Medicinrådet

The Danish Medicines Council methods guide for assessing new pharmaceuticals

This translation is based on the Danish document ”Medicinrådets metodevejledning for vurdering af nye lægemidler” (Version 1.2). Please note: The translation is provided as a service by the Danish Medicines Council to English-language readers. In the event of discrepancies, the Danish version prevails.

Version 1.2

Document.no.: 166866

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Language: English
Format: pdf
Published by the Danish Medicines Council, 25 februar 2021

Introduction

The aim of this methods guide is to clarify the requirements for companies wanting to have a new medicine or extension of indication for an existing pharmaceutical assessed by the Danish Medicines Council. The methods guide also serves as a tool for the three units under the Danish Medicines Council: The Council, the expert committees and the Secretariat. Furthermore, the methods guide may provide other stakeholders with insight into the Danish Medicines Council's methods for assessing new pharmaceuticals and extensions of indications for existing pharmaceuticals. In this document, the term "new pharmaceutical" refers to both new pharmaceuticals and extensions of indication for existing pharmaceuticals.

The process for assessment of new pharmaceuticals is described separately in the Danish Medicines Council process guide for assessing new pharmaceuticals. The two guides form the basis for how the Danish Medicines Council assesses new pharmaceuticals.

A company initiates the assessment process by submitting a request for assessment, which is further described in the process guide. This methods guide describes what should be included in the application to the Danish Medicines Council. An application to the Danish Medicines Council should include documentation and analyses of the clinical effect and safety, cost-effectiveness and the budget impact of the new pharmaceutical. The application should make it possible for the Danish Medicines Council to estimate the effect and costs of putting a new pharmaceutical into use, compared with the current treatment in Danish clinical practice. The company can contact the Danish Medicines Council Secretariat for guidance on its choices in connection with an application, for example the choice of comparator, search protocol and search strategy(ies), analyses, etc. This will be agreed with the Secretariat.

Application materials will generally consist of a completed application form, health economic analysis and budget impact analysis. The company must submit the health economic analysis and budget impact analysis in Excel format and the company can submit an additional technical document. The application form is on the Danish Medicines Council website.

A recommendation by the Danish Medicines Council is based on an assessment of whether the effect (measured as quality-adjusted life-years (QALY)) and safety of a pharmaceutical, is reasonably proportionate to the cost of bringing the pharmaceutical into use in Denmark. Assessment of a new pharmaceutical is within the political framework of the Danish Parliament's seven principles for prioritising hospital medicines and the two principles of caution and severity that the Danish Medicines Council can consider in exceptional circumstances. The seven principles of the Danish Parliament and a description of how the Danish Medicines Council applies the severity principle are available (in Danish) on the Danish Medicines Council website: www.medicinraadet.dk.

Pharmaceuticals with sparse data

All applications should follow this methods guide. In applications with only limited data, which may apply for pharmaceuticals for rare diseases, the company should present the clinical evidence as they would for other pharmaceuticals. The health economic analysis can include clinical expert assessments to a greater extent when only sparse data is available. In such cases, the Council, the expert committee and the Secretariat, will assess the validity of the specific assumptions included in the application, through expert assessment and determine their plausibility.

There may be situations in which it is not possible or appropriate to carry out a cost-utility analysis based on the sparse data. In these situations, the company should instead present the available effect, safety and cost data, and provide a rationale for why a cost-utility analysis was not possible, - (see section 6.2.1).

In cases where it is not possible to carry out a cost-utility analysis, the Council will be presented with the available data. Data on the effect, safety and cost of the new pharmaceutical will be assessed as specified in the relevant sections of this methods guide. The Council will make its recommendation on this basis. Pharmaceuticals with sparse data can be recommended just like other pharmaceuticals, if in the specific case, the Council assesses that the presumed effects are reasonably proportionate to the costs, and that the uncertainties within the data for the specific case, are acceptable.

The assessment process for pharmaceuticals with sparse data follows the same process described in the Danish Medicines Council's process guide for assessment of new pharmaceuticals.

Structure of the methods guide

The methods guide describes what an application to the Danish Medicines Council should contain and provides the specific requirements for the analyses to be conducted by the company.

For the Danish Medicines Council to assess whether the new pharmaceutical will have a better effect and/or safety than the existing treatment, information on the disease, patient population, pharmaceutical and current Danish clinical practice is necessary. Section 2 contains a description of how a company should address these topics.

Section 3 describes how the company should carry out the various literature searches to ensure transparency and a systematic approach.

Section 4 describes the requirements for how the company should present the studies used to demonstrate the effect and safety of the new pharmaceutical and comparator(s).

Section 5 describes the principles for statistical comparison that the company should use to document relevant differences in effect.

The basic requirements for the health economic analysis are described in section 6.

Sections 7 and 8 of the guide describe how the company should estimate health effects and costs, while section 9 describes how the company should approach uncertainty in the health economic analyses.

Section 10 describes how the company should conduct and present its budget impact analysis.

Use of experts

When this guide refers to the use of expert sources, the company should use experts other than members of the expert committee of the Danish Medicines Council. In general, it is preferable that the company uses international data and/or Danish expert sources as references when there is no Danish data available.

Experts advising the applicant company may not subsequently be involved in any part of the processing of the application for the pharmaceutical in question by the expert committee.

1. Summary of the application

The company should begin its application with a summary, including descriptions of which indication is covered by the application, the relevant patient population, the new pharmaceutical, the pharmaceutical(s) that the new pharmaceutical is compared with (comparator(s)) and the most important outcomes in clinical studies. The company should also describe the health economic analysis methods used in the application.

2. Description of the pharmaceutical and therapeutic area

2.1 The disease and current standard treatment in Denmark

In the application, the company should describe:

- The pathophysiology and clinical presentation of the disease.
- Incidence and prevalence of the disease in Denmark, and developments within the past five years. For small patient groups, the company should also describe the global medical history including incidence and prevalence.
- The existing standard treatment in Denmark with references. If there are no Danish guidelines, the company may use international guidelines and/or Danish expert sources.
- The prognosis with existing treatment options. The company should also describe the prognosis if there are no existing treatment options.

2.2 The new pharmaceutical

In the application, the company should describe the new pharmaceutical (the intervention), including:

- Mode of action
- Pharmacotherapeutic class (ATC codes)
- Form of administration
- Dosage
- Treatment plan, including whether treatment with the pharmaceutical includes combination therapy or premedication.
- Packaging type, size, durability, strengths and description of the device if relevant

- Handling requirements of the pharmaceutical that may affect usability
- Monitoring (for example the need for blood samples, biomarker measuring, scans)
- The expected position of the new pharmaceutical in existing Danish practice (the Danish treatment algorithm), including whether the new pharmaceutical may replace existing treatments, or whether the new pharmaceutical is expected to constitute a new line of treatment to supplement existing treatments.

