Process and methods guide – how the Danish Medicines Council develops joint regional assessments of the added clinical value of new medicines and new indications
Version 1.1

This translation is based on the Danish document ”Metodehåndbog for Medicinrådets arbejde med at udarbejde fælles regionale vurderinger af nye lægemidlers og nye indikationers kliniske merværdi” (Version 1.1). Please note: The translation is provided as a service by the Danish Medicines Council to English-language readers. In the event of discrepancies, the Danish version prevails.

Content

1. Introduction

1.0 About the process and methods guide

This process and methods guide explains how the Danish Medicines Council assesses the added clinical value of new medicines and new indications (new fields of application of known medicines).

The process and methods guide will provide patients, healthcare professionals and pharmaceutical companies with insight into the work and methods of the Danish Medicines Council. Additionally, the process and methods guide serves as a tool for the various units under the Danish Medicines Council, including the expert committees, the secretariat and the Council.

The process and methods guide comprises:

- A generic time schedule
- Guidance on how to develop the project protocol
- Guidelines on the content of applications from pharmaceutical companies
- Guidelines for the Danish Medicines Council's quality assurance of company applications
- Guidance on how to assess the added clinical value of a new medicine or a new indication.

A first version of this process and methods guide for assessment of the added clinical value of new medicines and new indications was developed by Danish Regions, the RADS secretariat and Amgros with input from the Chair of the Danish Medicines Council. DEFACTUM offered advisory services for the development of the process and methods guide and commented on contributions to the guide.

1.1 What are the tasks of the Danish Medicines Council?

In the spring of 2016, the board of Danish Regions decided to form the Danish Medicines Council. The Council is based on experiences from the Danish Council for the Use of Expensive Hospital Medicines (RADS) and "Koordineringsrådet for ibrugtagning af sygehusmedicin" (KRIS).

The Danish Medicines Council is to:

- Ensure fast and homogeneous use of new and existing medicines across hospitals and regions
- Impose stricter requirements for documentation to support that patients will benefit from new and existing medicines
- Enhance the basis for Amgros' price negotiations and calls for tenders. Amgros is the joint procurement service for the Danish regions and is mostly concerned with procurement of medicines for hospital use.

The Danish Medicines Council assesses:

- New hospital medicines (using the procedure described in this process and methods guide)

- Biosimilar medicines (according to RADS' previous procedure). A biosimilar medicine contains another version of the active substance but is as effective and safe as the original biological medicine.
- Several medicines within the same therapeutic area.

1.2 Distribution of responsibilities in the Danish Medicines Council

The Medicines Council consists of three units: The Council, the secretariat and the expert committees. The roles are distributed as follows when it comes to developing the joint regional assessments of the added clinical value of new medicines and new indications:

- *The Council* issues recommendations concerning the use of new medicines and new indications as standard treatment.
- *The Secretariat* has the overall responsibility for the methodological procedures/methodology and assists the various expert committees and the Council.
- *Expert committees* assist in the medical assessment of new medicines and new indications and produce drafts of classification of the added clinical value.

1.3 Joint regional assessments of the added clinical value of new medicines and new indications

Pharmaceutical companies can ask the Danish Medicines Council to assess new medicines and new indications (except for generic products and biosimilar products) under the following categories:

- Medicines only to be distributed to hospitals (BEGR)
- Medicines only to be distributed to hospitals and dispensed only once on the same prescription (AP4BG)
- Medicines only to be distributed to hospitals or prescribed by selected specialist physicians (AP4NB)
- Medicines only to be distributed to hospitals or prescribed by specialist physicians as determined by the Danish Health Authority on a case by case basis (NBS).

These four groups of distribution fall within the scope of the price-cap agreement concluded between the Danish Association of the Pharmaceutical Industry (Lif), the Ministry of Health and Danish Regions in 2016.

All new medicines and new indications go through this process. This applies to all cases, be it use of the medicine to treat a rare condition; expectations of modest sale of the medicine; applicant expecting no added clinical value; or the existence or non-existence of treatment guideline for the therapeutic area.

When the Danish Medicines Council recommends use of a medicine for standard treatment, the medicine concerned will be introduced as a standard offer to a group of patients and the medicine will be accessible through the hospital departments.

Generally, the Danish Medicines Council's recommendations of new medicines are established through three processes:

- A medical assessment and classification of the added clinical value to patients of the new medicine or the new indication.
- An economic assessment of the added costs per patient and an assessment of the impact on the overall budget of recommending the medicine.
- A negotiation to ensure a reasonable relationship between the added costs and the added clinical value of the medicine and to determine the conditions for public procurement of the medicine.

Generally, the Danish Medicines Council's recommendations of new indications are established through two processes:

- A medical assessment and classification of the added clinical value to patients of the new medicine or the new indication
- An economic assessment of the added costs per patient and an assessment of the impact on the overall budget of recommending the medicine.

