The Danish Health Technology Council's methods guide for the evaluation of health technology

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Behandlingsrådet

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1 Abbreviations

CUA	Cost-utility analysis
CCA	Cost-consequence analysis
CEA	Cost-effectiveness analysis
EQ-5D	EuroQol 5-Dimension Quality of Life measurement tool
EUnetHTA	European Network for Health Technology Assessment
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	Health technology assessment (evaluation of health technology)
ITT	Intention-to-treat
PP	Per-protocol
MAIC	Matched-adjusted indirect comparison
NICE	National Institute for Health and Care Excellence
PICO	Patient, Intervention, Comparator, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcomes
QALY	Quality-adjusted life years
RCT	Randomized controlled trial
SMD	Standardized mean difference
STC	Simulated treatment comparison

2 About the methods guide

This methods guide describes the methodological basis for applications for evaluation by the Danish Health Technology Council of new and existing health technology.

The objective of the methods guide is to guide companies, regions, and hospital management in preparing an application for submission to the Danish Health Technology Council. The objective of the methods guide is also to serve as a working tool for the Council, the expert committees, and the secretariat, as well as providing other stakeholders with insight into the methodological considerations behind the Danish Health Technology Council's work. These guidelines apply to the preparation of evaluations of single technologies and product categories. In order to reflect the Danish Health Technology Council's broad remit, the guidelines include methods for preparing evaluations of varying complexity. When preparing a specific application, it will therefore only be relevant for the applicant to apply some of these methods. See the Danish Health Technology Council's process guide for a more detailed description of how evaluation proposals are selected for evaluation as either a single technology, as part of a product category, or for inclusion in a more comprehensive analysis.

The methods guide should be seen in relation to the Danish Health Technology Council's process guide and the various templates to be used in the actual process through the Danish Health Technology Council. For information about practical aspects of the process, including information about the initial contact with the Danish Health Technology Council, dialogue meetings, contact about evaluation proposals and generic timelines for the application process, see the Danish Health Technology Council's process guide.

Several technical annexes have been prepared in conjunction with this methods guide. These annexes include more detailed descriptions of how to prepare the elements of the application, including cost statements. References are made to the technical annexes throughout the methods guide. The application itself should be prepared using the Danish Health Technology Council's application template.

The Danish Health Technology Council secretariat has prepared the methods guide based on Danish Regions' methodological framework. The methods guide will be reviewed regularly to reflect experiences gained from evaluations performed by the Danish Health Technology Council.

The methods guide is inspired by the Danish Medicines Council's methods guides for the assessment of new medicines and their treatment guides [1,2]; the Danish Health Authority's handbook for preparing national clinical guidelines [3] and by relevant methods guides from a number of foreign institutions performing health technology assessments, including the Norwegian Institute of Public Health's Guidelines for the submission of documentation for single technology assessments [4].

3 Introduction

The Danish Health Technology Council provides recommendations on the use of health technology, including medical devices,[1] but also other types of devices, such as diagnostic devices, as well as treatments, rehabilitation, prevention and types of organisation and collaboration in the provision of healthcare services. From now on, 'health technology' is used as an umbrella term for all of these types of technology etc. However, when compared with one or more alternative health technologies, the health technology examined will be referred to as 'the intervention'. The Danish Health Technology Council does not make recommendations concerning medicines and other products, the primary effect of which is exerted through a pharmacological, immunological, or metabolic action.

Due to the broad remit of the Danish Health Technology Council, it is not possible to draw up a completely standardized methodology for a true and fair evaluation of all types of health technology. However, all applications should cover four aspects in relation to the health technology examined. The four aspects are illustrated in Figure 1:

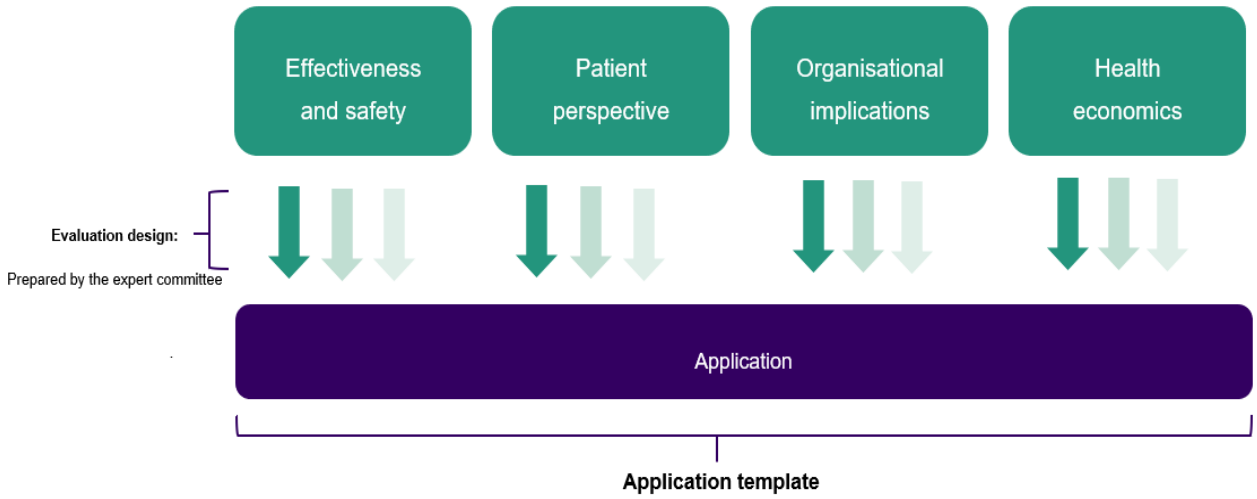

Figure 1 - Visualization of the four aspects to be included in applications to the Danish Health Technology Council. The different degree of shading of the arrows is to illustrate that weighting of these aspects may vary from case to case. The expert committee will prepare the evaluation design to be adhered to in the application. The evaluation design will specify what aspects which the expert committee have deemed essential for the assessment of the specific technology and what evidence should be presented. The application should be prepared using the application template from the Danish Health Technology Council.

The degree to which the four aspects are relevant to the evaluation of a specific health technology may vary. How much weight should be given to the individual aspects, including whether all aspects are necessary for

[1] In this context, the term 'medical devices' denotes apparatus, software and *in vitro* diagnostic devices/materials used in diagnosis, prevention, monitoring, treatment or alleviation of diseases or injuries, for example, or used as assistive devices for injuries or disabilities. For a full definition, see Part 1 of the Medical Devices Executive Order (*Bekendtgørelse om medicinsk udstyr* no. 1263 of 15/12/2008). Note that a new Executive Order entered into force on 26 May 2021 ((EU) 2017/745).

the evaluation, is determined by the evaluation design that the expert committee draws up for the specific application (see section 5).

Some health technologies are not likely to affect all four aspects. This may be the case if the health technology examined can replace another technology without affecting the organisational context, for example the work processes that involve use of the health technology, or without causing associated consequences elsewhere along the care pathway. In these cases, the evaluation proposal (see section 4) should describe how the health technology is used in the organisation and should state that there is no expected impact on the organisational structure or further along the care pathway (see section 5.4). In these cases, the expert committee will assess the reasonableness of this assumption when preparing the evaluation design.

The evaluation design and the application will always be based on the core outcome and on the context characterizing the health technology examined. The fundamental purpose of the application is to provide the Danish Health Technology Council with the information necessary to make a recommendation regarding use of the health technology examined. Thus, the expert committee's evaluation design will reflect what is required for the Council to make an informed recommendation. Similarly, the complexity of the analyses and descriptions required by the evaluation design will reflect the specific evaluation situation and the health technology examined. Applicants will not be asked to provide a higher degree of complexity in analyses and descriptions than what the Danish Health Technology Council finds necessary to support its recommendations.

Because the expert committee's evaluation design, and thus the application, will be prepared to reflect the specific health technology under examination, not all parts of the methods guide will be relevant when preparing the application. The applicant will identify the methods relevant for the individual evaluation in collaboration with the expert committee and the Danish Health Technology Council secretariat. The methods guide therefore contains instructions on how, in their applications, applicants can address and report on the four aspects mentioned above. However, the guidelines do not contain a detailed description of how applicants should address all elements of the application or to what degree of detail, as this is largely determined by the core outcome and the specific context of the health technology examined. For the same reason, it is not possible to give a clear indication of how much time and how many resources the applicant should expect to devote to the application process.

Applicants should base their applications on one or more focused clinical questions and the underlying PICO questions (*population*, *intervention*, *comparator*, *outcome(s)*; see section 5.1 for a more detailed description) determined by the expert committee in the evaluation design. The PICO questions define the scope of the evaluation, including to which population(s), intervention, and comparator(s) the Danish Health Technology Council's recommendation will apply. Applicants should base their examination of the patient perspective, the implementation and organisational considerations and the economic implications on the population, intervention and comparator defined by the expert committee. It is not possible to describe a generally applicable minimum level for what evidence base the different expert committees will require, as this will vary from evaluation to evaluation.

In its assessment of clinical evidence for a given health technology, the Danish Health Technology Council will use the GRADE method[2] [5] This is to ensure a standardized approach to the evaluation of technologies examined under the auspices of the Danish Health Technology Council. Due to the general nature of the Danish Health Technology Council's remit, the quality of the evidence will typically be categorized as 'low' or 'very low', see the GRADE approach [5], particularly for newer technologies. This is because, for certain types of health technology, it is not plausible and/or possible to conduct double-blind randomized controlled studies, which are otherwise considered to be at the top of the hierarchy of evidence. The Danish Health Technology Council will also accept evidence from other trial designs, such as observational studies, in the

[2] Grading of Recommendations Assessment, Development and Evaluation

analysis of Clinical effectiveness[3] and safety. The expert committee will supplement the evaluation of evidence quality, see GRADE, with an assessment of whether the evidence base is adequate in terms of the risk associated with use of the technology.

Figure 2 below illustrates the Danish Health Technology Council's process for evaluation of health technologies.