2.3 Patient population

The company should describe which patients they expect to be candidates for treatment with the new pharmaceutical, including number and patient characteristics, for example average age (median), gender and relevant disease-specific information. The clinical area will determine what information is relevant. The company should provide references for all figures and descriptions, for example registries and clinical databases. In general, the Danish Medicines Council prefers data from Danish sources. It is not sufficient to base information on the patient group in the clinical studies forming the basis for approval of the pharmaceutical.

The company should describe and justify any clinical and/or pharmaceutical rationale for specific sub-groups of patients responding differently to the pharmaceutical. The company should also describe the relevant diagnostic tests and studies that are to be used for selecting patients.

If the new pharmaceutical is dosed in accordance with body weight or surface area, the company should disclose the average body weight or surface area for the patient group in question, with references. If the patient group does not deviate from the general population, or there is no documentation of the patient group's average body weight or surface area, then the company may use the average estimates in the most recent National Health Profile (Nationale Sundhedsprofil).

2.4 Choice of comparator

Comparator(s) is/are the treatment alternative(s) that the new pharmaceutical will be compared with. The choice of comparator should always be the pharmaceutical(s) or other treatment(s) (including preventive and palliative treatments) in Danish clinical practice that represent real alternatives and current standard treatment. Information about current standard treatment in Danish clinical practice can be found in guidelines from the Danish Medicines Council, medical companies, outpatient departments or other sources. If there is no existing treatment alternative for the disease, the comparator will be a placebo or no treatment. The choice of comparator by the company will always be assessed by the expert committee.

If the studies available on the effect and safety of the pharmaceutical have not been carried out with an appropriate comparator in the Danish context, then the company

should carry out an indirect comparison. See section 5 for a more detailed description of indirect comparisons.

In some cases, it may be relevant to compare different treatment sequences. This not only means that the new pharmaceutical and comparator differ in the overall course of treatment; it also means that the introduction of the new pharmaceutical will result in changes to other treatment lines in an overall treatment pathway. In such cases, the company should describe the treatment sequences in detail. See also section 6.6.

In general, the application should include all relevant comparators. If the company chooses not to compare with one or more relevant comparators, then company should describe and justify their rationale for this.

The same information on the new pharmaceutical as described in section 2.2 should be given for all comparators.

2.4.1 Several comparators

In cases where there are several standard treatment alternatives in Danish clinical practice, the company should generally include these as comparators in its application.

The company should always include each comparator individually. This means that the company cannot combine data from two or more treatment alternatives and report it as the average effect or average costs in the health economic analysis.

In cases where the patient group used for comparison may have received one of several treatment alternatives, for example “investigator’s choice”, it will not always be possible or appropriate to assess treatment alternatives individually. The company should describe and justify if such treatment alternatives are used as individual comparators.

2.4.2 If a comparator has not previously been assessed by the Danish Medicines Council

If a comparator has previously been assessed by the Danish Medicines Council and recommended as a standard treatment for the indication, an analysis against the comparator will be sufficient.

If a comparator has *not* previously been assessed and recommended by the Danish Medicines Council, then a comparative analysis in which the new pharmaceutical is compared with this comparator will generally not be sufficient in an assessment of new pharmaceuticals and extensions of indication. This also applies when a comparator is a pharmaceutical taken into use before the Danish Medicines Council was established on 1 January 2017. In cases where a comparator has not previously been assessed by the Danish Medicines Council, it will be necessary to carry out an analysis against a placebo, for example, in order to provide the best possible decision-making basis for the Danish Medicines Council. There may be cases where the relationship between cost and effect for the comparator may not be reasonable. In such cases, a new pharmaceutical may

appear as disproportionately cost-effective compared to the comparator. Only comparing the new pharmaceutical with a comparator will therefore not provide a true and fair impression of the cost-effectiveness of the new pharmaceutical. In such cases, the company should carry out a health economic analysis using two comparators: one analysis using a comparator that reflects existing Danish clinical practice, and one analysis using a comparator that could reasonably be assumed to be cost-effective. For example, a placebo comparator.

In some cases, the Danish Medicines Council can accept that a company does not carry out a supplementary analysis with a second comparator as described above, if the comparator can be considered as an established standard Danish treatment practice over a longer period; if the pharmaceutical has a documented effect on the patient population that is relevant for the assessment by the Danish Medicines Council, and if the costs of the comparator are low. The company can discuss such cases with the Danish Medicines Council Secretariat and receive advice before applying.

3. Literature search and selection

The company should perform its literature search in accordance with the international principles and with a systematic and transparent approach to formulating focused questions defined by PICO[1], then it should assess, summarise and present the selected literature. The objective of the literature search is to ensure a systematic approach and transparency in relation to identifying the data sources used by the company in its application.

In this section, the Danish Medicines Council distinguishes between requirements for literature searches on clinical effect and safety and requirements for literature searches on other data included in the health economic analysis. The company should always carry out a systematic literature search in connection with identifying documentation on clinical effect and safety. This is also generally the case when identifying other data included in the health economic analysis. However, there will be cases where a literature search will not contribute additional relevant information and can therefore be omitted. For example when using cost estimates in the Danish Medicines Council's catalogue of unit costs (see section 8.1).

For all data used in the application, the company should describe how the data was identified to a degree that enables reproduction.

1. Each question should define the patient group (the population), the medicine being assessed by the Danish Medicines Council (the intervention), the medicine(s) the Danish Medicines Council are comparing with (the comparator(s)) and the outcomes. This is abbreviated to PICO (Population, Intervention, Comparison and Outcomes).

3.1 Documentation of clinical effect and safety for the intervention and comparator(s)

In general, the company should carry out a systematic and transparent literature search for documentation on the effect and safety of both the intervention and comparator(s). This includes sufficient documentation of search strings and the literature selection process to a degree that enables reproduction.

If one or several studies have already directly compared the new pharmaceutical with the relevant comparator(s), then the Danish Medicines Council can accept that the company does not carry out a systematic search for documentation of the effect and safety of the comparison in question. In such cases, the application should justify why a literature search is not likely to provide further relevant documentation on the effect and safety of both the intervention and comparator(s).