The medical assessment involves a systematic evaluation of the added clinical value of the new medicine or new indications compared to one or more comparators (medicines used to treat the same group of patients). Thereby the added clinical value constitutes the scientific and clinical arguments supporting the extra clinical value the new medicine offers compared to existing treatments.

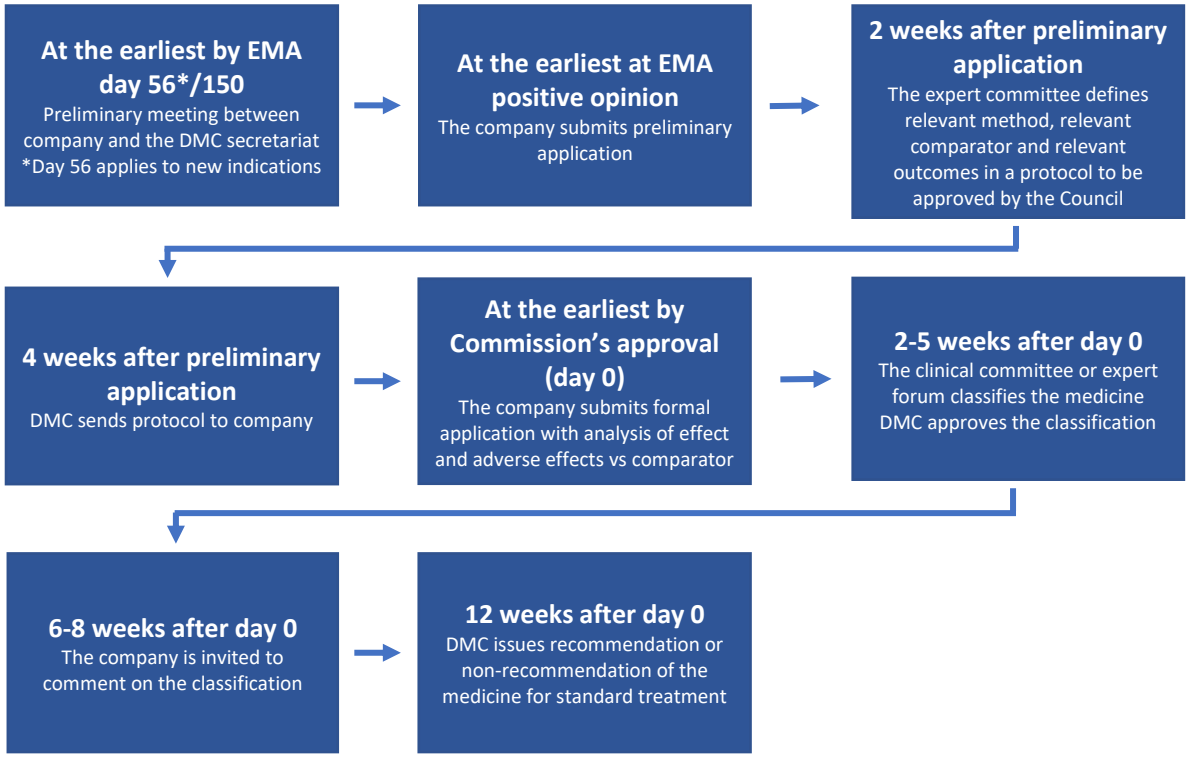
The added clinical value is classified as follows:

- Category 1: High added clinical value
- Category 2: Important added clinical value
- Category 3: Low added clinical value
- Category 4: No added clinical value
- Category 5: Negative added clinical value
- Category 6: Non-documentable added clinical value

Generally, the process follows these steps:

- The applicant and the Danish Medicines Council convene at a preliminary meeting.
- The applicant submits a preliminary application.
- The Danish Medicines Council develops a project protocol.
- The applicant submits a final application.
- The Danish Medicines Council conducts a quality assessment of the clinical part of the final application.
- The Danish Medicines Council classifies the added clinical value of the new medicine/new indications.
- The applicant is invited to comment on the classification of the added clinical value.
- Amgros validates the applicant's cost analyses and estimate of budget consequences.
- Amgros and the applicant negotiate.
- The Danish Medicines Council determines whether to recommend the new medicine or new indication as standard treatment.
- The regions implement the recommendation.
- Amgros monitors the use of the medicine.

The below figure illustrates the general time frame of the process.



The Danish Medicines Council can instigate a "clock-stop". This might, for example, take place if the external stakeholders do not comply with the deadlines, or if the quality of the final application warrants the Danish Medicines Council to carry out literature searches and analyses in-house.

2. Preliminary meeting and preliminary application

2.1 Preliminary meeting

The applicant may initiate an assessment process by asking for a preliminary meeting with the secretariat. For new medicines, the earliest time for a preliminary meeting is by day 150 of the approval procedure conducted by the European Medicines Agency (EMA). For new indications, the earliest time for a preliminary meeting is at EMA day 56.

The applicant and the secretariat will address the following issues at the meeting:

- The medicine
- Mechanism of action
- Relevant clinical studies (including subgroup analysis and comparator)
- Expected indication
- Expected time of EMA's recommendation to approve the medicine (positive opinion)
- Expected time of final application
- Expected dispensers in Denmark (only hospitals or not) etc.