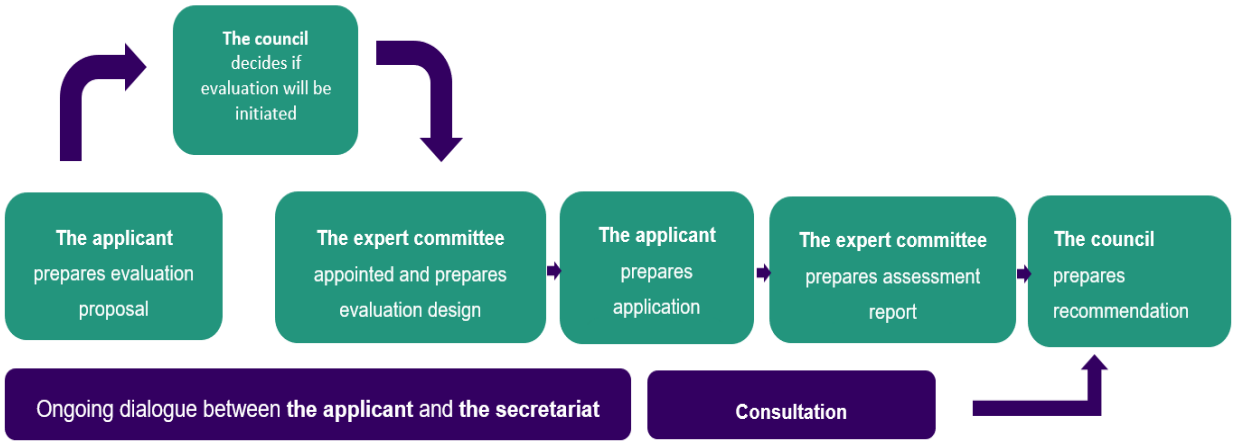

Figure 2 – The Danish Health Technology Council's process for evaluation of health technology

[3] The rules concerning medical devices and *in vitro* diagnostic medical devices include general requirements for safety and performance. Performance is the ability of the device to fulfil the declared purpose indicated by the manufacturer. From now on, the term 'clinical effectiveness' also covers performance, where relevant.

4 Evaluation proposal

Applicants should prepare an evaluation proposal as an official indication that they would like the Danish Health Technology Council to evaluate a certain health technology. Applicants can engage in dialogue with the Danish Health Technology Council secretariat for guidance before submitting their proposal. Applicants should use the Danish Health Technology Council's template for evaluation proposals.

The purpose of the evaluation proposal is to present the health technology and its area of application, including the indication and patient population at which the technology is aimed. In addition to an overview of the relevant health technology, the applicant should state the expected consequences of the technology for the following aspects:

- Clinical effectiveness and safety
- Patient perspective
- Organisational implications
- Health economics

When stating these aspects, the applicant may present a proposal for a relevant PICO (see section 5.1) on which the expert committee may base its specification of PICO in the evaluation design.

The applicant should describe any existing organisational experiences regarding the health technology, for example task shifting or the risk of function creep between sectors, as well as factors that may impact patient safety, such as the likelihood of confusion, wrong use, lack of maintenance, etc.

The applicant should include an overview of the health economic data available regarding the technology. This overview should include considerations on how the pressure on activities and resources will change in connection with use and phase-out of the health technology.

The Danish Health Technology Council secretariat will make an outline of costs available to applicants. The outline of costs can be used to provide an overview of the expected economic implications. When filling in the outline of costs, applicants should, as far as possible, consult the technical annex on cost statements for guidance on how to value unit costs etc. The outline of costs can be completed in dialogue with the secretariat.

For more information about the process regarding preparation of the evaluation proposal, see the Danish Health Technology Council's process guide which can be found at www.behandlingsraadet.dk.

5 Evaluation design

The evaluation design represents the expert committee's framework for how a specific health technology is to be evaluated. The evaluation design will be prepared by the expert committee assisted by the secretariat. The design will be published on the Danish Health Technology Council website after it has been approved by the Danish Health Technology Council. Preparation of the evaluation design will be based on the proposal submitted, including the applicant's proposal for PICO and any supplementary material from the applicant. However, the secretariat may seek further information, including expert assessments, where this is deemed necessary.

The evaluation design serves as a protocol for how applicants should prepare their application, including for example which comparator to use and how to perform the health economic analysis. The evaluation design is also an *a priori* specification of how the expert committee itself will prepare its evaluation when it has received the application. Moreover, the PICO section of the evaluation design will state whether the evaluation should be for a specific product/a single technology or for a specific product category. To make an evaluation of a product category, there must be a number of equivalent competitive technologies, and in these cases the PICO section will state which comparisons should be performed. In case of product categories, the methodological approach will generally be the same as for single technologies, although, for product categories, it may be relevant to make comparisons at class level.

The analysis of clinical effectiveness and safety, including the expert committee's assessment of evidence quality for the specific technology, should be based on the GRADE approach, to the extent relevant and possible. Because of the Danish Health Technology Council's broad remit, and because the evidence base for new health technology is often limited,[4] the expert committee will always carry out a qualitative assessment of the clinical evidence in addition to the GRADE assessment. This will be supplemented by an assessment of proportionality between the available evidence and the risk associated with the technology.

Table 1 describes the elements normally contained within the evaluation design.

Table 1 - The evaluation design normally consists of the following elements.

Parts of the evaluation design	Afsnit
PICO One or more evaluation questions and the associated specification of the population, intervention, comparator, and outcome (PICO), aiming to highlight the clinical effects of the technology	5.1
Effectiveness and safety Specification of how Clinical effectiveness and safety are further framed.	5.2
Patient perspective	5.3

[4] The evidence quality for many single technology assessments is expected to be ranked as 'very low', see GRADE. The Danish Health Technology Council is therefore also operating with an assessment of the appropriateness of the study design in relation to the properties of the health technology examined.

Specification of how the Patient perspective should be explored, including special considerations regarding accessibility and inequality for specific patient groups.	
Organisational implications Specifications for the report on Organisational implications of implementing/phasing-out the technology, including factors that are considered to potentially impact patient safety.	5.4
Health Economics Specifications for the design of the Health economic analysis.	5.5
Literature search Specification of how search strategy(ies) are outlined in the evaluation design, as well as the general approach for this.	5.6

5.1 PICO

In its assessment of the value of a health technology, the Danish Health Technology Council places crucial emphasis on the health technology being safe and effective. Sufficient evidence is needed to determine whether this is the case. When evaluating the clinical effectiveness and safety of a technology, the expert committee will define one or more evaluation questions to be answered in the application. This is to set the framework for how the technology is to be evaluated.

Definitions of the patient or target population (*population*), the technology in question (*intervention*), the technology to which comparison is made (*comparator*) and the relevant outcome and safety measures (*outcomes*) will be linked to each question. These parameters are abbreviated as PICO. For diagnostic technologies, the acronym PIROT is used instead of PICO. I in PIROT stands for the *index test* to be examined, and R refers to the *reference test* (*gold standard test*) to which comparison is made. T refers to the *target disease*, which is the disease(s) that index test diagnoses. For further information on how diagnostic test are evaluated in the Danish Health Technology Council, see the technical annex at www.behandlingsraadet.dk.

Population, intervention, and comparator also frame the evaluation of the Patient perspective, the Organisational implications and the Health economic analysis.

Population: Definition of the relevant population in accordance with the technology's area of application. If the technology represents a treatment or a step in a treatment, this will generally concern one or more patient populations. For other types of technology, for example diagnostic technology, the relevant population is not necessarily patients. Nonetheless, in both cases, there may be special clinical characteristics linked to the population. As far as medical devices are concerned, *intended use/purpose* is in principle decisive for the definition of the population. However, in its definition, the expert committee should consider the characteristics applicable to the potential Danish patient/target population, regardless of the evidence base.

Furthermore, it might also be relevant to specify the setting in which the alternatives are to be examined, which for instance could be in an outpatient clinic, ambulance, or other. For some evaluations, the setting is important to define and include in relation to the evaluation question and possibly with regards to the screening of literature.

Intervention: Description of the health technology assessed as well as how and where it is being used. The specific use evaluated is indicated, including duration, intensity, etc.

Comparator: Description of the health technology to which comparison is made. In principle, the comparator will be the best implemented alternative[5] technology and/or *standard of care* in the specific context. In cases in which there is no actual alternative, the comparator will for example be *no active treatment* or, as proxy for this, *placebo* and/or *sham.*[6]

Outcomes: Definition of the outcome and safety parameters[7] that the expert committee considers to be most appropriate for assessing the health technology. The outcomes are weighted on the basis of how important the expert committee considers them to be. Moreover, the specific measuring/calculation methods that the expert committee considers appropriate are given for each outcome measure and, if relevant, desirable follow-up period(s) for measuring outcomes. In principle, the longest possible follow-up period should be used, unless otherwise specified. If the expert committee finds that several measuring methods or follow-up periods are acceptable, these should be stated in order of priority.
In addition to outcomes demonstrating the clinical effectiveness/performance of the technology, safety in the form of adverse events and health-related quality of life should generally be investigated as two or more independent outcomes, but the specific measuring methods and tools will vary from case to case. Safety is typically described as the percentage of patients with one or more adverse events or adverse reactions. The use of generic instruments is preferred for measuring health-related quality of life, such as the EuroQoL – 5 Dimensions – 5 Levels (EQ-5D-5L) questionnaire (see section 6.4.3.1).

Surrogate outcomes should only be used when it is not plausible that useful data exists for the relevant outcome. If surrogate outcomes are used, the expert committee must argue that there is a valid connection between the surrogate outcome and the outcome(s) being replaced.

5.2 Effectiveness and safety

The expert committee defines one or more evaluation questions based on the defined PICO. The purpose of the evaluation questions is to establish the framework for how the alternatives are assessed in relation to the effectiveness and safety. The evaluation questions can include several critical and important outcomes, which form the basis for the assessment.

5.2.1 Weighting of outcomes

In accordance with the GRADE approach, the expert committee will classify outcomes based on how important they are considered to be for the evaluation of the specific health technology(ies). This results in a categorization of outcomes as either:

- critical for the evaluation
- important for the evaluation or
- less important for the evaluation

Critical and important outcomes are stated and defined, see section 5.1, and these will form the basis for the evaluation of clinical effectiveness and safety and to be included as effect estimates in the health economic evaluation. Less important outcomes are only included in the outcome table of the

[5] In Danish clinical practice.
[6] Treatment alternative pretending to be the intervention examined, although without an actual treatment effect, for example used as comparator in a randomized controlled study.
[7] In the analysis of clinical effectiveness and safety, 'safety' refers to the risk of adverse reactions, harms and/or adverse events that the patient may experience in connection with correct use of a treatment with a given health technology. For example, this could be nausea in connection with treatment with virtual reality equipment or perforations in connection with endoscopic procedures. It does not refer to indirect risks or safety specifications for the actual product.

evaluation design for transparency purposes, and the application should only include results for the critical and important outcomes.

5.2.2 Minimally clinical important difference

The minimally clinical important differences (MCID) are an expression of the absolute difference in effect that is considered to have clinical significance for the patient and which in clinical practice is crucial for whether one technology would be preferred over another. For frequently used continuous outcomes, such as health-related quality of life measured with the EQ-5D-5L questionnaire, validated threshold values are often found in the published literature. However, for many other outcomes, the determination of the MCID will depend on the expert committee's assessment.
When possible, the expert committee can specify in the evaluation design the MCID for the selected outcomes. However, there may be situations, for example, where it's assessed that the interdependence of MCID necessitates that they are first determined during the overall assessment of the results for the alternatives' effectiveness and safety (section 6).
MCID is used for interpreting the results and for assessing the quality of evidence, according to the imprecision domain in the GRADE assessment, see section 7. In addition to MCID, the evaluation design states the unit of measurement to which the MCID relates. For dichotomous outcomes, differences in effect are always determined not only on the absolute scale on which the MCID is defined but also on the relative scale, see section 6.4.