3.1.1 Documenting literature search and selection

Documentation of the literature search by the company should always include:

- Focused questions and relevant PICO.
- Search strategy and search strings (combination of search terms). As a minimum, the search strings should include the generic name and trade name of both the pharmaceutical and its comparator(s) combined with the indication terms. The indication should be as specific as possible, although such that the risk of overlooking relevant studies is minimised. The company should use both indexed terms (for example, Medical Subject Headings and Supplementary Concepts) and free text searches that contain alternative spellings and names. The company should document the applied search terms and their combinations for each database.
- An a priori definition of inclusion and exclusion criteria, as well as the reasons for these criteria.
- List of databases used for the searches (see minimum requirements regarding databases below).
- Description of the process for identifying and selecting studies, including whether one or several independent reviewers were involved, and how inconsistencies were handled. When screening references, the company should assess texts at title and abstract level first, and then based on a reading of the full text. Articles that are excluded after a full-text reading should be listed and their reason for exclusion briefly described. The company should document the entire selection process using a flow diagram as described in the PRISMA Statement (http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx).
- References identified via database searches should be screened by the company for consistency with the relevant question(s) (PICO for clinical questions) and the criteria for study types and types of publication.
- A justification for the selected time period for the searches (start date of the search). The literature search should have been completed within one year prior to

application. The dates of the literature search should be clearly stated. If the Secretariat assesses that the literature search is outdated, it can request that the company carry out an updated search.

- Discussion of the strengths and weaknesses of the literature search and the selection.

As a minimum, the company should perform a literature search on effect and safety using the following databases:

- MEDLINE (via PubMed or other platforms such as Ovid or Proquest).
- CENTRAL (via the Cochrane Library or Ovid) or EMBASE (via Ovid, Proquest or www.embase.com, etc.).

Furthermore, the company should draw up a list of ongoing studies and search for active or unpublished studies that include the intervention and comparator on the intended patient population in Clinicaltrials.gov and the EU Clinical Trials Register.

3.1.2 Use of unpublished effect and safety data

In general, documentation of clinical effect and safety should be derived from full-text articles published in scientific, peer-reviewed journals, European Public Assessment Reports (EPAR) prepared by the European Medicines Agency (EMA), reports by the Food and Drug Administration (FDA) or the HTA agencies.

In exceptional cases, the company can choose to include data from sources other than the above, including unpublished data if it is relevant, scientifically reasonable and it can significantly support the evidence base. For example, data with longer follow-up periods or data calculated differently than data in published materials. If the company uses unpublished data, the methods applied should always be clearly described, so it is possible for the Danish Medicines Council to assess the relevance and reliability of the data.

If the company expects its application to include unpublished data that is essential for the assessment, then the company should inform the Secretariat at the earliest opportunity.

Read a more detailed description (in Danish) in the Danish Medicines Council's paper of principles regarding the use of unpublished data [1].

3.1.3 European public assessment reports (EPAR)

The company should always consult EPAR in connection with a new pharmaceutical and its comparator(s). The company should describe and explain any significant discrepancies between EPAR and the submitted data. The Danish Medicines Council advises companies to submit their EPAR as soon as possible (even a preliminary or draft version).

3.2 Other sources of data for the health economic analysis

In addition to effect and safety data, the company should include certain additional data for the health economic analyses. This data includes utility values (*health state utility values, HSUV*) to estimate quality-adjusted life years (QALY), cost data and any additional information on assumptions in building the health economic model.

For most applications, it will be relevant to complete one or more literature searches for the data needed for the health economic analysis. However, it is rarely possible to identify all input through a literature search. It will often be necessary to use other sources as a supplement to traditional literature searches. This could include a review of reference lists, expert assessments, as well as non-literature-based methods to estimate costs. The company should explain its reasons if it chooses to base part of its health economic model on data that was not identified via a systematic search.

The company should describe the identification and selection process transparently so that it is clear how data was identified. This means that the company should always submit a detailed description of the documentation behind all data used in the model, including how information was obtained.

As with effect and safety data, the date(s) of the literature search should also be clearly stated. The Secretariat can request an updated search if the literature search is deemed outdated. As a rule, literature searches carried out more than a year prior to application will not be accepted.

See NICE DSU Technical Support Document 9 [2] and Papaioannou [3] for further information on literature-based utility values. See also section 7.1.2 on literature-based utility values for additional information.

3.2.1 Use of unpublished data in the health economic analysis

Clinical effect and safety estimates used by the company in the health economic analysis should always be based on literature identified through a systematic search as described in section 3.1.2. For other data used by the company in the health economic analysis, the Danish Medicines Council accepts unpublished sources if they help the health economic analysis to better reflect the context of the application than if only published data were used. For example in connection with cost estimates, extrapolation and mapping. If the company uses unpublished data, the methods applied should always be clearly described, so it is possible for the Danish Medicines Council to assess the relevance and reliability of the data.

4. Presentation of effect and safety studies

4.1 Presentation of effect studies

This section focuses on the presentation of studies used to document the effect and safety of an intervention and comparator. See sections 6-8 for other studies used in the health economic analysis.
The company should present all relevant information on the studies included in its application, including:

- Study design
- Intervention and comparator
- Follow-up period
- Number of randomised patients
- Inclusion and exclusion criteria for patients
- Outcomes of the study (primary, secondary and exploratory), including their definition, documentation of validity, and clinical relevance
- Baseline characteristics of patients included broken down by treatment groups
- Relevant sub-groups, and whether they were pre-defined in the study
- Other relevant information.

The company should discuss the internal and external validity of each study included. The company should present the most important variables that are prognostic factors and effect-modifiers that may impact the effect of treatments at an individual level. As far as possible, this should be through a literature review but it can also be based on statements by clinical experts, if literature on the disease area is limited.

A complete list of all primary, secondary and explorative outcomes examined in the study should be included in the application, regardless of whether or not the results of these have been published.

The company should present the results of the primary, secondary and explorative outcomes for each study that the company deems relevant. The definition of each outcome measure should be stated and the clinical relevance should be described and justified. For outcomes calculated as absolute risk reduction, the experimental and control event rates should be presented together with the effect estimate. All effect estimates should be accompanied by an estimate of the uncertainty when possible and a description of the analysis method applied. For composite outcomes, the event rates of individual events of all experimental and control groups should be presented when possible. The number of patients who withdrew from studies (*discontinuations*) and the reasons for withdrawals should be presented for each study group.

The company should describe all relevant effect and safety studies, regardless of whether or not they are used in the health economic analysis. The company should present which results have been used in the health economic analysis for all studies. In its application, the company may also include the results of outcomes not used in the health economic analysis. In such cases, the company should justify why the outcome was not used in the health economic analysis and how the outcome contributes relevant supplementary information. For all intermediary outcomes, including surrogate outcomes, the company should describe the documentation of the correlation between the direct outcome measure and intermediary (surrogate) outcome measures and substantiate this with references to sources.