If requested by the applicant, the secretariat can provide information about the process and method used by the Danish Medicines Council when assessing new medicines.

2.1.1 Expert committees

Following the preliminary meeting, the secretariat convenes the individuals who will conduct the clinical and the patient-related aspects of the assessment. The Danish Medicines Council can use existing expert committees or set up new expert committees to assess the new medicines and indications.

2.2 Preliminary application

When EMA has issued a recommendation for approval (positive opinion), the applicant can submit a preliminary application. The preliminary application should address the items discussed at the preliminary meeting (see section 2.1). The preliminary application may total a maximum of ten A4 pages. The expert committee will discuss the protocol based on the preliminary application.

3. Development and approval of the protocol

The joint regional assessments of the added clinical value of new medicines are developed according to a protocol. The secretariat collaborates with the expert committee to develop the protocol. The protocol is approved by the Chair of the Danish Medicines Council.

The protocol contains the following elements:

- Clinical questions with detailed PICO descriptions (see section 3.1).
- Weighting of all outcomes ("critical" vs "important" vs "less important") and an a priori definition of the minimal clinically important difference in absolute terms for the individual outcomes.
- A general search protocol.

The secretariat develops a draft of the protocol before the first meeting in the expert committee. At the first meeting, the expert committee discusses the draft to ensure that the protocol addresses relevant clinical problems.

In the process of developing the protocol, the secretariat and the expert committee familiarize themselves with the preliminary application in order to take into consideration the available data for the given medicine. The comparator chosen will, however, always depend on the standard treatment used in the Danish health sector. In the event of inconsistency between the comparator used in clinical studies of the medicine and the comparator selected by the Danish Medicines Council, it may prove necessary to conduct an indirect comparison in the assessment of the added clinical value.

The protocol forms the basis of:

- The subsequent final application from the pharmaceutical company
- The secretariat's quality assurance and adjustment, if applicable, of the final application
- The classification.

The approved protocol will be shared with the applicant immediately following approval. The protocol will be shared in writing and also in person, upon request from the applicant. Further, the protocol will be made available on the website of the Danish Medicines Council.

3.1 Focused questions and relevant PICO

For the purpose of assessing the added clinical value of the medicine, the expert committee must predefine the clinical question(s). For each of the clinical questions the intended group of patients, the interventions (the medicines under scrutiny), the comparators (the medicines compared with) and the outcomes will be defined. This is abbreviated PICO (Population, Intervention, Comparison and Outcomes).

Population: Definition of the disease/condition and the group of patients featuring the relevant characteristics, such as performance status. The populations for whom the assessment of the added clinical value of the medicine concerns will depend on the indication that is expected for the medicine and any questions concerning subgroups.

Intervention: The definition of the intervention, which is the new medicine. This includes describing the various potential applications of the intervention (such as dose, form of administration etc.) and which of these to be included in the assessment.

Comparison: The definition of the alternative(s) to the new medicine. Since the Danish Medicines Council is tasked with assessing the added clinical value of new treatments, the choice of comparator will be in line with which medicine is the genuine alternative in daily clinical practice, as determined by the expert committee.

Outcome: Definition and weighting of the outcomes used to assess the added clinical value of the medicine and the definition of minimal clinically important differences.

3.1.1 Choice of clinical outcomes

Outcomes can be clinical events (such as death, disease progression, stroke) and other patient-relevant outcomes (such as symptoms, quality of life, functional ability). Relevant adverse effects must always be included. Relevant outcomes related to adverse effects could for example be discontinuation due to adverse events or bleeding related to the medicine.

In addition to determining the outcomes of relevance to the assessment, the expert committee should also suggest how the outcomes can be measured.

Further, it is essential to determine the relevant time periods. This is critical, since both efficacy and adverse effects can vary considerably over time. Thus, it can be of great importance whether one chooses to evaluate the new medicine over six weeks, months or years. Since clinical studies often look at new medicines over a relatively short period of time, the aspect of time in relation to the outcomes will depend on the follow-up times used in the studies. The Danish Medicines Council does not model the effects in time periods extending the follow-up time used in the clinical studies. This means that the assessment of the added clinical value of the medicine is an expression of the actual effect observed during the follow-up time and not future efficacy and adverse effects.

The expert committee makes the final choice and weighs the outcomes (critical vs important vs less important) according to the GRADE approach (see section 6.4.1). Using this approach, the weight of each outcome determines how great significance the outcome will have on the final classification of added clinical value of the new medicine.

The weight of specific outcomes varies from one disease area to another (for example, prolonged survival time will be critical in some instances and quality of life in others, whereas mitigation of non-severe although very frequent adverse effects will be critical for some disease areas).

The final application should include and describe results for all critical and important outcomes and the classification will be based on these. The results of less important outcomes need not be described, nor form the basis of the classification.