5.2.3 Evidence base

The comparison of Effectiveness and safety should, if possible, be based on literature from the systematic literature search. The analysis of Effectiveness and safety should be based on the evidence that most accurately reflects the alternatives' effectiveness and safety compared to the comparator.
If possible, the analysis of Effectiveness and safety should be based on randomized controlled trials (RCTs). However, there might be cases where such studies are not available, or it might be relevant to include data from, for instance, observational studies (see section 6.3.1). It's worth noting that for certain types of alternatives, it may not be plausible, possible, or ethically defensible to conduct randomized controlled trials.

5.2.4 Diagnostic technologies

Special circumstances apply for diagnostic technologies, depending on the intended use (replacement, add-on, etc.). New diagnostic technologies are often only examined to establish diagnostic accuracy (sensitivity and specificity). In principle, the expert committee should always consider involving patient-relevant outcomes – also when no *end-to-end* studies are available. If the expert committee conducts an assessment of diagnostic technology where no data is available on patient-relevant outcomes, the clinical implications of this should be considered and described in the assessment report.

The Danish Health Technology Council's methodological approach to diagnostic tests is further elaborated in the technical annex for the analysis of diagnostic interventions, which is available on The Danish Health Technology Council's website. Furthermore, references are made to the GRADE handbook [5] and the Danish Health Authority's Handbook for the preparation of national clinical guidelines [6].

5.3 Patient perspective

The concept of ‘patient’ denotes a user of a health technology: a patient, a former patient or a relative. Healthcare professionals/healthcare staff as users are therefore not part of the patient concept. Their interaction with the health technology is expected to be identified in the description of the Organisational implications of the health technology, see section 5.4 and the application template. The

effectiveness of health technologies will often depend on an interaction between the user and the technology, and the patient perspective is therefore relevant to examine.

The Patient perspective may be included to a varying extent in the evaluations. If, for example, the evaluation concerns a new monitoring device used in conjunction with surgery under general anaesthesia, and the device does not otherwise affect the patient's care pathway, then the patient perspective is only likely to be included to a minor extent. However, if the evaluation concerns a changed contact pattern in connection with rehabilitation, the patient perspective is likely to be decisive for the evaluation.

It is not relevant to include general considerations concerning the disease area, disease burden, etc., unless these are directly linked to the properties of the technology examined. Furthermore, the 'maturity' of the technology will also be important for how the patient perspective should be examined. Therefore, in the evaluation of a more 'mature' technology, the patient perspective could be described through peer-reviewed literature, whereas it may be relevant to search for other sources if the technology is relatively new.

5.3.1 Selection of topics

It is the role of the expert committee to define and specify how the Patient perspective should be covered in the evaluation. The patient representatives in the expert committee play a vital role in developing and selecting relevant topics to investigate. Patient representatives are, among other reasons, appointed as members of the expert committee because they can provide specific experiences, insights, and knowledge about the alternatives, and how patients are affected in their daily lives. The patient representatives provide specific experiences, insights, and knowledge about the Patient perspective in relation to the health technology being evaluated. This includes their own experiences and the experiences of fellow patients, e.g., concerning satisfaction with and the general experience of a specific health technology.

What the Patient perspective specifically should include depends on the individual health technology but might cover elements such as:

- expectations and experiences with the technology being examined
- satisfaction with the technology under investigation
- treatment adherence (compliance/adherence)
- social factors, including family and work life
- communicative factors, e.g., the impact on the relationship between patient and relatives
- ethical considerations, e.g., concerning patient autonomy
- economic factors that, for instance, influence attitude towards/experience with the alternatives
- perceived ability of self-care

5.3.2 Evidence base

The evidence base can rely on both qualitative and quantitative data. When investigating the Patient perspective, it's essential to look into the published literature, including, for example, scientific studies as well as national reports in the form of clinical guidelines or grey literature.
It is preferred that the evidence presented concerning the Patient perspective originates from patients who have specific experiences with the health technology or comparator(s). If there aren't any - and it's not possible to obtain - specific patient experiences with the health technology and comparator, the investigation of the Patient perspective can be supplemented with knowledge about patients' preferences, attitudes, and expectations towards the health technology, even if this information isn't experience-based.

Initially, it's not expected that data collection will be carried out in connection with the preparation of applications to the Danish Health Technology Council. In other words, it is generally expected that the Patient perspective will be investigated by published literature.

For further information regarding the Patient perspective, including factors that may be relevant to investigate and the provision of data, see section 6.5.

5.4 Organisational implications

For the Danish Health Technology Council to make an informed recommendation about the health technology examined, it is important to describe the organisation in which the technology is expected to be used/phased out. Similarly, it is important to gain insight into how the technology is expected to be implemented or phased out, where this is relevant, and the organisational conditions necessary for a successful implementation/phase out. Among other things, the purpose of this is to provide the Danish Health Technology Council with insight into whether organisational changes are necessary in Danish treatment practice to support the use or phase out of the health technology examined. The term ‘organisational implications’ refers to both organisational and implementation/phase out implications.

See section 6.6 and the application template for a more detailed description and identification of organisational implications.

5.4.1 Selection of topics

It is the role of the expert committee in the work with the evaluation design to define and specify how Organisational implications should be investigated in the evaluation. The clinical representatives of the expert committee play a crucial role in drafting and selecting topics. These clinical representatives are appointed as members of the expert committee primarily because they can provide specific knowledge and experience with the use of the alternatives in clinical practice.

Topics within Organisational implications might include:

- Attitudes and experiences of healthcare professionals and possibly other professional groups with the use of health technology in clinical practice.
- How the use of the health technology influences the clinical practice of staff, focusing on areas the technology is presumed to change/improve, e.g., labor-saving focus, working environment focus, increased accessibility to technology, etc.
- Changes in workflows with the application of the health technology.
- For instance, task shifts between departments, across sector boundaries, or from the health service to the patient's home.
- Modifications in the organisation of patient pathways, including areas like diagnostics, treatment, rehabilitation, etc.
- Changes in resource allocations concerning staff when using the intervention.
- Consequences and changes related to implementation or phasing out.
- This might include the need for skill development of relevant staff in relation to the use of the health technology by different professional groups.
- Compatibility adjustments regarding existing equipment or aids, IT systems, etc.
- Describing if there are special considerations when scaling up to broader national use.

The extent of Organisational implications in a specific evaluation will always depend on the evaluation questions and the defined PICO composition. The scope of Organisational implications is based on the expert committee's specific assessment. Therefore, the committee will specify, in the evaluation

design, the degree to which Organisational implications should be elaborated and identify and select the relevant topics to frame the illumination of this perspective

5.4.2 Evidence base

The evidence base can rely on both qualitative and quantitative data. When investigating the Organisational implications, it's essential to look into the published literature, including, for example, scientific studies as well as national reports in the form of clinical guidelines, governmental material, process descriptions, and other grey literature.

The evidence presented concerning Organisational implications should be based on specific experiences with the use and possibly the implementation of a given intervention. The practical experiential basis should, where possible, be rooted in Danish practice. Experiences from foreign health systems that organisationally resemble the Danish health system can be incorporated if deemed transferable. In this context, it should be qualified to what extent the organisational circumstances identified in foreign literature can be transferred to a Danish setting.

5.5 Health economics

The assessment of health technologies requires an overview of the extent to which the technology examined generates value for money, but also of the budgetary consequences if the Danish Health Technology Council chooses to recommend the technology. Applications to the Danish Health Technology Council should therefore include a health economic analysis and a budget impact analysis. In the evaluation design, the expert committee can set requirement specifications for the economic documentation for the health technology evaluated, including for the analysis method, modelling, time horizon, etc. applied.

See section 6.7 and the technical annex on cost statements.

Because of the broad remit of the Danish Health Technology Council, it is not possible to standardize the approach to the health economic analysis. The evaluation design depends on the current context of the individual health technology. However, the analysis should fall within the overall methodological framework shown in Table 2. This section, along with the technical annexes, contains the methodological approaches that can be used in the health economic analyses. The expert committee may introduce specific requirements for the health economic analysis in the evaluation design. These requirements will depend on the health technology to be evaluated and will be defining for the scope of the analysis. For this reason, applicants should not use all of the methods described in this section but only those methods that are relevant to the specific evaluation situation. Applicants can receive guidance and feedback from the Danish Health Technology Council secretariat on work with the health economic analysis, so that they can prepare the most appropriate analysis.

Table 2 – Methodological framework for the health economic analysis, which forms a basis for an evaluation in the Danish Health Technology Council,

Element	Methodological framework	Section
Time horizon	The time horizon for the evaluation should be long enough to capture all significant differences in relevant health impacts and costs between the alternatives.	5.5.1
Analysis method	Cost analysis Cost-consequence analysis Cost-utility analysis	5.5.2
Comparator	The technology(ies) constituting the best existing treatment options in Danish clinical practice.	5.5.3

Health economic modelling	On the use of health economic models	5.5.4
Discounting	The current discounting rate from the Danish Ministry of Finance should be used for both health effects and costs.	5.5.5
Analysis perspective	Limited societal perspective	5.5.6
Methods for addressing uncertainty	Deterministic sensitivity analyses and possibly probabilistic sensitivity analyses[8]	5.5.7
Budget impact	The regional budget impact of a positive recommendation of a technology over a 5-year time horizon	5.5.8

5.5.1 Time horizon

The time horizon for the economic analysis should be long enough to include all relevant health effects and costs of the intervention and the comparator(s). This means there will typically be a strong relationship between the time horizon, the chosen outcome(s) and the choice of analysis. The time horizon, the outcome(s) and the type of analysis are specified in the evaluation design and are based on the health technology examined. In this context, 'relevant health effects' are the outcome(s) specified by the expert committee in the in the evaluation design.

Figure 3 shows a generalized picture of the relationship between time horizon and analysis method.

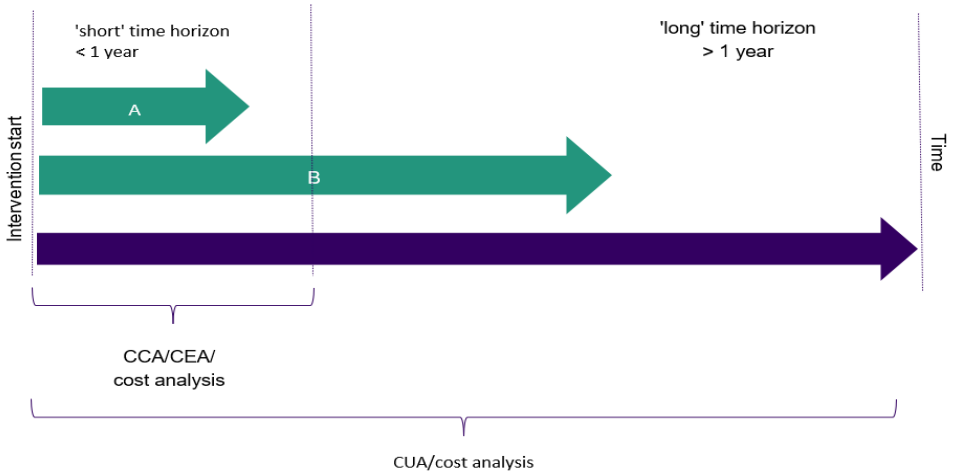

Figure 3 - Illustration of how time horizon and choice of analysis method are often related. The time horizon should be long enough to capture all the differences in accumulated costs and benefits between the intervention and the comparator(s). Thus, for 'evaluation A', you can choose a cost-consequence analysis (CCA), a cost-effectiveness analysis (CEA), a cost analysis or a cost-utility analysis (CUA). Whereas for 'evaluation B', for which the intervention and its comparator(s) are likely to affect the accumulation of costs and benefits over a longer period of time, you can choose a cost analysis or a cost-utility analysis (CUA). CCA: cost-consequence analysis, CEA: cost-effectiveness analysis, CUA: cost-utility analysis.

