributions, as well as whether the data has been adjusted. For example, this will be relevant if there are adjustments for change of treatment. In Annex 10.7 to the application, the applicant should describe the methods applied and the choices made. The practical application of any adjustment methods should also be described here.

More detailed information on standard methods, specifications of requirements, guidelines for extrapolation and validation of the projection models is available in the Danish Medicines Council guidelines on the use of process data in economic analyses. For more information about validation and reporting when using models, see NICE DSU technical support document 14.

3. Health economic modelling and cost-utility analyses

3.1. Outcome measures

If the expert committee has specified that the applicant is to prepare a cost-utility analysis, the applicant must use quality-adjusted life years, QALYs, as outcome measures. For information about QALYs, see other sources [3,5].

3.2. Inclusion of the impact of health-related quality of life in health economic modelling

When drawing up a cost-utility analysis using health economic modelling, the applicant should describe and document relevant health states and expected adverse effects and, in this respect, the associated health-related quality of life (HRQoL) and possibly mortality.

In the description of the model (see application template, section 8.2.4.2 and Annex 10.5), the applicant should describe how adverse effects and late complications that may arise from using the health technology in Danish clinical practice have been included in the model. Therefore, this also includes how potential adverse effects, etc. that are caused by interventions affect the HRQoL. If relevant safety data and its implications for the HRQoL have not been included in the economic analysis, the applicant should also explain why this is the case. If the adverse effects are not ascribed any impact on HRQoL, the applicant should account for the reasonableness of this assumption.
The impact of adverse effects on HRQoL can be identified using the EQ-5D-5L questionnaire, for example (see section 3.3). Similarly, if the economic analysis is populated with literature-based data on HRQoL (see section 3.5), it should be stated how the impacts of adverse effects have been included.

The applicant should state whether the HRQoL is expected to be constant over time and how long any incidents, such as adverse events, are likely to influence the HRQoL after they arise.

3.3. Instruments for measuring the HRQoL and reporting

The Danish Health Technology Council recommends that applicants base their cost-utility analysis on data collected using the EuroQoL-5Dimensions-5Levels (EQ-5D-5L) questionnaire, where this is possible. The Danish Health Technology Council also recommends that preference weights based on the Danish population in general be used in the cost-utility analysis to estimate the HRQoL[6].

If the preference weights cannot be found using the EQ-5D-5L questionnaire with associated Danish weights, the applicant should explain why in an annex to the application (Annex 10.8).

If the clinical studies presented in the application include data collected on the HRQoL, but the applicant has used alternative estimates, the applicant should also state reasons for this in Annex 10.8.

3.3.1. Exemptions from the use of EQ-5D-5L data

If there is no EQ-5D-5L data, or data that can reasonably be mapped to EQ-5D-5L data (see section 3.4), the cost-utility analysis may be carried out on the basis of other instruments to evaluate the HRQoL. In this respect, if possible, the applicant should use generic instruments, e.g. the Short Form-6Dimensions (SF-6D) questionnaire. If this applies, the applicant should in the application state why it was not possible to obtain EQ-5D-5L data, which instrument has been used as an alternative, how this instrument differs from the EQ-5D-5L questionnaire, and how it is likely to affect the results of the analysis.

There may also be situations in which use of the EQ-5D-5L questionnaire is inappropriate to evaluate the effect of the health technology. The applicant should account for why the EQ-5D-5L questionnaire has not been used. The applicant should reason based on empirical evidence that demonstrates problems with the construct validity or responsiveness of the questionnaire in relation to the patient population being studied. This evidence should be based on a systematic synthesis of the published literature.

Applicants are invited to consult the Danish Health Technology Council secretariat if it is not possible to base the cost-utility analysis on EQ-5D-5L data, in order to find the best alternative approach.