Additionally, the protocol will state which of the four categories the individual outcomes belong to since this is important for classification purposes (see section 6.3.1):

- All-cause mortality

- Severe symptoms and adverse effects
- Health-related quality of life
- Non-severe symptoms and adverse effects.

3.1.2 Health-related quality of life as outcome

Health-related quality of life constitutes an outcome in the overall assessments of the added clinical value of new medicines and new indications. The Danish Medicines Council preferably uses data from generic instruments and only makes use of disease-specific instruments in very selected cases.

3.1.3 Use of surrogate outcomes

Use of surrogate outcomes (an outcome that serves to substitute a clinical outcome) is only relevant when data on a clinically important outcome is unavailable. A relationship between a surrogate outcome and a clinical event must be evident and documented. Consequently, based on the epidemiological, pathophysiological, therapeutic or other scientific evidence, the surrogate outcome should be expected to predict clinically important effects.

When using surrogate outcomes instead of clinical outcomes, the confidence in the evidence must be down-graded one level (according to GRADE, grading of evidence (see section 6.5.2)). The reason for this is that the evidence is indirect and it is not 100% certain that the surrogate effect predicts the clinical effect.

Generally, the Danish Medicines Council accepts progression-free survival (PFS) as a critical outcome and this would not be considered a surrogate outcome for overall survival (OS) in cases when EMA (the European Medicines Agency) has accepted PFS as the primary outcome during the approval process.

3.1.4 Definition of minimal clinically important differences

Once the expert committee has defined "critical" and "important" outcomes, it is essential that the committee considers and makes a predefinition of the minimal clinically important difference for individual outcomes. This predefinition should be specified in the protocol. Determination of clinically important differences is often a difficult process. However, making a predefinition of clinically important differences is essential in order to avoid subjective ad hoc decisions based on, for example, the available evidence. Validated catalogues exist of "clinically important differences" for a limited number of therapeutic areas and outcomes. These are based on evidence from questionnaire surveys in the patient group.

A universally accepted and validated method that can be used to search for clinically important differences does not exist. It is essential that the final threshold of clinically important differences is defined by the expert committee.

The minimal clinically important difference expresses the difference of the effect that determines whether the well-informed patient or clinician selects one medicine instead of another.

For binary outcomes (such as dead or alive), the clinically important difference is often expressed as a reduction of risk. At the same time, the definition of a clinically important difference will depend on the specific outcome.

For continuous outcomes (such as severity of pain), the clinically important difference is often expressed in one of two ways: either as an average difference for the total group of patients or as the share of patients whose benefit of the treatment will exceed the clinically important difference.

If the difference of an effect is equivalent to or larger than the minimal clinically important difference the medicine has an added clinical value (category 1-3) for this outcome.

3.2 Search strategy

The expert committee describes the literature search strategy in the protocol by specifying databases, search terms, and delimitation of the literature regarding study design and publication languages.

Generally, the literature search is based on searching for published randomised controlled trials through Medline.

In addition to this, the applicant must consult the European Medicines Agency's Scientific Discussion, both as regards the new medicine and the comparator. This is to ensure that there are no inconsistencies between EMA's report and the identified, published data. In some cases, EMA's assessment offers important information, especially about the adverse effect profile of the concerned medicines. The applicant may add other relevant data for use in the assessment process. The applicant must state arguments in favour of the data in the event of inconsistencies between published data and EMA's Scientific Discussion.

3.2.1 Types of study design

Generally, the Danish Medicines Council only makes use of randomised controlled trials to assess differences in the effect between treatments. The reason for this is that randomised controlled trials have the most valid research design for assessing effect differences between various treatments. If EMA's approval of the new medicine and the new indication deviates from this, the Danish Medicines Council will consider including data from studies of other research designs.

4. The final application

Once the European Commission has granted authorization to market the new medicine, the company may submit the final application.

4.1 Joint application form

To facilitate the process, the applicant completes a joint application to the Danish Medicines Council and Amgros. When the Danish Medicines Council has received the final application, the Council provides Amgros with the basic information about the applicant and the cost analysis. The final application form is an Excel file comprising three separate sheets.

Sheet 1: Basic information (for the Danish Medicines Council and Amgros)

- Contact information
- Generic name and proprietary name of the medicine
- Marketing authorization holder
- Pharmacotherapeutic group, active substance, pharmaceutical form, ATC code (the ATC system is a system for classification of medicine products according to substance and mechanism of action)
- Mechanism of action
- Therapeutic indication
- Dosage regimen including pre-treatment and combination therapy, if applicable
- Route of administration, including treatments per year/therapeutic schedule and frequency of administration
- Type of packaging, size of packaging in units and strength of medication
- General description of patient group and division into subgroups as specified in the protocol:
    - Incidence
    - Prevalence
    - Average weight/surface area, if applicable
    - Gender
    - Age.

Sheet 2: Clinical evidence (for the Danish Medicines Council)

- Selection of evidence
- List of study characteristics for included studies
- List of baseline characteristics for the patients in the clinical studies
- List of results per outcome for included studies
- Comparative analysis (direct or indirect) for individual outcomes based on the included studies (HR, OR or RR for all outcomes).