[8] The expert committee will specify, in the evaluation design, the type of sensitivity analyses to be conducted, including whether probabilistic sensitivity analyses should be conducted.

5.5.2 Analysis method

The choice of analysis method depends on the individual health technology and the outcome(s) used. If an applicant can demonstrate convincing arguments and evidence that the effectiveness of a given health technology is equivalent to that of the specified comparator(s), it may be sufficient to perform a cost analysis. The expert committee may decide that a cost analysis will be sufficient if, when preparing the evaluation design, they find convincing evidence that the intervention examined is clinically equivalent to the chosen comparator. The expert committee may decide that a full economic analysis is relevant and required and, if so, this could be prepared as either a cost-consequence analysis or a cost-utility analysis.[9]

If a cost-utility analysis is performed using health-related quality of life to compare the effect of the intervention against that of the comparator, then quality-adjusted life years (QALYs) should be used. See the technical annexes concerning cost-utility analyses (link to follow) and health economic models (link to follow).

Where a cost-consequence analysis of the technology is deemed relevant, such an analysis should be based on the outcomes that have been assessed to be critical for the evaluation, see section 5.2.1. The outcomes must be relevant and comparable between the alternatives. The cost-consequence analysis should be supplemented by a cost-effectiveness analysis for the outcomes that have been assessed by the expert committee to be most critical. If the expert committee assesses that a single outcome measure out of several critical outcomes is decisive for the evaluation, the applicant should only perform *one* cost-effectiveness analysis for this outcome. Similarly, if the expert committee has only identified one critical outcome, the applicant should only prepare a cost-effectiveness analysis for this measure.

For cost-effectiveness analyses in which the intervention is compared to a single comparator, the result should be expressed as the incremental cost-effectiveness ratio (ICER)[10]:

$$ICER = \frac{\Delta Costs}{\Delta Effectiveness} = \frac{Costs_{Intervention} - Costs_{Comparator}}{Effectiveness_{Intervention} - Effectiveness_{Comparator}}$$

If the expert committee decides that the intervention should be compared to more than one comparator, the applicant should determine whether there are aspects of dominance or extended dominance between the interventions included. Furthermore, the applicant should present the relative cost-effectiveness of the intervention examined compared to the other comparators.

5.5.3 Comparator

In their health economic analysis, applicants should include the comparator(s) indicated by the expert committee in the evaluation design. Usually, the relevant comparators are the technology(ies) constituting the best existing treatment options in Danish clinical practice.

[9] A cost-consequence analysis is a form of economic analysis that compares costs and a range of different outcomes of a health technology with those of relevant alternatives to the health technology. Cost-consequence analyses present the difference in costs and effects separately. A cost-effectiveness analysis is an analysis method that calculates the ratio between the difference in health benefits and the difference in costs between a health technology and its comparator. Outcomes (health effects/health benefits) are usually expressed in natural units, such as life years, reduction in blood pressure (mmHg), infections, etc. Cost-utility analyses are often perceived as a subgroup of cost-effectiveness analyses in which outcomes are expressed in quality-adjusted life years, for example.

[10] If an applicant instead performs a cost-utility analysis, 'effectiveness' is replaced by 'QALY'.

5.5.4 Use of health economic models

It may be necessary to use a health economic model for the economic analysis. The expert committee can set out technology-specific requirements in the evaluation design to inform the development of a representative health economic model. Applicants can find more information about the use of health economic models in the Danish Health Technology Council's technical annex on this (link to follow).

5.5.5 Discounting

Applicants should use the discount rate specified in the evaluation design, if relevant. However, effects and costs accumulated within the first year of the time horizon of the economic analysis should not be discounted. If an applicant believes this principle should be deviated from, the applicant should provide reasons to support this.

5.5.6 Perspective and cost statement

Applicants should apply a limited societal perspective in the health economic analysis. This means that all costs within all sectors and areas concerned must be included, such as hospitals, general practice, specialist practice, home care, nursing homes and nurses and costs of aids and appliances, plus social care. Furthermore, the treatment-related costs of patients and relatives, such as time consumption, transport costs and costs of prescription drugs, should be included. A description of how costs are calculated should always be provided (see the application template).
For information about cost statements[11] and valuation of unit costs, see the technical annex on cost statements. The Danish Health Technology Council's guidance on cost statements is updated regularly, and any recent update may be found on www.behandlingsraadet.dk.

5.5.7 Sensitivity analyses

It is not possible say which sensitivity analyses should be used as standard because the choice depends on the health technology and evaluation design. However, applicants should always identify the elements of the health economic analysis that they expect could have a significant impact on the result. In addition to the sensitivity analyses initiated by the applicant, the expert committee may, in the evaluation design, request sensitivity analyses of specific elements.

If the health economic analysis comprises a cost-consequence analysis, it will be sufficient to conduct the sensitivity analyses on the basis of the cost-effectiveness analysis for the most critical outcome (see section 5.2.1, unless the expert committee stipulates otherwise).

The uncertainty associated with all input parameters (including cost, effect and probability parameters) that the applicant expects could potentially have a significant impact on the result should be examined in one-way sensitivity analyses. The result may be presented in a tornado diagram. The applicant must clearly describe what input intervals have been used in such one-way analyses. In addition to one-way analyses for input parameters, applicants should perform supplementary scenario analyses, in which several input parameters are changed simultaneously. Among other things, scenario analyses may include best-case/worst-case scenario analyses. Applicants are expected to provide reasons for their choice of scenario analyses, and for how the parameters have been changed. Furthermore, the expert committee may indicate, in the evaluation design, the scenario analyses to be performed.

[11] This also includes information about indexation, depreciation and lifespan of resources, calculation of overheads, use of allocation keys, etc.

Furthermore, applicants should perform deterministic sensitivity analyses of how methodological assumptions may impact the result of the economic analysis, including, where relevant, how the choice of time horizon and discount rate affects cost-effectiveness. It is also recommended that expected, significant structural uncertainty be examined in deterministic sensitivity analyses, including, where relevant, functions used for extrapolation of data beyond the time horizon observed (see the technical annex on health economic models (link to follow).

In addition to the deterministic sensitivity analyses, applicants may submit a probabilistic sensitivity analysis if they consider this to be informative.

Furthermore, the Danish Health Technology Council itself may conduct sensitivity analyses based on the application materials submitted. To allow for this, the Danish Health Technology Council secretariat may request additional material from the applicant.

See the Danish Health Technology Council technical annex on sensitivity analyses, for more information about the probabilistic sensitivity analyses, which can be found at www.behandlingsraadet.dk.

5.5.8 Budget impact analysis

In addition to the health economic analysis, the applicant must prepare a budget impact analysis, which shows the expected impact on the regional health budgets, calculated collectively for the five regions, if the examined health technology is used/phased out. This must be compared to what otherwise constitutes the existing treatment option in Danish clinical practice without the examined health technology. The analysis consists of estimates, including the expected market uptake of the examined health technology, as well as the prevalence and incidence of the patient population expected to be treated. The analysis should illustrate how the budget is expected to be impacted over a period of five years by recommending the examined health technology. Thus, the applicant must describe and compare two scenarios: Treatment with and without the examined health technology.

5.6 Literature

As part of the preparation of the evaluation design, the secretariat conducts systematic literature searches in collaboration with the expert committee to identify existing published literature describing the technology examined within the four aspects of clinical effectiveness and safety, patient perspective, organisational implications and health economics.

The search strategy for the individual evaluation will depend on the specific technology, as well as on the perspectives that the expert committee finds relevant to cover. Moreover, the extent of the search will depend on factors such as the maturity of the technology, and whether the evaluation concerns a single product or a product category.

The applicant is expected to prepare their application based on the results from the systematic searches. In addition to the systematically searched literature, the applicant can include grey literature in addressing the perspectives of the Patient Perspective and Organisational Implications. The applicant is responsible for the subsequent screening and literature selection (see section 6.3).

Existing literature is identified using a pragmatic approach in three consecutive steps as shown in Figure 4.

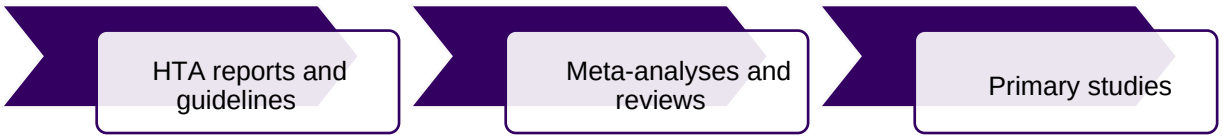

Figure 4 – Identification of existing literature. HTA: Health Technology Assessment (evaluations of health technology).

5.6.1 Existing HTA reports

The Danish Health Technology Council secretariat will conduct an ad hoc search for existing, published evaluations (HTA reports) of the health technology examined. The search is conducted in the following databases:

- INAHTA (International HTA database)
- NICE (National Institute for Health and Care Excellence, United Kingdom)
- MSAC (Medical Services Advisory Committee, Australian)
- CADTH (Canadian Drug and Health Technology Agency)

In cases where potentially relevant HTA reports are identified, the expert committee will assess whether these can be used wholly or partly in the Danish Health Technology Council's recommendation decision on the health technology examined. The expert committee will decide on the following:

1. Are the frameworks (patient population, area of application, outcome, comparator, setting, etc.) for the existing evaluation in line with the expert committee's position on how the technology examined should be evaluated (see the evaluation design)?
2. Is the overall methodological quality of the existing evaluation sufficient, and are there significant methodological deviations from the Danish Health Technology Council's methods guide?
3. Is the existing evaluation recent enough, or is it probable that significant new evidence has emerged since its publication?
4. Confidence in the general transferability of the analysis, including concerning clinical effectiveness and safety, patient perspective, organisational implications, and health economic analysis

It will often be most suitable to still evaluate clinical effectiveness, for example if the expert committee expects that new evidence has emerged since the publication of the existing evaluation, if the comparator used is not representative of Danish clinical practice or if there are significant deviations with regard to the methodology applied etc. Furthermore, in practice, it will always be relevant to conduct a health economic analysis tailored to Danish conditions (see section 6.7 for a more detailed description of how to carry out the health economic analysis).