4.2 Presentation of safety data

The application should include safety data from the same studies and reports used to document the effects of both the intervention and the comparator(s). In cases where there is data from a safety population that is significantly larger than the one included in the studies of clinical effect, then this data should be used instead. As a rule, the following safety data should be included in the application:

- Number of patients with at least one adverse event, irrespective of reason (adverse events [all cause/regardless of attribution])
- Number of patients with at least one serious adverse event, irrespective of the reason (serious adverse event[2]) For pharmaceuticals used in cancer treatment, the number of patients with at least one CTCAE grade 3-4 event should be calculated (CTCAE v.5.0 preferred).
- Number of patients with at least one adverse reaction.
- Number of patients who discontinue treatment irrespective of the reason
- Number of patients who discontinue treatment due to adverse events/effects.

All safety data should be defined.

In cases where one or more of the above calculations of safety data is/are not available for the intervention and/or comparator, the company should instead submit data that is as far as possible equivalent to the above.

4.3 Relatives

Relatives can play an extremely important role in the care pathway of patients and they can likewise be affected by the course of the illness. In the application, the company

2. A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

should describe and document whether the new treatment results in changes for relatives, for example the quality of life of relatives measured in studies.

The effects of the treatment on relatives should not be included in the health economic analysis. However, they will be considered in the overall decision and evidence base for the assessment. Any changes to the quality of life of relatives due to the new treatment should be described and documented in the same way as other outcomes not included in the health economic analysis.

Costs incurred by relatives in connection with patient treatment should be included in the health economic analysis as described in section 8.1.3.

5. Documenting effect differences between the intervention and comparator(s)

The Danish Medicines Council prefers that effect differences between the intervention and comparator have been assessed in one or several studies that directly compare the two (*head-to-head*) and where the follow-up period is sufficiently long to bring relevant effect differences to light. When it is necessary to use indirect comparisons, extrapolation or *real-world data* to estimate effect differences, the estimates should be applied with appropriate caution.

5.1 Direct comparisons and meta-analyses

If the intervention has been directly compared with one or more relevant comparators in one or more randomized trials, the company should base its application on these studies.

If there is more than one head-to-head study, the company should aggregate results via a meta-analysis, provided conditions for such an analysis have been met. The application should account for why the studies are sufficiently comparable to be included in a meta-analysis.

It may be relevant for the company to supplement the direct comparison with an indirect analysis, if the direct comparison does not correctly reflect the Danish population and context and it is possible to conduct an indirect analysis better reflects the Danish clinical context.

5.2 Indirect comparisons

If there is no data available from a direct comparison between the intervention and relevant comparators, the company should undertake indirect comparisons, where possible. This includes pairwise-adjusted indirect comparisons, network meta analyses (NMA) or other validated methods. In all cases, the company should use appropriate, transparent and validated statistical methods. The company should describe and discuss the assumptions and conditions on which the method applied is based. When using network meta analyses, the Danish Medicines Council recommends that the networks analysed be limited to the treatment alternatives (active, as well as any placebo, best supportive care or standards of care) necessary to clarify the comparison between the new pharmaceutical and the selected comparator(s).

5.3 Other statistical methods

In cases where there is no existing cohesive network of studies that connects the intervention and relevant comparator, the company should base its documentation of the relative effect on a comparison of effects from single-arm clinical studies or individual study arms. The company should use statistical methods that improve the possibility of comparing the relative effects rather than unadjusted indirect comparisons (naive comparisons), if it is possible to adjust for all relevant parameters. If the company has access to individual patient data for at least one of the studies, then it can also apply methods such as a matching-adjusted indirect comparison (MAIC) or simulated treatment comparison (STC). This requires that the relevant conditions for such analyses are met. The company should describe the methods applied, and discuss the strengths and weaknesses of the analyses.

5.4 Use of real-world data (RWD)

RWD means data from cohort studies, phase IV studies and register data. RWD is non-randomised studies and observation data from clinical practice. The preferred source of effect data is data from the randomised controlled studies.

If the company uses RWD to demonstrate the effect and safety of a historical control, the application should contain a more detailed discussion of source quality, study design including the definition of outcomes, inclusion and exclusion criteria, date of data collection, patient characteristics, and finally statistical methods, for example how the lack of data was handled and adjusted for. The company should present the similarities and differences between the study used as the basis for approval of the new pharmaceutical and the RWD used for the historical control. A discussion of how well the RWD represents the population should also be included.

5.5 Presentation of results of the comparative analysis

The company should describe, in detail, the statistical method applied to complete the comparative analysis (across studies), including any assumptions that do not implicitly

follow the selected method. If the company does not carry out a formal statistical analysis across studies, and instead carries out the comparison narratively, then the company should account for the differences between the studies that contraindicate a formal statistical analysis.

The company should discuss the internal and external validity of all effect estimates, including the impact of any prognostic factors and effect-modifiers.

5.6 Assessment of evidence quality

The quality of the effect and safety evidence for the new pharmaceutical and comparators will be assessed by the Danish Medicines Council in connection with preparation of the assessment report. The quality of evidence will be assessed in accordance with the five domains of GRADE (Grading of Recommendations Assessment, Development and Evaluation, https://gradeworkinggroup.org). These include:

- Risk of Bias
- Inconsistency
- Imprecision
- Indirectness
- Publication bias

The domains are used to ensure a systematic approach to the description and assessment of evidence quality in the Danish Medicines Council's assessment report. Elements of GRADE that do not deal with the evaluation of evidence quality are not used in the Danish Medicines Council's assessment of new pharmaceuticals and extensions of indication.

6. Health economic analysis

6.1 Standard analysis

The standard analysis describes the methodological specification of requirements for the health economic analysis. In general, health economic analyses should follow the standard analysis. The objective of the standard analysis is to ensure a consistent methodological approach.

There will be situations where it is necessary to deviate from the standard analysis. In sections 6-9, the methodological requirements are described in more detail, and there are examples of possible exemptions from the standard analysis.

Table 1: Standard analysis

Component of the health economic analysis	Standard analysis	Section
Type of analysis	Cost-utility analysis	6.2
Comparator	Treatment(s) that constitute current treatment options in Danish clinical practice.	2.4
Analysis perspective	A limited societal perspective.	6.7
Time horizon	The time horizon for the analyses should be long enough to include all significant differences in health benefits and costs between the alternatives.	6.8
Discounting	The current discounting rate from the Ministry of Finance should be used for both health effects and costs.	6.9
Measuring health effects	Health effects expressed as quality-adjusted life years (QALY). EQ-5D-5L is the preferred instrument for measuring life quality.	7.1
Method of valuing health effect	Danish-population-based preference weights.	7.2
Methods of addressing uncertainty	Probabilistic sensitivity analysis and relevant deterministic sensitivity analyses.	9

6.2 Type of analysis

The health economic analysis is a cost-utility analysis. The result of the analysis is expressed by an incremental cost-effectiveness ratio (ICER):

$$\text{ICER} = \frac{\Delta\text{Costs}}{\Delta\text{QALY}} = \frac{\text{Costs}_{\text{New pharmaceutical}} - \text{Costs}_{\text{Comparator}}}{\text{QALY}_{\text{New pharmaceutical}} - \text{QALY}_{\text{Comparator}}}$$

In cases where the company finds that the new pharmaceutical has an effect that is equal to the current comparator, the company can choose to carry out a cost-minimisation analysis rather than a cost-utility analysis.