Sheet 3: Cost analysis (for Amgros)

- Cost analysis
- Estimate of budget consequences.

4.2 Selection of evidence

The company searches for and selects literature according to the protocol. The final application must comprise a description of the search strategy used to identify literature. In the final application, the applicant must also state reasons for why studies were excluded, both when excluded at title and abstract level, and when excluded after reading the full text.

The description of the search strategy ensures transparency and should entail sufficient level of detail to enable replication of the search leading approximately to the same result. The identified literature must be sorted and assessed following each search. This means that the studies must be compared with the PICO (see section 3.1) described in the protocol. The applicant must provide a PRISMA flow diagram illustrating the number of references identified, the number excluded and the reasons for exclusion.

The final application must describe all deviations from the protocol stating reasons for each deviation.

4.3 List of study characteristics

In the final application, the applicant must provide a table with descriptions of the study characteristics of all included studies. The study characteristics comprise among others:

- Study design
- Intervention and comparator
- Follow-up period (follow-up)
- Number of randomised patients
- Patient inclusion and exclusion criteria
- Other relevant information.

4.4 List of baseline characteristics for the patients

In the final application, the applicant must provide a table with descriptions of the baseline characteristics of included patients. The disease area will determine which information is relevant and the line of treatment concerned etc. Baseline characteristics may comprise the following data:

- Age
- Performance status
- Previous treatment
- Distribution by gender
- Organ function

4.5 Data extraction

By data extraction is meant how to extract relevant information from studies. What relevant information is, is defined in the protocol by the focused questions and PICO (see section 3.1). The applicant must provide the extracted data in the application form.

4.6 Comparative analysis

In the final application, the company must offer a comparative analysis of the new medicine and the comparator for all outcomes possible. If one or more studies exist that compare the new medicine and the selected comparator, these studies can be used to assess the added clinical value. If several studies present the same type of data, it would be an advantage to make a meta-analysis.

If the Danish Medicines Council has selected another comparator than the one the applicant used in comparative clinical trials, the applicant must search for studies that describe the effect and adverse effects of the comparator for a relevant group of patients (cf. PICO). Using this data, the applicant must make an indirect comparative analysis. The method to be chosen (for example adjusted indirect analysis or network meta-analysis) depends on the available data. The applicant must decide which method is appropriate considering the identified data. It must be possible for the secretariat to assess the quality of all meta-analyses and indirect comparisons. For this reason, it is important that the application describes the key choices made regarding the analysis. The results of the comparative analysis must be stated in absolute and relative effect measures (RR, HR or OR).

If a statistical comparative analysis is deemed inappropriate, the applicant must provide a narrative analysis and explain the reasons for the choice.

5. The Danish Medicines Council assesses the final application

The secretariat and the expert committee conduct a quality assessment of the final application. They may contact the applicant if the application is inadequate. If the applicant is unable to provide relevant information, the secretariat may conduct literature search, data extraction and comparative analysis again. This instigates a clock-stop of the process. Of course, the applicant will be notified of this.

6. The Danish Medicines Council classifies the added clinical value

A core aspect of assessing new medicines is to classify the added clinical value.

The added clinical value is classified as follows:

- Category 1: High added clinical value
- Category 2: Important added clinical value
- Category 3: Low added clinical value
- Category 4: No added clinical value
- Category 5: Negative added clinical value
- Category 6: Non-documentable added clinical value

The following is a description of the method used in the classification process.

The expert committee assesses the added clinical value. The assessment is based on the following four elements:

- Weighting of outcomes (critical and important)
- Assessment of the absolute effect of the medicine compared to the clinically important differences
- Assessment of relative effect measures compared to the inferential thresholds.
- Critical appraisal of the evidence.

The added clinical value of the medicine is first assessed for individual outcomes. Then an overall assessment is made in order to reach the final classification.

6.1 How the Danish Medicines Council weighs outcomes

Outcomes are weighed in the protocol as described in section 3.1.1. In the composite assessment of the added clinical value (the classification), the added clinical value of the critical outcomes will weigh heavier than the added clinical value of the important outcomes. If, contrary to expectations, it is necessary to deviate from the weighting predefines in the protocol, this must be described and justified reasons must be given.

6.2 How the Danish Medicines Council assesses differences in the absolute effect estimates

The protocol defines the minimal clinically important difference for individual outcomes. The expert committee compares the results of the comparative analysis with these definitions to assess whether the magnitude of the effect of each outcome represents an added clinical value; meaning whether the effect meets the minimal clinically important difference when compared to the effect of the comparator. Only if the minimal clinically important difference is achieved, can the expert committee classify the effect of the individual outcomes as having an added clinical value (category 1-3). Consequently, the variation in the classification of the added clinical value will primarily depend on the magnitude of the difference between the absolute effect and the minimal clinically important difference as assessed by the expert committee.