3.4. Mapping

If there is no EQ-5D-5L data on the outcome from the health technology under examination, the applicant may predict expected EQ-5D-5L-questionnaire responses from other generic, preference-based instruments used in studies of the technology. However, this is only possible if there is a published, validated mapping algorithm between the instrument used and the EQ-5D-5L questionnaire.

If disease-specific instruments to assess the HRQoL are applied in the clinical trials, the applicant may predict expected EQ-5D-5L responses on the basis of these instruments, provided there is a published, validated mapping algorithm. If both generic, preference-based instruments and disease-specific instruments are used, the Danish Health Technology Council recommends that applicants predict EQ-5D-5L responses on the basis of the generic instruments.

If it has been necessary to predict EQ-5D-5L responses, applicants should give reasons for the choice of method and clarify the method used for the prediction. If possible, applicants should compare the predicted data on the HRQoL with any published data on HRQoL for the patient population being studied. See NICE DSU technical sup- port document 12 for a detailed description of relevant methods for this.

3.5. Use of literature-based data on health-related quality of life

It is possible that no data has been collected on the HRQoL in connection with studies of the health technology under examination and/or some of the health stages included in the health economic model. It is also possible that an applicant considers that the evidence available is inadequate to support the economic analysis.

In such cases, the applicant may potentially estimate the HRQoL from other scientific literature. This situation can arise if the health technology under examination postpones late complications from a disease, for example blood clots, and, although clinical studies have documented the occurrence of blood clots, they have not collected data on the HRQoL for patients. In this situation, it may be relevant to base estimates of the HRQoL for patients who have suffered from a blood clot on the literature. Thus, these estimates do not directly relate to the health technology under examination and instead they relate to the late complication; the blood clot. However, the estimates may still be used in the model. If the effect on the HRQoL is included in the model in the form of literature-based data, the applicant should account for how this was done in the description of the model in Annex 10.5 to the application template.

The Danish Health Technology Council recommends that literature-based data on HRQoL be based on the EQ-5D-5L questionnaire as far as possible.

3.6. Age adjustment to health-related quality of life

It can often be necessary to adjust data related to the HRQoL for increase in age. If the HRQoL is assumed to fall or rise over time, the applicant should describe how and why, and how this has been incorporated in the economic analysis.

If the average age of the study population for which data is available significantly deviates from the expected age of the Danish patient population, the applicant should also age-adjust the observed data on the HRQoL, so that it more closely reflects the expected Danish patient population. If data on the HRQoL is not adjusted for age, and there is evidence that this should be done, the applicant should justify making no adjustment and describe how this is likely to affect the results of the economic analysis.

In general, the applicant should make age adjustments by using a multiplicative method. There is an example of this method in NICE DSU technical support document 12.

4. References

1. J.J. Caro, A.H. Briggs, U. Siebert, K.M. Kuntz, Modeling good research practices-overview: A report of the ISPOR-SMDM modeling good research practices task force-1, Med. Decis. Mak. 32 (2012) 667–677. https://doi.org/10.1177/0272989X12454577.
2. A. Briggs, M.J. Schulpher, K. Claxton, Decision Modelling for Health Economic Evaluation, 1st ed., Oxford University Press, Oxford, 2006.
3. M. Drummond, M.J. Schulpher, K. Claxton, G.L. Stoddart, G.W. Torrance, Methods for the Economic Evaluation of Health Care Programmes, 4th ed., Oxford University Press, Oxford, 2015.
4. J. Fox-Rushby, J. Cairns, Economic Evaluation, Open University Press, 2005.

5. S.J. Whitehead, S. Ali, Health outcomes in economic evaluation: The QALY and utilities, Br. Med. Bull. 96 (2010) 5–21. https://doi.org/10.1093/bmb/ldq033.
6. C.E. Jensen, S.S. Sørensen, C. Gudex, M.B. Jensen, K.M. Pedersen, L.H. Ehlers, The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data, Appl. Health Econ. Health Policy. (2021). https://doi.org/10.1007/s40258-021-00639-3.