6.2.1 Pharmaceuticals with sparse data

There may be circumstances in which there is not enough data to carry out a cost-utility analysis. For example in connection with some pharmaceuticals for rare diseases.

In cases where the company assesses that it is not possible to carry out a cost-utility analysis, the company should present the data available on effect, safety and costs. The company should explain why a cost-utility analysis is not possible based on the data submitted.

When an application does not include a cost-utility analysis, the data available on the effect, safety and costs of the new pharmaceutical will be assessed as specified in the relevant sections of the methods guide. The expert committees and the Secretariat will assess the data and the rationale for not carrying out a cost-utility analysis.

6.3 Comparator

Choice of comparator is described in section 2.4.

6.4 Health economic model

In the majority of applications, it is necessary to use a health economic model to conduct the health economic analysis. Health economic models allow for a synthesis of relevant evidence from several sources to estimate cost-effectiveness.

The company should prepare models in Excel. The model should be intuitive and easy to understand, which can be aided by a technical description of the model. The model may not be locked or have any hidden elements. All inputs in the model should be fully manipulable, and automatically update all the results, sensitivity analyses, etc.

The company may use international models if they are adapted to a Danish context in relation to clinical practice, patient characteristics, health effects, costs and discounting, etc. In such cases, the adaptation of the model to Danish conditions and the sources used should be documented. The company should remove all content that is irrelevant for the application to the Danish Medicines Council.

6.4.1 Model specifications

The company should always justify the choice of model and its structure. The model should reflect the course of the disease and Danish clinical practice, as well as possible.

It is not possible to draw up an exhaustive list of the characteristics of a high-quality model, as this will depend on the specific context of the pharmaceutical. Instead, the Danish Medicines Council refers to Briggs [4], Drummond [5], and Caro [6] for good practice within health economic modelling.

The application should include descriptions and justifications for all choices and assumptions on which the model is based, as well as for all methods used to select and estimate data input. The company should present all the parameters of the model in a straightforward manner, including sources. Effect estimates should always be based on a systematic literature review and analyses, as described in sections 3-5. When relevant, the company should describe and justify the cycle length and inform whether a half-cycle correction has been applied. The health economic analysis should report deterministic and probabilistic results. The company should therefore account for the rationale behind the probability distributions assigned to each model input parameter.

If only surrogate outcomes are available in the primary studies, then the company should clearly describe how these measurements were applied to estimate the endpoints in the model by referencing studies on the causal relationship between surrogate measurements and endpoints. The company should quantify and analyse the uncertainty of the relationships in the sensitivity analyses.

6.4.2 Extrapolation

It will often be necessary to extrapolate effects in order to achieve the relevant time horizon in the health economic analysis. When extrapolating effects beyond the study period, the company should describe and justify the assumptions made. This description should contain detailed information on the software used to carry out the extrapolation. When extrapolating clinical effects, the company should present graphs of observed data or Kaplan-Meier plots with the fitted extrapolation curves as well as any external data the company has used for validation. Standard methods, specifications of requirements, the guideline for extrapolation, and validation of the projection models are described (in Danish) in the Danish Medicines Council guide on the use of process data in health economic analyses [7]. Read NICE DSU Technical Support Document 14 [8] for additional information on validating and reporting results using modelling.

6.4.3 Model validity

The company should discuss the model's internal and external validity in its application. There should be consistency between the model and the clinical documentation. For example, external validity should be assessed by comparing the predicted values from the model with external data from epidemiological studies or clinical databases. The external validation should be thorough and should be presented in a straightforward

manner using both graphs and tables. Read NICE DSU Technical Support Document 14 [8] for additional information on validating and reporting results using modelling.

6.5 Adverse effects

The company should describe the management of adverse effects in clinical practice, including monitoring, follow-up, use of resources, costs and other relevant information. The company should justify any exclusion of relevant safety data in the health economic analysis, see section 4.1. If safety data is included in the analysis, the company should describe how it was modelled in relation to quality-of-life assessments, and monitoring and treatment costs.

6.6 Treatment sequences

In some cases, it may be relevant to model the effects and costs of other treatments that are part of a treatment sequence in order to better reflect Danish clinical practice. This means cases where the company assumes that patients in the two comparative groups receive different treatments after being treated with either the new pharmaceutical or the comparator. As far as possible, modelling of treatment sequences should be based on empirical data. In cases where the analyses of treatment sequences are significantly based on assumptions, the company should carry out sensitivity analyses of alternative assumptions.

6.7 Perspective

The company should use a limited societal perspective in the standard analysis. This means that the company should estimate the health effects for patients using QALYs and include all relevant treatment-related costs. This also applies to derived effects and costs resulting from adverse effects and administration of the pharmaceutical. All relevant hospital-related costs, costs covered by public health services, treatment-related costs incurred by the patient and municipal costs should be included. Relevant transport costs and time spent in connection with treatment for both patients and relatives (including informal-care) should also be included.

The company should describe the rationale for the included costs, and should provide references for all costs included. The Danish Medicines Council may also ask the company to include specific costs.

The company should always include effects on the expected lifetime of patients and health-related quality of life. Treatment-related costs and derivative costs resulting from adverse effects and administration are always relevant and should therefore always be included. Other costs listed above should be included when relevant.

The company should never include the following:

- VAT costs for public expenditure

- Production losses and gains (productivity costs)
- Transfer incomes (transfer payments)
- Future health costs and savings not related to the current disease situation.

6.8 Time horizon

The time horizon for the analysis should be long enough to catch all significant differences in effects and costs between the alternatives. This means that an extension of the time horizon would not affect the results to a significant degree.

6.9 Discounting

The company should convert QALY gains and costs to present values. The company should use an annual discount rate that corresponds to the current socio-economic discount rate from the Danish Ministry of Finance (available at www.fm.dk). The annual discount rates stated should be applied, and they may not be converted to another time unit, e.g. a monthly discount rate.

7. Measuring and weighting health effects

The company should summarise health effects using quality-adjusted life years (QALY) in the health economic analysis.