When the Danish Medicines Council assesses the added clinical value based on health-related quality of life measures, the difference in the absolute effect weighs more. The reason for this is that the Danish Medicines Council does not apply inferential thresholds to the effect estimates of quality of life measurements.

6.3 How the Danish Medicines Council assesses relative effect measures

6.3.1 Inferential thresholds

The expert committee uses the point estimate and the confidence interval (safety limit) from the comparative analysis when assessing the relative effect measures for individual outcomes. If the upper limit of the confidence interval of the point estimate is below the inferential threshold, the effect of this particular outcome is given a preliminary classification (see table below listing inferential thresholds).

During the protocol phase, each of the outcomes is classified according to the following four categories:

- All-cause mortality
- Severe symptoms and adverse effects
- Health-related quality of life
- Non-severe symptoms and adverse effects.

The inferential threshold depends on the type of outcome concerned. Generally speaking, to achieve a high added clinical value the most severe outcomes must fulfil less stringent demands than the less severe outcomes. The inferential thresholds are based on the threshold values of relative effect measures as defined by the Institute for Quality and Efficiency in Healthcare, IQWIG (*General Methods - Version 4.2. IQWIG. April 2015*).

The table lists the specific inferential thresholds for categories 1-3 for each group of outcomes. Since health-related quality of life is not assessed using the inferential thresholds, the table will not show this.

			Inferential thresholds per group of outcomes*		
			All-cause mortality	Severe symptoms and adverse effects	Non-severe symptoms and adverse effects
Preliminary category	1	High added value	0.85	0.75 and risk ≥5 %[a]	Not possible
	2	Important added value	0.95	0.90	0.80
	3	Low added value	1.00	1.00	0.90

* In order to qualify for the preliminary category, the upper threshold of the confidence interval of the relative effect measure (relative risk, odds ratio or hazard ratio) may not exceed the significance criterion.
[a] The risk must be > 5% for at least one of the compared groups.

The table shows that the demands for moderate and high added clinical values are lower for all-cause mortality than for severe adverse effects and symptoms. Any statistically significant

reduction in all-cause mortality or severe symptoms and adverse effects will, as a minimum, be assessed as a low added clinical value. This is reflected in the upper limit of the confidence interval which does not exceed 1.00. For the difference to result in a Category 1 – High added value classification, the risk must be > 5% for at least one of the compared groups for both all-cause mortality and severe symptoms and adverse effects. With this, the prevalence in the general population is of importance to the classification.

A reduction in non-severe symptoms and adverse effects can never result in a Category 1 – High added value classification. Here, the inferential threshold starts at 0.90. This means that even statistically significant differences where the upper confidence limit exceeds 0.90 must be classified as having no added clinical value.

By using the upper limit of the confidence interval as a starting point for the preliminary classification, the uncertainty of the point estimate is partly taken into consideration. In some cases, there are valid explanations for why confidence interval is wide (such as ethical or practical reasons why the medicine was tested on a relatively small group of patients, or if the follow-up period for the study is long). Consequently, the confidence interval must always be compared to the point estimate when allocating the category for the added clinical value of individual outcomes.

6.3.2 Categories 4-6

Outcomes whose upper limit of the confidence interval exceeds the inferential threshold for category 3, are categorised as having no added clinical value compared to the comparator. Consequently, such outcomes can only be classified as categories 4-6:

- Category 4: No added clinical value compared to standard treatment/other treatments (documentable equal clinical value of treatments)
- Category 5: Negative added clinical value compared to standard treatment/other treatments (documentable negative added clinical value of new medicine)
- Category 6: Non-documentable added clinical value compared to standard treatment/other treatments (scientific evidence is not appropriate for quantifying effect differences)

Category 4 will be relevant when the upper limit of the confidence interval overlaps 1.00 (equivalent to a non-significant difference between the two medicines). If the confidence interval is entirely above 1.00, the comparator is statistically significantly better than the new medicine. This allows the effect to be classified in category 5. In some cases, the evidence of an added clinical value of individual outcomes will be so modest that an assessment cannot determine whether the medicine does in fact provide an added clinical value for the patients compared with already existing treatments, that is the comparator. In such cases, the classification will be category 6.

6.4 How the Danish Medicines Council assesses the added clinical value of individual outcomes

The added clinical value of the medicine for individual outcomes is classified as follows.

1. The estimated difference of the effect in absolute values is compared with the minimal clinically important difference as defined in the protocol. If the effect is identical to or

better than the minimal clinically important difference, the medicine can be classified as having an added clinical value (category 1-3).

2. For the estimated relative effect measures (HR, OR or RR), the upper limit of the confidence interval is compared to the inferential thresholds to assess where the relative effect measure places the preliminary category. The width of the confidence interval is assessed in relation to the point estimate, and the expert committee evaluates whether significant factors influencing the width of the confidence interval warrants a change in the preliminary categorization.
3. The final category of the individual outcome is determined by considering the assessments of both the absolute effect difference relative effect measures.