There will thus be situations in which the Danish Health Technology Council's evaluation will ultimately be based on *parts* of an already published assessment of the health technology.

The expert committee make the final decision on whether assessment report, in full or in part, can be based on an existing technology assessment. The expert committee will make this decision before the evaluation design is published.

Upon publication of the evaluation design, the applicant will be informed about whether the Danish Health Technology Council intends to base its evaluation, in full or in part, on an existing health technology assessment. In some situations, this may be important for the applicant's work on the application. For example, it will not be necessary to submit an analysis of clinical effectiveness if the expert committee has assessed that an analysis is already available and is fully transferable.

5.6.2 Meta-analyses, reviews, and primary literature

The literature search for reviews, meta-analyses and primary studies is made in the following databases:

- MEDLINE via PubMed
- EMBASE

- Cochrane Library

In regards the Patient perspective, Organisational implications, and Health economics, it can be relevant to supplement the search by also searching in the following databases:

- PsychINFO
- CINAHL
- Web of Science (including Social Sciences Citation Index)
- Scopus

In some cases, it will *not* be necessary to conduct a systematic literature search. This includes situations in which a specific single new product is evaluated and in which one or a few studies are known to exist that compare the new technology directly to the relevant comparator, and where no further published literature is expected to exist. In this case, the evaluation design will state that the expert committee's view is that there is no need for a systematic literature review.

5.6.3 Documenting the literature search and screening

The search is organized based on the need to elaborate on the four aforementioned perspectives, which highlight Clinical Effectiveness and Safety, the Patient perspective, Organisational Implications, and/or Health Economics. The search is based on the defined PICO. The Danish Health Technology Council conducts the systematic literature search(es) and hands over the combined results of the search(es) at the title/abstract level to the applicant after deduplication when the evaluation design is published. The applicant should secure access to the resulting full-text articles on their own.

The applicant screens the search results identified in the literature searches to select literature according to the PICO specification. Inclusion and exclusion criteria should be detailed in the application itself, along with a description of the process for identification and selection of studies. The Covidence program is used for screening references from literature searches, where initial screening is done at the title and abstract level, followed by full-text reading. This selection process should be documented in a PRISMA[12] flow diagram. Further reference is made to the Cochrane Handbook for Systematic Reviews of Interventions (Chapter 4) [9] for best practices regarding literature selection.

[12] Preferred Reporting Items for Systematic Reviews and Meta-analyses.

6 Application

The application must be prepared by the applicant and should follow the specifications described by the expert committee in the evaluation design. The applicant may discuss the application with the Danish Health Technology Council secretariat. A full application must be available at least one year after publication of the evaluation design. If not, the expert committee will reassess and perhaps change the evaluation design to ensure that it reflects current clinical practice and the most recent evidence.

The application should be structured on the basis of the application template available on the website of the Danish Health Technology Council. The template contains the sections listed in Table 3. The table includes references to sections in the methods guide specifying how to complete the application, as well as to the technical annexes containing a description of methods that may be relevant to use.

Table 3 – Relationship between the Danish Health Technology Council's application template, the methods guide and the technical annex's to the guide.

Components of the application	See section	Detailed description in technical appendices/application template
Introduction Basic information on the specific health technology and its area of application	0	Application template
Summary The applicant's summary of the main findings for the four aspects of the application	6.2	Application template
Evidence base Data basis behind the application	6.3	Application template
Clinical effectiveness and safety Answer(s) to the clinical question(s) in the evaluation design, including appropriate comparative statistical analyses	6.4	Application template
Patient perspective The applicant's summary of existing evidence regarding patient experiences and preferences with regard to the health technology examined	6.5	Application template and technical annexes
Organisational implications The applicant's description of the organisational implications of the health technology examined	6.6	Application template
Health economics A health economic analysis and a budget impact analysis	6.7	Technical annex: Guideline on cost statement

If the applicant cannot provide the analyses, results and/or information requested in the evaluation design, the best possible alternative(s) should be submitted as well as a brief explanation of why the

requested information cannot be submitted. For example, the evaluation design may request data on a given outcome calculated after a one-year follow-up. If the applicant does not possess, or have access to, such data, a statement must be submitted which, in terms of follow-up period, is as close as possible to what the expert committee has defined.

If important requested information cannot be provided, the applicant must notify the secretariat before submitting the application.

The following describes the individual components of the application:

6.1 Introduction

This section sums up information on the health technology and its area of application. The comparator(s) stated in the evaluation design by the expert committee should also be presented in this section.

6.2 Summary

In this section, the applicant should sum up the methods used as well as the most important results of the analysis of clinical effectiveness and safety, as well as the health economic analysis. Moreover, the applicant should sum up findings regarding patient preferences for, and experiences with, the health technology examined, as well as the evidence forming the basis for these findings. In the same way, the applicant should give a brief summary of the likely implications that the use or phase out of the health technology will have for the organisation, as well as whether there are likely significant challenges to the use or phase out of the technology.

6.3 Evidence base

In this section, the applicant should present the selection of literature and the data material forming the basis for the application.

6.3.1 Selection of literature

In this section, the applicant should present how literature on the four aspects of the application has been selected based on the search results delivered by the secretariat in connection with publication of the evaluation design.

The applicant should screen the search results identified in the database searches to reflect the population, the intervention and the comparator stated in the evaluation design. For the literature review concerning clinical effectiveness and safety, the applicant should also carry out the screening with regard to outcome (PICO). In some cases, the expert committee will have specified requirements in the evaluation design (for example requirements concerning study design) that the applicant should comply with in the literature screening.

When screening articles, the applicant should first exclude at title/abstract level, and then at full-text level. A list of titles of all articles excluded by the applicant at full-text level should be enclosed with the application.

The applicant’s selection of literature for the analysis of clinical effectiveness and safety should be documented with a PRISMA flowchart. See also [7] for good practice regarding searching for and selection of literature.

6.3.2 Effectiveness and safety

The actual comparison of clinical effectiveness should, as far as possible, be based on literature from the systematic search. Applicants should base their analysis of clinical effectiveness and safety on the evidence that is most likely to reflect the effectiveness and safety of the health technology compared to the comparator. If possible, applicants should base their analyses of clinical effectiveness and safety on randomized controlled trials. However, there may be cases in which such studies are not available or in which it is relevant to include data from observational studies, for example (see section 6.4.5.4). The Danish Health Technology Council is aware that, for certain types of health technologies, it is neither plausible nor possible or ethically appropriate to conduct randomized controlled trials.
Applicants should draw up a list of ongoing own studies and search for ongoing unpublished studies that include the intervention and comparator for the intended patient population on Clinicaltrials.gov and the EU Clinical Trials Register.

6.3.2.1 Unpublished data on effectiveness and safety

In situations in which the analysis of the clinical effectiveness and safety or parts thereof cannot be properly based on existing published and systematically found literature, other sources of data may be used, including *data-on-file,*[13] 'grey literature'[14] and expert statements.[15]

A clear description must always be available of how the data has been obtained. Therefore, in cases in which *data-on-file* is used, for example, a study protocol or a detailed description of the underlying study should be available. It should always be possible for the Danish Health Technology Council to assess relevance and reliability of the data not available in a peer-reviewed published format. In addition to the above, the Danish Health Technology Council follows the Council's policy paper on the use of unpublished data. The Danish Health Technology Council will rarely be able to assess the clinical effectiveness and safety of a healthcare technology based solely on unpublished data.

In cases where expert statements are used, the applicant should enter the name and function of the expert in question.

6.3.3 Patient perspective, Organisational implications, and Health economics

In addition to their selection of literature on the basis of search results provided by the secretariat, applicants may cite other literature on the patient perspective, as well as organisational and economic implications. If applicants know about other studies that were not found via the search but that are nonetheless likely to be relevant, for example to identify patient preferences, they can choose to include these studies. Thus, applicants can supplement literature searches with findings from

[13] *Data-on-file* refers to data that the applicant may hold, but which has not (yet) been published.
[14] 'Grey literature' means literature that has not been published commercially via a publishing house, and which cannot be found via bibliographic databases such as CENTRAL and PubMed. Grey literature includes reports, discussion papers, conference publications, PhD dissertations, material from authorities, etc.
[15] A general guiding principle for use of foreign experts as reference in the application, for example, should be that their knowledge is likely to be representative of what you can expect of Danish clinical practice. As such, it is not a prerequisite that they have experience of using the health technology in the Danish healthcare system, but that experience and knowledge can be expected to be transferable and representative of what could be expected from Danish clinical practice.

unpublished material, 'grey literature', *data-on-file*, literature that was not found in the systematic literature search, etc.

6.3.3.1 Patient perspective

Applicants are encouraged to always report published or unpublished evidence on the patient perspective for the health technology examined. If possible, published literature on the patient perspective should be identified via the literature search prepared by the Danish Health Technology Council secretariat. However, in addition to the published literature, it may often be necessary for applicants to explore other sources not indexed in databases. Such sources may include grey literature, such as dissertations or reports about the patient perspective. Evidence may also be obtained through observational studies, formal or informal individual interviews, focus-group interviews with patients and questionnaire surveys.

Relevant questionnaire surveys may, for example, relate to PRO data (patient-reported outcomes),[16] which can help to clarify whether the patients experience benefits and value from using the health technology. Data on the patient perspective may come from published as well as unpublished sources, regardless of the type of data concerned.

If there is no literature on patient experiences and preferences, the applicant may examine whether there are scientific results within closely related fields for which it is reasonable to expect that preferences and experiences are transferable. In such situations, applicants must argue why they believe the data from these sources to be transferable to the health technology examined.

6.3.3.2 Organisational implications

As far as possible, applicants should base their description of organisational implications on concrete experiences of use of the health technology. The applicant is generally not expected to obtain additional evidence, but a practical experience base in relation to using the health technology must be available.

The Danish Health Technology Council accepts a varied evidence base for the description of the organisational implications. Where relevant, applicants should include evidence from the systematic literature search in the description of the organisational implications. In addition, evidence from available literature can be incorporated, including scientific studies not identified in the systematic literature search but assessed to be relevant for the context examined, or other literature such as management reports, dissertations, guidelines, etc. The applicant may also draw on expertise from users of the technology, key opinion leaders, procurement officers, etc. The data basis for this may consist of observational studies, written statements, formal or informal individual interviews, focus-group interviews, as well as questionnaire surveys with staff who have used the healthcare technology examined.

6.3.3.3 Health economics

If, via the literature search or due to prior knowledge, an applicant has identified existing health economic analyses of the health technology examined, the applicant may choose to use these analyses in connection with the application. Existing health economic analyses can be used as reference to assess the reasonableness of the results in the applicant's own health economic analysis.