QALY combines gained life years and gained quality of life into a single index. In a health economic analysis, QALY is calculated by giving a health-state utility value to all health states observed during the time horizon of the analysis. The utility value reflects the health-related quality of life directly associated with the specific state. To calculate QALY, the utility value associated with a given health state is multiplied by the number of years lived in that health state.

The utility value for a specific health state is normally calculated in two steps; first a descriptive step and then a valuation step:

1. Patients describe their health-related state within the framework of a generic descriptive system. The EQ-5D-5L should be used as the generic instrument.
2. Each unique health state is given a value based on preference weights. Preference weights based on a representative cross section of the Danish adult population should be used.

The company should describe the health states and adverse effects relevant for the current patient population and treatments. The company should thoroughly describe and discuss how the utility value of each is calculated and incorporated in the analysis. The following elements should be included when relevant:

- Description of the number and percentage that have reported their quality of life during all follow-ups and for all patient groups. This should include a report and analysis of non-responses and differences among patient groups.
- Description of how missing data is managed. This should include a full description of the methods used.
- Description of the statistical models used in analyses of health-related quality of life. This should include a full description of the assumptions and co-variables used in the calculations.
- Description of how differences between treatment groups in baseline utility values have been accounted for.
- Reporting of sensitivity analyses that highlight relevant sources of bias. For example in connection with the choice of method to account for missing data.

7.1 Instrument for measuring health-related quality of life

The instrument used to calculate health-related quality of life is decisive for the results. It is possible to achieve different utility values for the same patient depending on which instrument is used. In order to ensure consistency in the calculation of QALYs across assessments, the company should, generally, use EQ-5D-5L in its health economic analysis.

EQ-5D-5L is a generic validated instrument used for many patient populations and in many countries. It is composed of five questions covering five dimensions of health-related quality of life: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

7.1.1 Mapping

In cases where EQ-5D-5L data is not available in the clinical studies, the company may estimate the health-related quality of life by using other generic preference-based instruments included in the studies. In such cases, the company should map data for EQ-5D-5L by using validated methods, in order for the Danish Medicines Council to maintain consistency in the calculation of QALY across applications.

In some cases, disease-specific instruments that can be mapped to predict EQ-5D-5L will be available. If this can be done by using validated methods, then the company can also use these instruments. If there are both generic and disease-specific instruments that the company can map to EQ-5D-5L, then the company should use the generic instrument. The company can then use the disease-specific instrument in a sensitivity analysis.

The application should include a description and justification of the method used to map quality of life data to EQ-5D-5L. Where possible, the company should compare the mapped utility values with any published quality of life data on the patient population in question. For a more detailed description of the methods, please refer to NICE DSU Technical Support Document 10 [10].

7.1.2 Literature-based utility values

In cases where EQ-5D-5L is not available in the clinical studies for all relevant stages of the disease, the company can identify and use EQ-5D-5L data from other scientific literature. The company should also do this in cases where study data is not of sufficient quality or based on a limited number of patients. In cases where it is possible and meaningful to calculate QALY based on both study data and data from other literature, the company should use both methods in the health economic analysis. This also applies to study data that the company can map to EQ-5D-5L.

The company should identify data systematically and transparently, and the approach should be documented as described in section 3. If more than one set of EQ-5D-5L data is available, the company should justify the selection of data and complete sensitivity analyses that show the results using the other EQ-5D-5L data available. Read the NICE DSU Technical Support Document 9 [2] for further information on literature-based utility values.

7.1.3 Exemptions from EQ-5D-5L

There may be situations where use of EQ-5D-5L is not appropriate. In such cases, the Danish Medicines Council can accept health-related quality of life calculations using other instruments. The company should justify such a deviation from the use of EQ-5D-5L based on empirical evidence that shows the issues with construct validity and responsiveness for EQ-5D-5L and the specific patient population. The company should ensure that evidence is based on a systematic synthesis of published literature. The company should always carry out sensitivity analyses using EQ-5D-5L data if it is available. Please refer to NICE DSU Technical Support Document 11 [11] for additional information on when the use of EQ-5D-5L is not appropriate.

There may also be situations where it is not possible to identify EQ-5D-5L data or other data that can be mapped to EQ-5D-5L. Other instruments may be used in these cases. Generic instruments are preferred to disease-specific instruments. The company should account for why it is not possible to use EQ-5D-5L. The company should also account for how the type of instrument used differs from EQ-5D-5L.

7.2 Preference weights

The company should use preference weights based on the general Danish population to calculate health-related quality of life [9].

There may be cases where it is not possible to use Danish preference weights. In these cases, the company may exceptionally use foreign preference weights. The company should account for why it is not possible to use Danish preference weights and how the foreign preference weights differ from the Danish. Preference weights based on the general population are preferred.

When the Danish preference weights [9] are not used, the company should describe the method used to derive the applied preference weights. Among other things, this should include a description of the study population and applied elicitation techniques and statistical methods.

7.3 Age adjustment of health-related quality of life

The increased morbidity and disabilities generally associated with increasing age means that the health-related quality of life of the general population decreases with age. For this reason, the company should make age adjustments for these changes in utility value for patients in analyses with health economic modelling. The company should present justification if they choose not to make age adjustments for the changes in utility value. If there are significant differences in age between the study population and the current Danish patient population, then the company should also adjust the observed utility values for age.

In general, the company should make age adjustments by using a multiplicative method. An example of this in another context is in NICE DSU Technical Support Document 12 [12].

When changes in utility values are calculated using a multiplicative method, the company multiplies the original utility value by an adjustment index to find the age-adjusted utility value. An adjustment index based on Danish standard values is available on the Danish Medicines Council website (in Danish) [14].

7.4 Adverse effects

The company should describe how the adverse effects of treatment with the new pharmaceutical and comparator, respectively, affect health-related quality of life. The effects can be estimated using EQ-5D-5L, for example. The company should include the description, regardless of whether or not the adverse effects are directly included in the health economic model. If the adverse effects are not directly included, the company should explain why they have been omitted. Costs associated with adverse effects should always be included in the health economic analysis, see section 6.7.

8. Costs

In order to identify and compare the costs, the company should identify, quantify and value direct and derived resource consumption for each pharmaceutical included in the analysis. As far as possible, the company should divide all costs into two elements and report them separately: consumed quantities and related unit costs. In the health economic analysis submitted, it should be possible to distinguish between regional costs, municipal costs and costs associated with transport and the time spent by patients and relatives.

As far as is possible, the company should use market prices as estimates for calculating unit prices and costs, as well as Danish unit costs. The company should justify any deviation from this. In the event that the company uses foreign costs, they should be adjusted using relevant purchasing power parities. See for example (https://www.oecd.org/sdd/prices-ppp/specificpurchasingpowerparitiesforhealth.html) Exchange rates should be based on the annual average for the relevant year, as calculated by Danmarks Nationalbank (Central Bank of Denmark) (https://nationalbanken.statistikbank.dk/statbank5a/default.asp?w=1843).