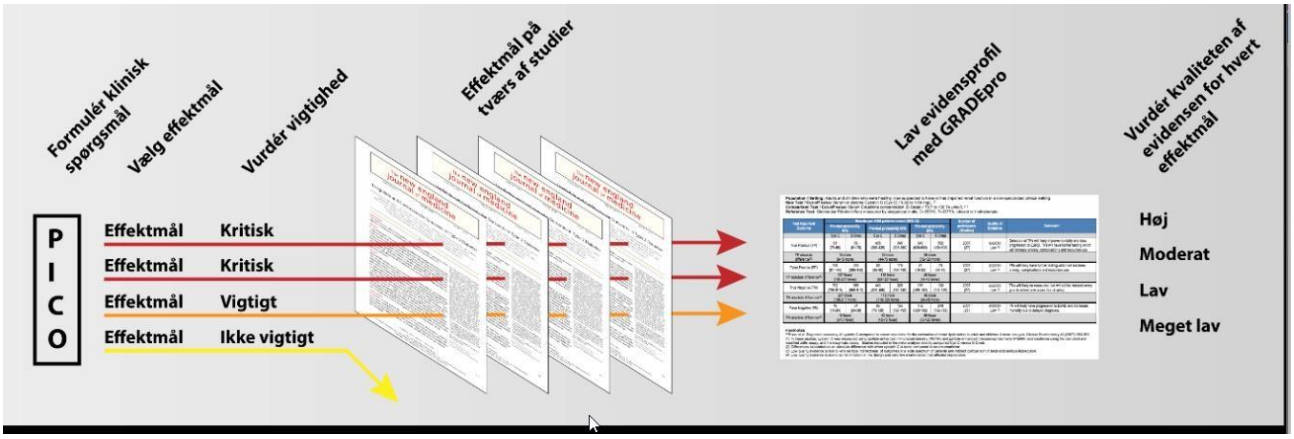
6.5 How the Danish Medicines Council assesses the quality of evidence

When the added clinical value of the medicine has been classified for each outcome, the secretariat and the expert committee assess the quality of the provided evidence.

In this context, quality of evidence means *the confidence in the estimated effect*. For this purpose, the Danish Medicines Council uses the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation system). The GRADE approach is an internationally applied system used, among others, to assess the quality of evidence and establish the strength of recommendations in a systematic and transparent manner. When the Danish Medicines Council assesses the added clinical value of new medicines, only elements of GRADE related to rating of the quality of evidence are used.

6.4.1 General information about the GRADE approach

The GRADE approach differs from other evidence assessment tools in that the quality of evidence is assessed for individual outcomes across studies. This means that all available data from the included studies is collected for the individual outcomes, and the quality of the total volume of evidence is assessed for the outcome – and not separately for each study. Once the quality of the evidence has been assessed for the individual outcomes, the overall quality of evidence for the clinical question can be assessed. This is done by considering the quality for the individual outcomes and the importance of the outcomes. When assessing the added clinical value of new medicines, the quality of evidence expresses the degree of certainty of the classification.



The evidence is assessed across five domains:

- Risk of bias
- Inconsistency
- Imprecision
- Indirect evidence (indirectness)
- Risk of publication bias.

If the domain weakens the confidence in the evidence slightly, the evidence is downgraded one level (for example from moderate to low). If the domain weakens the confidence in the evidence substantially, the evidence is downgraded two levels (for example from high to low). Generally, we have confidence in the evidence provided by randomised controlled trials. The assessment is presented using an evidence profile.

Below is a brief presentation of GRADE and how the tool is used for the assessment of the added clinical value of new medicines. For further details, please visit the website of the GRADE working group. This website provides links to a series of articles in the Journal of Clinical Epidemiology presenting the various aspects of the GRADE process (see www.gradeworkinggroup.org).

6.4.2 The five domains used to assess the quality of evidence

Risk of bias
The Cochrane Risk of Bias Tool is used to assess the risk of bias for both randomised controlled trials and observational studies.

The Cochrane Risk of Bias Tool for randomised studies assesses the risk of bias based on:

- The method of randomisation/allocation
- The degree of blinding (blinding of patients, investigators and/or outcome assessors)
- Handling of missing data
- Selective reporting of results (lack of data on primary and secondary outcomes)
- Other forms of risk of bias in the included studies.

The Cochrane Risk of Bias Tool for observational studies assesses the risk of:

- Failure in developing and applying appropriate inclusion criteria
- Flawed measurements of exposure and outcomes
- Failure to adjust for confounding
- Incomplete follow-up in study.

Inconsistency
An inconsistency is an inexplicable and significant difference in the effect estimate across studies. When the secretariat and the expert committee assess inconsistency, they use the relative effect estimate (HR, RR or OR). Inconsistency may for instance be caused by differences in the characteristics of the patient populations, interventions, treatment in the control group, or definition of effects. If the secretariat and the expert committee are unable to identify a natural explanation to the differences of the effect estimates, the quality of evidence is downgraded.