[16] The focus of PRO data is the patient's condition, including physical and mental condition, symptoms, health-related quality of life and level of function. The expert committee can therefore also include PRO data as independent clinical endpoints used to identify the effectiveness and safety linked to the health technology. However, PRO data is reported directly by the patient, and, as such, is not objectively quantifiable.

It will rarely be possible to use the results of existing health economic analyses directly in the application. In some cases, however, applicants may use evidence of resource consumption (time consumption, consumption of materials, etc.) from existing health economic analyses if it is reasonable to expect that the clinical practice in which the data was collected resembles Danish practice (see the technical annex on cost statements for a more detailed description).

6.4 Effectiveness and safety

In this section, applicants should present the studies that form the basis for the analysis of clinical effectiveness and safety, and the comparative analysis that illustrates differences regarding clinical effectiveness and safety of the intervention in relation to the comparator. Where possible and appropriate in relation to the properties of the health technology examined, the Danish Health Technology Council prefers that data on effectiveness and safety originate from randomized controlled trials (RCTs) but is aware that, for many technologies, it is not possible to conduct double-blind randomized trials. This means that it may sometimes be necessary to deviate from the procedure described in section 6.4.5 for the analysis of clinical effectiveness, for example where the data basis exclusively concerns diagnostic accuracy.

For medical devices, in addition to the analysis of clinical effectiveness and safety, applicants must enclose relevant documentation on the risks associated with the health technology.

6.4.1 Review of study characteristics

Significant study characteristics for all studies included should be summarized in tabular format in the application template, including design/study type, conditions relating to blinding, intervention/comparator, duration/follow-up period and outcomes.

6.4.2 Review of patient characteristics

Significant inclusion and exclusion criteria as well as baseline characteristics (for example age, gender, duration of disease, etc.) for all studies included should be summarized in tabular format in the application template.

6.4.3 Outcomes

The applicant should indicate all relevant outcomes from each study, see the evaluation design. The exact definition and calculation method should be stated for each outcome. It should be stated clearly if there are definition or calculation differences in outcomes between the identified studies and the evaluation design.

6.4.3.1 Health related quality of life

It is important to collect information on the health-related quality of life of the patients, as this relates to their physical and mental wellbeing, which is not necessarily captured in full by other outcome measures. Health-related quality of life can be measured using generic and disease-specific instruments, including a number of PRO tools.

Because of the broad remit of the Danish Health Technology Council, it is not possible to give a standardized approach to how applicants can or should collect data on patients' health-related quality of life, including which instruments are best suited for specific evaluations. This depends on the specific health technology as well as on the context and purpose of the evaluation. For this reason, the Danish Health Technology Council also accepts data on health-related quality of life that has been collected using different instruments, as long as validation studies exist for these.

Reporting data on health-related quality of life

Given that different instruments have different strengths and weaknesses, the Danish Health Technology Council recommends that applicants report data on patients' health-related quality of life using

the EQ-5D-5L questionnaire, if the applicant has such data. The EQ-5D-5L questionnaire covers five domains (i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) to which the patient can provide answers on a 5-level scale from 'no problems' to 'extreme problems'. If there is no data available that has been collected using the EQ-5D-5L questionnaire, applicants can use other generic instruments, such as the *Short Form* (SF-36) survey or disease-specific questionnaires relating specifically to the population examined. See the Danish Health Technology Council's technical annex on handling health-related quality-of-life data (link to follow). See Faria et al. [8] for information on how to handle missing data for health-related quality-of-life.

6.4.4 Presentation of results at study level

All results regarding clinical effectiveness and safety that the applicant, based on the evaluation design, assesses to be relevant for the evaluation should be presented at study level. For all outcomes, applicants should state relevant estimates of the outcome differences between intervention and comparator(s), calculated as absolute and relative differences, as well as the distribution of the outcomes in the individual arms of each study. For dichotomous outcomes, this could be the relative risk and risk difference as well as the observed event rates for the intervention group and comparator group, respectively. For continuous outcomes, this could be the difference in mean change and the mean value before and after commencement of treatment with the intervention and the comparator. For all results, the statistical method used should be stated as well as an appropriate uncertainty estimate when possible. It should also be stated under which principle the population of the analysis has been defined, for example *intention-to-treat* (ITT),[17] *complete case* or *per protocol (PP),*[18] as well as any dropouts in the intervention group or comparator group.

Where possible, the proportion of patients with at least one serious adverse event,[19] irrespective of the reason, should be stated for the intervention and comparator groups in all studies included.

6.4.5 Analysis of Effectiveness and safety

In the application, the applicant should present statistical analyses of the effectiveness of the intervention, compared with the comparator, and for all the outcomes where this is possible. For outcomes where this is not possible, for example if there is no data available for the outcome specified, the applicant should submit data resembling the data requested to the extent possible.

Sources for use in the comparative analysis should be identified, see the search strategy in the evaluation design, and all sources should be presented in accordance with section 6.4.4. If unpublished data is used, this should be clearly specified: There should be an explanation of why it is necessary to use unpublished data, and the applicant should ensure appropriate descriptions of the study or studies behind the data are provided.

The applicant should use validated methods for all statistical calculations, and the methods used should be suitable for the data basis in question as well as for assessing clinical effectiveness. Finally, the approach used in statistical calculations should be clearly described.

[17] *Intention-to-treat* analyses are based on data from all patients randomized into the intervention or comparator group, regardless of whether the treatment has commenced.
[18] A *per-protocol (PP) analysis* is a pre-specified analysis, typically conducted on a subset of patients with special characteristics.
[19] An event or adverse effect that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or leads to a congenital anomaly or birth defect (see the complete definition from the International Council for Harmonisaton of Technical Requirements for Pharmaceuticals in Human Use).

Different analyses can be applied for different outcomes depending on the data. Regardless of the choice of analysis, the applicant should clearly indicate the analysis population for each study (in prioritized order: ITT and PP), as well as the statistical method applied.

Applicants should avoid using post-hoc analyses. If post-hoc analyses are used nonetheless, for example to comply with the evaluation design or because the analysis is presented as supplementary evidence, then the applicant should make sure this is clearly indicated. The rationale for, and results of, the analysis should be presented in summary form and compared with results from ITT and/or PP analyses.

The applicant should present the results from the comparative analysis of dichotomous outcomes as both relative (*hazard ratio*, HR, or *risk ratio*, RR, for example) and absolute values (*risk difference*, RD, or *number-needed-to-treat/number-needed-to-harm*, for example). The applicant should provide outcome differences for continuous outcomes as absolute values, for example *mean difference* (MD) or, if necessary, *standardized mean difference* (SMD).[20] Outcome estimates should always be accompanied by relevant uncertainty estimates.

6.4.5.1 Direct comparisons

If the intervention in a standalone study is compared directly to the specified comparator (*head-to-head*), then the outcome estimates from the comparison can be used directly without any further processing (example 1 in Figure 4). If this is the case, the applicant may disregard sections 6.4.5.2, 6.4.5.3 and 6.4.5.4 below. If the applicant chooses to disregard these sections, then presentation of results at study level, see section 6.4.4, will be sufficient.

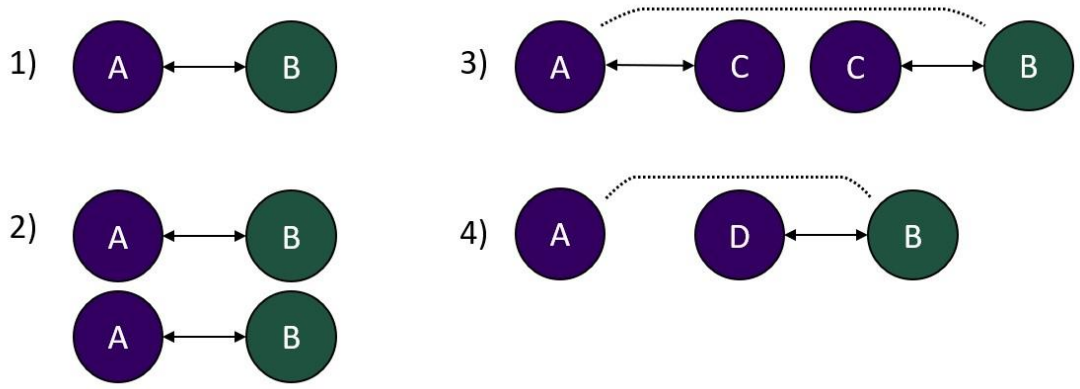

Figure 5 - Scenarios for the types of evidence that can be used to compare the clinical effectiveness of intervention (A) and the comparator (B) specified in the evaluation design. Arrows illustrate direct evidence, i.e. studies directly comparing interventions. Dotted lines indicate the desired comparison (always A versus B). 1) There is only a single direct comparison study. Results from this direct comparison between A and B can be used without further processing. 2) There are several direct comparison studies between A and B. The results from these can be aggregated in a pairwise meta-analysis. 3) There are no direct comparison studies between A and B, but both interventions have been compared with an intermediary alternative (C). An adjusted indirect comparison can be made. There may be several intermediary alternatives or more pairwise comparisons. Here, as a general rule, it will be relevant to perform a network meta-analysis. 4) There are no direct comparison studies between A and B (A was examined in a single-arm study design), and A and B cannot be linked via a network. An MAIC, STC or a naïve comparison can be performed. MAIC: Matched-adjusted indirect comparison, STC: Simulated treatment comparison.

[20] Typically, when using meta-analyses, for example when different psychometric tests have been used to evaluate the same outcome across the different studies included. If possible, the Danish Health Technology Council prefers results to be displayed in their original units, as this is often most intuitive from a clinical perspective. However, this should be compared to any methodological challenges, including heterogeneity.

If there is more than one direct comparison study, the results from all of these studies should be aggregated in a pairwise meta-analysis (example 2 in Figure 4) if the conditions for this are met. If there is an existing meta-analysis in which PICO matches the evaluation design, this meta-analysis may be used and submitted as an appendix to the application.

In their application, applicants should explain why the studies are sufficiently comparable to be included in a meta-analysis. Furthermore, where meta-analyses are carried out, the applicant should describe, or refer to a description of, the statistical approach used. The description should be at a level of detail allowing reproduction of the analysis. The applicant should also perform sensitivity analyses as they deem relevant and examine and describe causes of heterogeneity. Outcome estimates derived from pairwise meta-analyses should be displayed as Forest plots.

See also the Cochrane Handbook for Systematic Reviews of Interventions [9].

6.4.5.2 Indirect comparisons

In cases where there are no direct comparative studies between the intervention and the comparator specified in the evaluation design, the applicant should synthesize evidence using indirect comparison methods, where possible. This presumes that the literature search must have identified studies that connect the intervention with the relevant comparator via a network (example 3 in Figure 4). Relevant statistical methods include adjusted pairwise indirect comparisons, Bucher's method and network meta-analyses. The Danish Health Technology Council refers to the EUnetHTA guidelines [10] in this area and to the Cochrane Handbook for Systematic Reviews of Interventions [9], and stresses that the methodology and assumptions used should be clearly described in the application.