All costs that do not have a present value should be projected using the consumer price index without energy. The consumer price index is available on the Statistics Denmark website (www.statistikbanken.dk Table PRIS114). If foreign costs are used, they should be converted into DKK on the basis of the year of calculation before they are projected.

Resource consumption and the costs of treatment for the same patient group may vary significantly from country to country. Costs based on foreign data may have limited relevance for Danish conditions due to differences in clinical practice, differences in health service capacity and organisation, as well as differences in the subsidies/reimbursement systems. If international models are used, the company should replace the cost data with Danish data to adapt the analysis to Danish conditions. If foreign information on quantities is used, the company should separately argue the relevance of using this data and whether the estimate is representative of Danish practice. The company should always replace unit costs with Danish data.

The company should document all costs included with references, including expert sources if relevant. A detailed and thorough description of how costs are calculated should always be provided. The company should describe and justify any assumptions and methods used to calculate costs. In cases where there is uncertainty regarding cost estimates, as far as possible, the company should quantify the uncertainty.

8.1 Unit costs

The Danish Medicines Council maintains a catalogue for valuing unit costs and references to sources [13] that outlines how the company should estimate unit costs for the most common types of resource consumption in health economic analyses. To ensure comparability across applications, the company should use unit costs from the Danish

Medicines Council catalogue. The company should justify any derogations from using unit costs from the Danish Medicines Council catalogue.

8.1.1 Costs of pharmaceuticals

The company should always present prices of pharmaceuticals as pharmacy purchase price (Apotekernes indkøbspris, AIP) in Denmark. The company should justify the relevance and validity of the quantities and unit costs applied. Pharmaceutical waste and administration costs should always be considered. Sources for cost data can be studies, expert assessments or a combination. The source should always be clearly stated. If the source is subject to limited public access, the company should submit the source as an annex (the company is responsible for ensuring that it is entitled to share the material). If the company uses expert assessments, the company should supply the name and function of the experts used. The summary of the product characteristics (SPC) of the new pharmaceutical and comparator(s) should form the basis for estimating the costs of using them. The company should justify any derogation from this. Assumptions about future changes to pharmaceutical costs as a result of patent expiry or other expected competitive elements may not be included in the analysis.

8.1.2 Hospital costs

The company may use DRG tariffs for hospital costs as average estimates rather than dividing into sub-elements. The company should use the latest available DRG tariffs. The company should include all relevant and documented resource consumption in its analysis and justify inclusions and exclusions, including decisions regarding administration costs.

8.1.3 Transport costs and time spent by patients and relatives

The costs incurred by patients and their families as a consequence of the pharmaceutical treatment (transport costs and time spent) should be included, if relevant. References should be supplied. The company should value transport costs and time spent for patients and relatives using a rate equivalent to the average hourly rate of an employee in Denmark after tax. The rate is included in the Danish Medicines Council's catalogue of unit costs (in Danish).

8.1.4 General practitioners and practicing medical specialists

Valuing visits to general practitioners and practicing medical specialists should be with reference to the latest available collective agreement between the Danish Medical Association (PLO), *Regionernes Lønnings- og Takstnævn* (RLTN) for general practitioners, and *Foreningen af Speciallæger* (FAS) and RLTN for medical specialists. This is further described (in Danish) in the Danish Medicines Council’s catalogue of unit costs.

8.1.5 Municipal costs

Municipal costs include costs associated with at-home care, rehabilitation (general and specialist rehabilitation in accordance with the Danish Health Act and continued

rehabilitation in accordance with the Social Services Act) and disability equipment costs. Staff costs should be calculated on the basis of the average gross pay of the staff group as calculated by the municipal and regional salary data office (*Kommunernes og Regionernes Løndatakontor*). This is further described (in Danish) in the Danish Medicines Council's catalogue of unit costs.

9. Uncertainty in health economic analyses

All health economic analyses are subject to uncertainty. It is important for the decision-making process, that the most significant uncertainties are managed systematically so that it is clear how the uncertainties affect the cost-effectiveness. This is necessary in order for the Council to make the best possible informed decision.

The uncertainties in the analysis should therefore always be identified, described, analysed and discussed. There are a number of different sources of uncertainties in health economic analyses and different ways to analyse them.

9.1 Sources of uncertainty

There are a number of sources of uncertainty in health economic analyses. The following section briefly introduces them. See Briggs [4] and Drummond [5] for more detailed descriptions.

- Variability: Patients with the same characteristics may experience different effects of diseases or treatments due to random variation at individual level. This type of uncertainty cannot be reduced by collecting more data.

- Heterogeneity: Heterogeneity refers to cases where different effects of diseases and treatments can be explained in full or in part on the basis of observable variables. This type of uncertainty can be reduced by analysing relevant sub-groups.

- Parameter uncertainty: This refers to the accuracy of data estimation used in the health economic model. The uncertainty is due to basing estimated data for the entire patient population only on a limited section of the population. In principle, this type of uncertainty can therefore be reduced by collecting more data, as this would reduce the uncertainty in the estimate.

- Decision uncertainty: The decision uncertainty refers to the overall parameter uncertainty that is analysed in a probabilistic sensitivity analysis. This analysis indicates the probability that a decision to put a new pharmaceutical into use will

meet the expected cost-effectiveness.

- Model uncertainty or structural uncertainty: This relates to the uncertainty associated with assumptions and choices made when structuring the model. Models used in health economic analyses will never perfectly reflect the real world. Model uncertainty can be analysed by using sensitivity analyses to analyse different scenarios. Model uncertainty can also be analysed as part of overall decision uncertainty.

9.2 Managing uncertainty in the analysis

The company should identify, analyse and discuss the most important uncertainties in the results of the health economic analysis. This should be done by submitting sensitivity analyses. The Danish Medicines Council may also decide to carry out individual sensitivity analyses or request the company to do so.

It is not possible to give a general description or exhaustive list of how the company should address uncertainties in the health economic analysis, as this will depend on the disease, patient population, treatment and available data of each individual case.

9.2.1 Deterministic sensitivity analyses

The company should analyse all relevant parameters and assumptions using deterministic sensitivity analyses and present the results in a table and a tornado diagram. Generally, the company should always include time horizon, pharmaceutical prices, utility values, parametric functions of event data and effect parameters.

In the deterministic sensitivity analyses, the company should amend one or several parameters in order to analyse the sensitivity of the results to one or several estimates. The company should carry out this type of analysis using one-way, two-way or multi-way sensitivity analyses, where one, two or more of the parameters are analysed simultaneously.