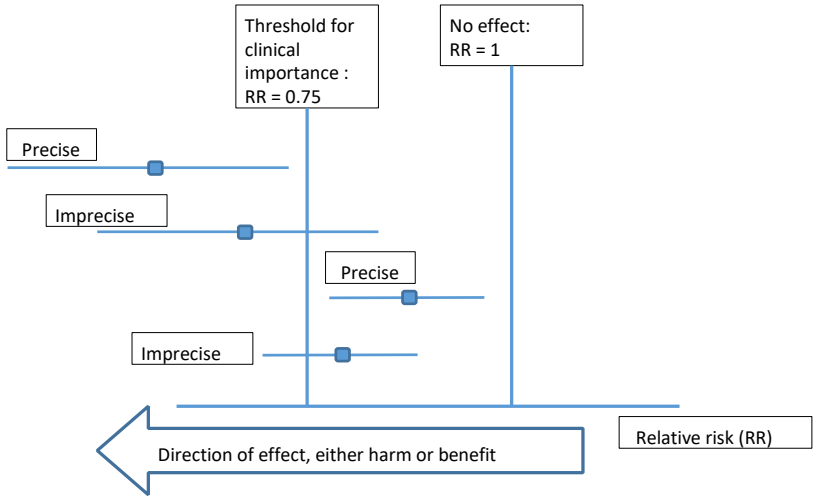
Indirect evidence (indirectness)

The evidence may be considered indirect for two reasons:

1. Two medicines which were supposed to be compared to each other have only been compared with placebo or other treatment.
2. There are differences in the characteristics of the patient population, the intervention, the control group, or the way in which the effects were measured between the clinical question and the studies.

If the evidence does not relate directly to the clinical question, the quality of the evidence is downgraded.

Imprecision
The secretariat and the expert committee assess whether the confidence interval overlaps the minimal clinically important difference and whether they would reach different recommendations at each end of the confidence interval. If the effect estimate is imprecise, meaning the confidence interval is wide, the quality of the evidence is downgraded.



Publication bias
The evidence is downgraded if there are signs of publication bias (lack of publication of entire studies) or selective reporting of effects (only the most positive effects are reported).

6.4.3 Definition of the confidence in individual effect estimates

Before the overall assessment is made of the quality of the evidence, the evidence is assessed for the individual outcomes. GRADE operates with four levels of quality of evidence:

High (⊕⊕⊕⊕)
We are very confident that the true effect lies very close to the estimated effect.

Moderate (⊕⊕⊕◯)
We are moderately confident of the estimated effect. The true effect is likely to be close to the estimated effect but it might be substantially different.

Low (⊕⊕◯◯)

We have limited confidence in the estimated effect. The true effect may be substantially different from the estimated effect.

Very low (⊕○○○)
We have very little confidence in the estimated effect. The true effect is likely to be substantially different from the estimated effect.

6.4.4 How the overall quality of the evidence is assessed

When the confidence in the individual effect estimates has been assessed for individual outcomes, the secretariat and the expert committee assess the overall confidence in the evidence across outcomes. The overall assessment is determined by the outcomes defined as critical. Generally, the overall level of evidence is determined according to the critical outcome with the lowest rating.

6.5 Overall assessment of the added clinical value

The overall classification of the added clinical value of the medicine is partially a qualitative process where the expert committee compares the classifications of the individual outcomes in order to form an overall view of the effects and adverse effects of the medicine and the effect on health-related quality of life compared to the comparator. In the overall classification, the individual classifications of the critical outcomes will be given a higher weight than the important outcomes. The expert committee describes the assessment in a detailed and transparent manner, stating reasons for the final categorisation.

Along with the category of added clinical value of the medicine, the expert committee also indicates the level of confidence in the evidence. The classification can look like this example:

- **Category 2** ⊕⊕⊕○ **-** The assessment is that the medicine offers patients an important added clinical value compared to standard treatment. The evidence supporting this classification is of moderate quality.

If particularly good reasons exist why information other than the preliminary categories for the individual outcomes should be considered, very good arguments and a clear description must be provided. One case could be that there are well-founded reasons to believe that the clinical effect is either higher or lower in daily clinical practice due to a high degree of indirect evidence from the clinical studies (for example due to a highly-selected study population).

All considerations used in the overall classification of the added clinical value of the medicine will be described in a similar transparent manner in the Danish Medicines Council's report.

7. Approval of the report on added clinical value

The Danish Medicines Council secretariat compiles and writes a draft of the final report on the joint regional assessment of the added clinical value of new medicines. The expert committee provides comments, edits the draft and approves the final draft report and classification which is then presented to the Council at a meeting.

When the Council has approved the report and the classification, the applicant is invited to comment on the classification. The expert committee discusses the comments of the applicant and considers whether to make changes to the arguments and/or classification. If the comments from the applicant leads to changes in the classification, the Council must discuss the revised report at a meeting. Changes in the report with no impact on the classification can be discussed by e-mail.

The Danish Medicines Council publishes the report when it has been finally approved. The Danish Medicines Council also publishes the version of the report prior to comments, the comments of the applicant and the final application (without confidential data, if applicable).