If network meta-analyses are used, the recommended approach is to limit the network to the comparisons that are needed to provide outcome estimates for the intervention compared with the specified comparator. Indirect comparisons generally constitutes observational evidence, and as such confidence in outcome estimates will generally be weaker if they are based on indirect comparisons [11]. This is particularly the case if there is only one study for each direct comparison in the network, or if the network includes more than one intermediary alternative.

In exceptional cases, it may be relevant to include estimates based on network analyses, even if there is one or more direct comparative studies, if it is assessed that this will provide a truer presentation of the effectiveness and safety of the health technology.

6.4.5.3 Population-adjusted indirect comparisons

There may be situations in which there is no network of interventions connecting the intervention with the comparator. For example, this could be if the intervention has only been studied in one or several single-arm studies (example 4 in Figure 4). If the applicant has access to individual patient data (most likely for the intervention examined), methods such as matching-adjusted indirect comparison (MAIC) or simulated treatment comparison (STC) can be used (see [12] for details on this), if the conditions for such analyses are met.

The Danish Health Technology Council only accepts this type of analysis in situations in which there is no network of evidence connecting the intervention and the comparator, or if the conditions for this type of analysis are not met. If the latter is the case, the applicant should describe how it has examined the possibilities and argue why it is not possible to perform an indirect comparative analysis, see section 6.4.5.2.

For more information, see NICE DSU *technical support document* 18 [12], and Phillippo et al. 2018 [13], who provides a summary of the same report.

6.4.5.4 Naïve comparisons and observational data

Unadjusted indirect comparisons (naïve comparisons), for example between data from two single-arm studies, may be submitted if the conditions necessary for performing proper statistical analyses are not met, see the three sections above. Similarly, naïve comparisons with real-world data may be used (for example cohort studies, register data to establish historical benchmarks/controls) in situations in which no better basis of comparison exists.

The Danish Health Technology Council is aware that it is not plausible, possible, or ethically appropriate to conduct RCTs for certain types of technologies, and, in particular, that it is not always possible to blind participants and/or staff. In such cases, the observational data can be an important source in the evaluation of clinical effectiveness and safety. However, the Danish Health Technology Council stresses that naïve comparisons as the only basis for an analysis of clinical effectiveness will often be insufficient. Whether or not this is the case will be determined on a case-by-case basis, and it will depend on the quality of the observational data and the risks associated with use of the technology, as well as the severity of the condition being treated and the existence of alternative treatment options.

When using observational data, applicants should always include a thorough discussion of the risk of bias, including confounders, selection bias, etc. The statistical methods applied must be described in detail and unambiguously.

6.4.6 Summary of results from the comparison of clinical effectiveness

In addition to a brief summary of key results from the comparison of clinical effectiveness, the results should be presented in tabular format, see the application template (one table per clinical question).

6.5 Patient perspective

The expert committee will specify in the evaluation design how the patient perspective should be included in the evaluation of the health technology examined. Applicants should base their examination of the patient perspective on what has been identified as relevant in the evaluation design. There may be situations in which the clinical effectiveness of a technology will not be sufficient to show the full implications for the patient, and it therefore may be relevant to examine other parts of the patient perspective. For example, if a patient has been transferred from hospital treatment to home treatment, and the clinical effectiveness relates to the patient avoiding infections, then the patient is likely to have an opinion about the transfer (because of changed sense of security, comfort, empowerment, etc.).

Applicants are expected to submit relevant information about the patient perspective in relation to the health technology. The patient perspective can comprise specific patient experience of the technology and more generalized knowledge about patient conditions, but it can also comprise preferences for, or expectations of, the properties of the technology. The Danish Health Technology Council prefers applicants to present evidence concerning the patient perspective from patients who have specific experience of the technology in question. However, if there is a lack of evidence based on patient experiences, it may be relevant to describe the patient perspective based on general considerations about the properties of the technology. For example, this could be the general reflection that patients would typically prefer a small insulin pump to a large one, which could lead an applicant with a smaller insulin pump than the comparator to conclude that their own pump is to be preferred based on this aspect.

The patient perspective should concern how the health technology affects the patient, and this may include several aspects, such as social aspects relating to family life and working life, or personal aspects, such as degree of satisfaction or stigmatization. Economic aspects or communication aspects,

including implications for the relationship between the patient and healthcare professionals, may also be significant. Furthermore, ethical aspects and issues may be considered, such as whether the health technology affects the patient's self-determination. It may also be relevant to describe the accessibility of the health technology. For example, whether restrictions, such as blindness, dementia, or immobility, mean that the technology is used more or less within specific patient groups. Such restrictions may occasion unwanted unequal access to health services and, at a more general level, either increased or reduced health inequalities.

6.5.1 Summary of evidence for the patient perspective

In accordance with the evaluation design, applicants should submit a summary of any experiences that patients have had with the health technology, and they should account for the methodologies behind and context of any such findings. Patients' experiences and preferences with regard to a health technology should be included in the summary regardless of the origin of the data. Applicants may use the application template for reporting the available knowledge about patients' experiences and preferences with regard to the health technology examined. The findings are to be provided at an aggregate level. The expert committee will carry out a quality and outcomes assessment based on the applicant's summary of available data.

Applicants are generally not expected to collect empirical data in connection with their preparation of applications for the Danish Health Technology Council.

6.6 Organisational implications

The level of detail required in the description of the organisational implications of the health technology depends on the properties of the technology in question. It is therefore not possible to indicate a single best approach for the examination of this aspect. Similarly, the Danish Health Technology Council cannot say how comprehensive the description should be for the Council to be able to make a recommendation, because there may be significant differences with regard to this across the various types of health technology covered by the Danish Health Technology Council's remit. The expert committee will indicate in the evaluation design whether and how the applicant should describe the organisational implications.

This section should be understood in relation to the application template, which includes a detailed description of the items to be included in the applicant's description. Please note, however, that these items may not necessarily be enough to adequately describe the technology in question. What is to be included depends on the properties and the context of the technology. In addition to the items in the application template, the expert committee may include further implementation and organisational aspects in the evaluation design, which should be described for the health technology in question.

There may also be situations in which (new) use/phase-out of a health technology is not expected to have any significant organisational implications. For example, this may be the situation if the health technology replaces an existing technology, but the working procedures associated with use of the technology remain unchanged, including with regard to procuring paraphernalia, training in the use of the technology, use of the technology, disposal of the technology, etc. If the expert committee finds that use/phase-out of the technology has no organisational implications, then this will be reflected in the evaluation design.

Applicants are expected to describe the data underpinning their description of organisational implications. This applies even if the applicant has relied on qualified assumptions and has no empirical data to support these assumptions.

6.6.1 Organisational description and use/phase-out

If the expert committee finds that the health technology is likely to have organisational implications, applicants should describe the organisational conditions under which the health technology is (expected) to be used. Implicitly, this means that the description should address how the technology is expected to be used in a Danish setting. The objective of this is to provide the Danish Health Technology Council with insight into the context in which the technology will be used, as well as identifying the implications for the organisation of using/phasing out the technology. It will also be relevant to identify any organisational requirements for successful use or phase-out of the technology. Finally, the organisational description can be used to identify any areas that can be omitted from the further description of implications of use/phase-out of the health technology.

The description of the organisation and any aspects of use or phase-out of the health technology will also form the basis for the health economic analysis and the budget impact analysis (see section 6.7). Information about use (for example implementation, procurement, use of staff resources, qualification enhancement of staff, impact on the consumption of other materials, phasing out, etc.) of the health technology is a determining factor for the cost components to be included and valued.

When drawing up the organisational description, applicants should describe the organisation in general terms. In other words, the description should *not* be of local conditions, such as the conditions at a specific unit at a specific hospital.[21] Rather, the organisational description should identify the *general* characteristics of the situation in which the health technology is used.

In their organisational description, applicants should address the items[22] described in the application template and describe the conditions pertaining to the items relevant to the health technology examined. The expert committee may specify additional items in the evaluation design that the applicant should address. If the applicant identifies areas of importance for understanding how the health technology interacts with the surrounding organisation and impacts further steps along the care pathway, such areas may also be included in the description.

Applicants are encouraged to illustrate working procedures/treatment with and without the health technology if they think this will help illustrate how the health technology impacts the organisation in practice. For example, applicants can use illustrations to provide an outline of which staff groups are involved at what stage of the use of the technology, and what impact such use has on patient flow.

Based on the organisational description, applicants should describe the potential consequences of using/phasing out the health technology as related to a number of aspects (items) listed in the application template.[23] Among other things, these include factors likely to impact patient safety. The evaluation design from the expert committee may include additional aspects to be addressed. If the applicant identifies areas of importance for the process related to use/phase-out of the health technology, such areas may also be described here.

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[21] This applies *unless* it is expected that the health technology will only be relevant to use/phase-out in a single place, for example at a highly specialized hospital unit where local conditions determine whether use/phase-out of the technology is successful.

[22] This includes requirements for the physical environment, the degree to which the technology will be used across treatment levels and treatment groups, whether use of the technology requires users to have a certain level of qualifications, etc. The items in the organisational description are described in more detail in the application template.

[23] These items have been identified based on Leavitt's expanded system model and include aspects such as the demand for task shifting, the risk of function creep, the need for training, expected user requirements, etc. Applicants can choose to use Leavitt's expanded system model as their basis for examining the organisational aspects under or from which the health technology is expected to be used/phased out, and for their subsequent analysis of how implementation/phase-out of the health technology is likely to affect the organisation.

6.6.2 Information concerning organisational aspects in clinical studies

If the expert committee finds that the health technology is likely to have organisational implications, applicants should look for relevant information concerning the technology's organisational implications in the studies used to evaluate the clinical effectiveness and safety of the technology (see section 6.4).[24]

In this connection the applicant should consider to what extent the organisation used in the clinical studies reflect what is likely to be true in a Danish setting with regard to organisation and use/phase-out of the technology. Among other things, the applicant should identify whether the conditions characterizing the organisation described in the clinical studies differ significantly from those characterizing the expected organisational situation for the technology in Danish practice. For example, this could be if the health technology were used by anaesthesiologists in the clinical studies, while in a Danish practice context the technology is expected to be used by nurse anaesthetists. This means that studies will not always fully reflect the organisational conditions and workflows to be expected under Danish conditions, and this may be of significance for the health economic implications of implementing the health technology (see section 6.7). Furthermore, the applicant should also consider whether there are special considerations to make with regard to scaling up the conditions described in the clinical studies to reflect more widespread use of the technology.

6.7 Health economics

Because of the broad remit of the Danish Health Technology Council, it is not possible to standardize the approach to the health economic analysis. The evaluation design depends on the current context of the individual health technology. However, the analysis should fall within the overall methodological framework shown section 5.5. This section, along with the technical annexes, contains the methodological approaches that can be used in the health economic analyses.