The company may use scenario analyses to evaluate the impact of alternative values on a selected set of parameters in the model. The company can adjust the values and parameters so that they represent different plausible scenarios, for example a worst-case and best-case scenario.

The company should illustrate the impact of the price of the new pharmaceutical on the ICER in a table, and/or graph showing all ICERs estimated using different prices for the new pharmaceutical, from AIP (pharmacy purchase price) to a price where the ICER is negative.

9.2.2 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) analyses the total parameter uncertainty by defining all or selected variables as stochastic variables with probability distributions. See Briggs [4] for a more in-depth method description for PSA.

The company should account for the selection of variables included and excluded from the PSA, as well as the associated probability distributions. In cases where a parameter has not been estimated empirically, the company should account for how the uncertainty of the estimate is determined.

The company can also analyse uncertainties in model assumptions using a PSA by allocating alternative assumptions to the probability distributions. In cases where this can be done meaningfully, the company should carry out such an analysis.

The company should present the results of a PSA as a scatter plot of the simulated results and as a cost-effectiveness acceptability curve (CEAC).

10. Budget impact analysis

In addition to the health economic analysis, the company should prepare a budget impact analysis that estimates the impact on regional hospital budgets. The analysis describes how budgets will be affected over a five-year period after a new pharmaceutical is recommended. In the budget impact analysis, the company should present the expected number of patients and expected market share both given a recommendation and given a non-recommendation of the pharmaceutical. Relevant sources should be used to substantiate this.
The company should present the budget impact as the annual cost for the first five years for a scenario where the pharmaceutical is recommended as a standard treatment, and a scenario where the pharmaceutical is not recommended as a standard treatment. Budget impacts should be reported for each of the five years separately. The analysis should use estimates for market take-up, prevalence and incidence. The analysis should assume that patients commence treatment at the start of each year.

The company should estimate budget impacts based on the following factors:

- The total additional costs for regions in connection with use of the new pharmaceutical as a standard treatment for the indication. This includes both costs of pharmaceuticals and other treatment-related costs for the regional sector.
- The cost of the new pharmaceutical, calculated at AIP (pharmacy purchase price) level.
- Costs estimated without discounting.

- The expected market share of the new pharmaceutical during each of the first five years after possible recommendation as a standard treatment. The costs should not be estimated as accumulated for the first five years.
- Costs of existing pharmaceuticals financed by the regions which will be replaced by the new pharmaceutical, if the Danish Medicines Council recommends the pharmaceutical as a possible standard treatment.
- Expected future costs for the new pharmaceutical within the indication, if the Danish Medicines Council does not recommend the pharmaceutical as a possible standard treatment.

The company should calculate the estimate of budget impacts for the regions as the difference between the following two scenarios:

1. The Danish Medicines Council recommends the new pharmaceutical as a possible standard treatment for the indication being applied for.

2. The Danish Medicines Council does not recommend the new pharmaceutical as a possible standard treatment for the indication being applied for.

Additionally, the following estimates may be relevant:

1. If sub-group analyses have been completed, the company should account for budget impact if the new pharmaceutical is recommended as a possible standard treatment by the Danish Medicines Council for the overall population and the individual sub-groups.

2. If sensitivity analyses have been carried out in which the central assumptions and data have been changed, the company should submit these if:
    - The estimates are sensitive to changes in the assumptions.
    - Important assumptions in the estimates are uncertain.

11. Entry into force of the methods guide

This methods guide and the Danish Medicines Council's process guide for assessing new pharmaceuticals replaces the previous *Process and methods guide – how the Danish Medicines Council develops joint regional assessments of the added clinical value of new pharmaceuticals and new indications*. This guide is applicable for all applications to the Danish Medicines Council in which a request for assessment is submitted to the Danish Medicines Council from 1 January 2021. Cases for which a provisional application in line with the Danish Medicines Council's previous process was submitted before 1 January 2021 will generally be finalised according to the process and methods described in the

12. Changes to the methods guide

The Danish Medicines Council will publish changes to the methods described in this guide on the Danish Medicines Council website and update the guide (see version log). The Secretariat will inform companies about any changes in connection with an application process.

13. Version log

Version log		
Version	**Date**	**Change**
1.3	8 March 2023	The links have been removed from the list of references.
1.2	17 February 2021	Amendment of section 3.1.2: Criteria paper regarding the use of unpublished data has been replaced by the Danish Medicines Agency's principles for the use of unpublished data.
1.1	3 February 2021	Reference for Danish EQ-5D-5L preference scales was added and text on temporary use of Danish EQ-5D-3L scales was removed.
1.0	19 November 2020	Danish version approved by the board of Danish Regions

14. List of references

[1] Danish Medicines Council. Paper of principles regarding unpublished data. 22 February 2020

[2] NICE, National Institute of Health and Care Excellence. NICE DSU (Decision Support Unit) Technical Support Document 9: The identification, review and synthesis of health state utility values from the literature. 2010.

[3] Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013; 16(4):686-95.

[4] Briggs A, Sculpher M, Claxton K. Decision Modelling for Health Economic Evaluation. Oxford University Press, 2006.

[5] Drummond M, Schulper M, Claxton K, Stoddart G, Torrance G. Methods for the Economic Evaluation of Health Care Programmes 4th Edition. Oxford University Press, 2015.

[6] Caro JJ, Briggs AH, Siebert U, Kuntz KM; ISPOR-SMDM Modeling Good Research Practices Task Force. Modeling good research practices--overview: a report of the ISPOR-SMDM Modeling Good Research Practices. Value In Health. 2012. 15(6).

[7] Danish Medicines Council. Anvendelse af forløbsdata i sundhedsøkonomiske analyse.

[8] NICE, National Institute for Health and Care Excellence. DSU (Decision Support Unit) Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level data. 2013.

[9] Jensen CE, Sørensen SS, Gudex C, Jensen MB, Pedersen KJ, Ehlers LH. The Danish EQ5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. Applied Health Economics and Health Policy 2021.

[10] NICE, National Institute for Health and Care Excellence. NICE DSU (Decision Support Unit) Technical Support Document 10: The use of mapping methods to estimate health state utility values. 2011.

[11] NICE, National Institute for Health and Care Excellence. NICE DSU (Decision Support Unit) Technical Support Document 11: Alternatives to EQ-5D for generating health state utility values. 2011.

[12] NICE, National Institute for Health and Care Excellence. NICE DSU (Decision Support Unit) Technical Support Document 12: The use of health state utility values in decision models. 2011.

[13] Danish Medicines Council. Værdisætning af enhedsomkostninger og kildehenvisninger.

[14] Medicinrådet. Appendiks: Aldersjustering for sundhedsrelateret livskvalitet