The expert committee may introduce specific requirements for the health economic analysis in the evaluation design. These requirements will depend on the health technology to be evaluated and will be defining for the scope of the analysis. For this reason, applicants should not use all of the methods described in this section but only those methods that are relevant to the specific evaluation situation. Applicants can receive guidance and feedback from the Danish Health Technology Council secretariat on work with the health economic analysis, so that they can prepare the most appropriate analysis.

The health economic analysis should be reported in accordance with the application template. In their report, applicants should explain the methods, assumptions and included data that have been used in the analysis and should provide references. This way the various steps in the health economic analysis can be easily followed and the analysis can be repeated with alternative assumptions, should the expert committee or the Council find this relevant.

6.7.1 Presentation and discussion of results

The overall results, assumptions and uncertainties associated with the health economic analysis should be summed up and discussed by the applicant (see the application template).

For cost analyses, the results should be presented so that they provide a general picture of costs per patient for the health technology examined and its comparator over the time horizon set out in the

[24] The Danish Health Technology Council is aware that there is often only limited information about organisational aspects in clinical studies, but nevertheless encourages applicants to report the information that *is* available.

evaluation design. The incremental costs per patient relative to comparator(s) should be presented separately.

For full health economic analyses, the costs and effects of the health technology examined, and its comparator(s) should be reported separately over the time horizon set out in the evaluation design. Furthermore, the incremental cost-effectiveness ratio or dominance/extended dominance should be reported if there is one or more comparators.

6.7.2 Budget impact analysis

The budget impacts should be reported separately for each of the five years. The analysis should comprise estimates of expected market share of the health technology examined, as well as the prevalence and incidence with regard to the patient population expected to receive the treatment. The budget impact analysis and the underlying estimates, assumptions, sensitivity calculations, etc. should be enclosed with the application as appendices (see the technical annex on cost statements for more on how to conduct the budget impact analysis).

7 The expert committee's assessment report

The submitted application forms the basis for the expert committee's assessment report. The expert committee prepares the assessment report, in which it considers the application materials submitted. However, the committee may also supplement the data material in the application based on its members' own clinical experience, knowledge about evidence in the area and any supplementary analyses performed by the Danish Health Technology Council secretariat. The expert committee's evaluation of the materials submitted will be based on the evaluation design that has been established for the health technology examined.

The expert committee will also assess whether each of the four aspects – Clinical effectiveness and safety, Patient perspective, Organisational implications, and Health economics – have been sufficiently covered in the application. Because the evaluation design reflects the core outcome and specific context of the individual health technology, balancing the four aspects cannot be standardized to fit all topics within the broad remit of the Danish Health Technology Council.

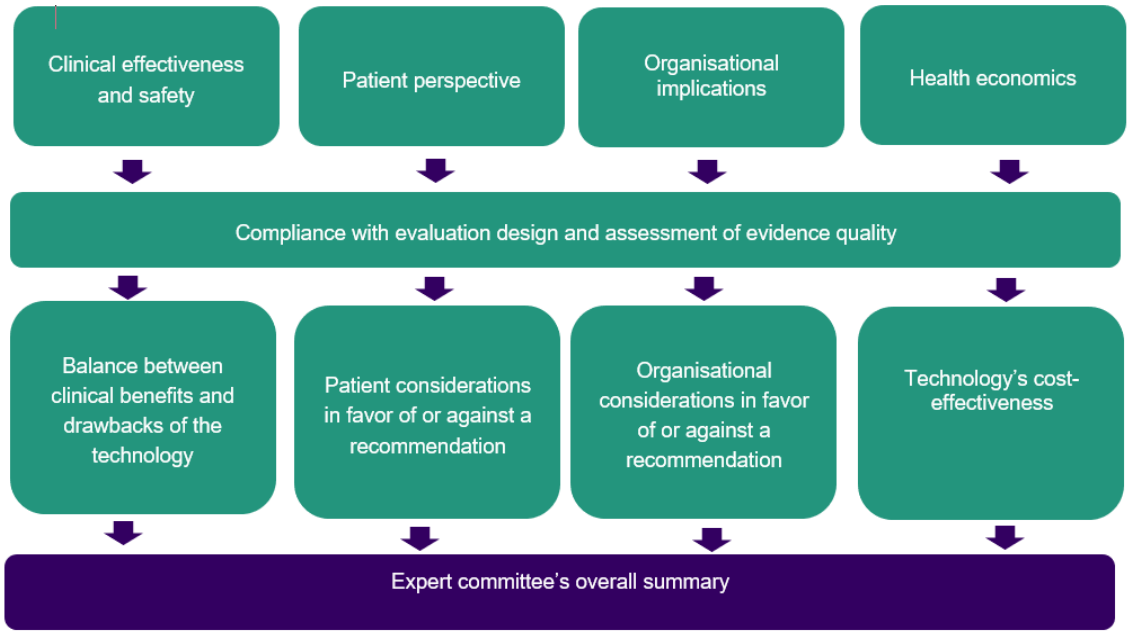

Figure 6 – Overview of the process for preparing the expert committee's summary of the evaluation.

Figure 6. Overview of the process for preparing the expert committee's summary of the evaluation.

In its review of the application's results with regard to clinical effectiveness and safety, the expert committee will consider specifically whether the observed differences in outcome can be considered to be clinically relevant. This requires the expert committee to identify minimal clinically important differences for each of the reported outcomes.

When possible, the expert committee will specify the minimally clinical important differences already in advance (in the evaluation design), but in some situations the expert committee may deem that the minimal clinically important differences should not be determined until in the assessment report. The

minimal clinically important differences will be used again in the expert committee's assessment of evidence quality, see GRADE.

The expert committee bases its quality assessment of the materials submitted on the instruments listed in Table 4.

Table 4 - Tools for quality assessment of evidence.

Secondary literature	**Type of evidence**	**Tool for assessment of quality**	
	Systematic Reviews	AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews) [14]	
	Guidelines / existing HTA-reports	AGREE-II (Appraisal of Guidelines for Research & Evaluation Instrument). See section 5.6 for futher information on the use of this type of evidence. [15]	
Primary literature	**Type of evidence**	**Risk of bias**	**Quality of evidence**
	Randomised Controlled Trials (RCT)	RoB version 2 (Cochrane Risk of Bias tool version 2) [16]	GRADE (Grading of Recommendations Assessment, Development and Evaluation) [6]
	Observational studies of interventions	ROBINS-I (Risk of Bias In Non-randomized Studies of interventions) [17]	
	Studies of diagnostic accuracy	QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) [18]	
	Type of evidence	**Methodological quality**	**Quality of qualitative evidence synthesis**
	Qualitative studies	CASP (Critical Appraisal Skills Programme) qualitative studies checklist [19]	GRADE-CERQual (Confidence in the Evidence from Reviews of qualitative research) [20]
	Type of evidence	**Methodological quality**	
	Cross-sectional studies	AXIS (Appraisal tool for Cross-sectional studies) [21]	
	Mixed methods studies	MMAT (Mixed Methods Appraisal Tool) [22]	
	Health Economic analyses/studies	CHEC (Consensus on Health Economic Criteria) [23]	

In its overall summary in the assessment report, the expert committee will compare and consider the most important findings regarding clinical effectiveness and safety, the patient perspective, the organisational implications, the health economic analysis and the overall quality of evidence in the data material. On the basis of this assessment, the expert committee then prepares an overall assessment of the technology (see Figure 6). The assessment report by the expert committee is passed on to the Council, which will make the final decision on a recommendation.

8 The Council's recommendations

The starting point for the Council's recommendation is the assessment report from the expert committee. The recommendation relies on a comparison of the four aspects and the Council's as well as the expert committee's reflections on these. The recommendations will always be worded with an indication of the specific patient/target population (as a general rule corresponding to the PICO population) and, where relevant, the clinical context covered by the recommendations. The Council provides a summary of the factors decisive in the choice of recommendation.

The sections below describe the possible final recommendations that can be given as a result of the Danish Health Technology Council's evaluations.

8.1.1 The technology is recommended

This option is used when there is sufficient evidence and knowledge to conclude that the health technology:

1. as a minimum can be considered clinically equivalent to the comparator(s) (for the whole or parts of the target group or for the healthcare system as a whole) and is cost-reducing or cost-neutral; or
2. is better than the comparator with regard to its clinical effectiveness (for the whole or parts of the target group or for the healthcare system as a whole) and is cost-reducing, cost-neutral or considered cost-effective.

In its decision, the Council will also include considerations as to whether patient or organisational considerations speak against or in favour of recommending the technology.

8.1.2 The technology is recommended for knowledge acquisition

This option is used when the evidence base is insufficient to decide whether or not to recommend the technology, but the results available are promising. This could be in cases where the data suggests:

1. that the technology may potentially be *significantly* better than existing alternatives (for example if the technology appears superior to the comparator for a number of outcome parameters but more key data is needed about its safety and cost effectiveness), or
2. that the technology may potentially be *highly* cost-effective compared to existing alternatives (for example if the technology appears highly cost-effective but there is insufficient evidence that it is as effective or safe as the comparator).

In the absence of the above, that is when it is *not* probable that the technology may potentially be significantly better or considerably more cost-effective than the comparator, the Council will not recommend use of the technology (section 8.1.3).

In these cases, the company, on its own initiative, may collect data to support the decision basis and reapply based on the new evidence.

The Council will always provide further details on this type of recommendation, for example:

1. The Council does *not* recommend further use of the technology until the results of the ongoing knowledge acquisition process are available.

2. The Council recommends further use of the technology until the Danish Health Technology Council reassesses the recommendation based on the results of the knowledge-acquisition process.
3. Based on the data available, there is no basis for a recommendation in favour or against using the technology during the knowledge-acquisition process (*status quo).*

8.1.3 The technology is not recommended

This option is used when the criteria for recommending use or for recommending knowledge acquisition (see sections 8.1.1 and 8.1.2) are not met.
In other words, when the evidence base is considered sufficient but:

1. the available evidence suggests that the technology examined is inferior to the comparator with regard to its clinical effectiveness, or
2. the available evidence suggests that the technology examined is not cost-effective.

Or in cases where the evidence base is insufficient, and the available data fails to render probable:

1. that through knowledge acquisition, the technology could prove to be considerably better with regard to clinical effectiveness, or
2. that through knowledge acquisition, the technology could prove to be highly cost-effective.

In its decision, the Council will also include considerations as to whether patient or organisational considerations speak against or in favour of recommending the technology.

9 Version log

Version no.:	Date:	Change
2.0	04-07-2023	Restructuring the methods guide. Changes made to PICO-specification, budget impact analysis, and adjustments of sections regarding Patient perspective and Organisational implications.
1.1	16-05-2023	Operationalization of “Product categories” Removal of documentation for the likelihood of cost neutrality/cost saving Minor adjustments concerning core outcome
1.0	03-06-2021 16-04-2021	Approved by the Danish Health Technology Council Submitted for consultation

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