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Process and methods guide – how the Danish Medicines Council assesses several medicines within the same therapeutic area

Version 1.1

This translation is based on the Danish document ”Metodehåndbog for Medicinrådets vurdering af flere lægemidler inden for samme terapiområde” (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 the procedures of the Danish Medicines Council when assessing several medicines within the same therapeutic area. The assessment forms the foundation for the joint regional treatment guidelines.

The process and methods guide will provide patients, healthcare professionals and pharmaceutical companies with insight into the work of the Danish Medicines Council. The guide also serves as a tool for the various units under the Danish Medicines Council (see section 1.2).

The process and methods guide comprises:

- A model showing how the Danish Medicines Council develops joint regional treatment guidelines, including a general time schedule.
- Guidelines on how the Danish Medicines Council develops project protocols.
- Guidelines on how the Danish Medicines Council searches for and assesses literature.
- Guidelines on how the Danish Medicines Council uses selected methodological tools in their work with evidence to form the foundation of the final joint regional treatment guidelines.

The model on how to develop joint regional treatment guidelines 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. The methodology described in the guide builds on the model for development of national clinical guidelines [Model for udarbejdelse af Nationale Kliniske Retningslinjer, Metodehåndbog version 2.1] issued by the Danish Health Authority. It has been adapted to suit the Danish Medicines Council's area of work and processes.

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 builds on experience 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 supporting that patients will benefit from new and existing medicine
- 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 medicine for hospital use.

The Danish Medicines Council assesses:

- New hospital medicines (according to the method described in the publication "Process and methods guide – how the Danish Medicines Council develops joint regional assessments of the added clinical value of new medicines and new indications")
- 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 Danish Medicines Council consists of three units: The Council, the secretariat and the expert committees. The roles are distributed as follows between the three units when it comes to developing the joint regional treatment guidelines:

- *The Council* approves recommendations for decision-making, commissions, project protocols and the joint regional treatment guidelines.
- *The secretariat* has the overall responsibility for adherence to the method and assists the various expert committees and the Council.
- The expert committees assist in the medical assessment of medicines in a therapeutic area and produce a draft for the joint regional treatment guidelines.

1.3 Joint regional treatment guidelines

The Danish Medicines Council determines which therapeutic areas to develop joint regional treatment guidelines for, based on one or more of the following criteria:

- Does this medicine constitute a significant cost for the hospitals?
- Is this medicine characterized by a steep growth in expenditures?
- Could the quality of the treatment within this therapeutic area be enhanced, and does a joint regional consensus seem to be required?

The Danish Medicines Council develops the joint regional treatment guidelines, which include the medical assessment of the medicines compared. This means that the guidelines constitute the scientific and clinical argumentation of the following:

- Which medicines will be regarded as equivalents (typically limited to 1st to 3rd line of treatment)
- Who to treat with the medicines
- Which criteria to use for initiation of treatment
- Which criteria to use for changing treatment, including changing of medicines to patients already being treated
- How and how often to measure effects and adverse effects
- Which criteria to use for discontinued treatment

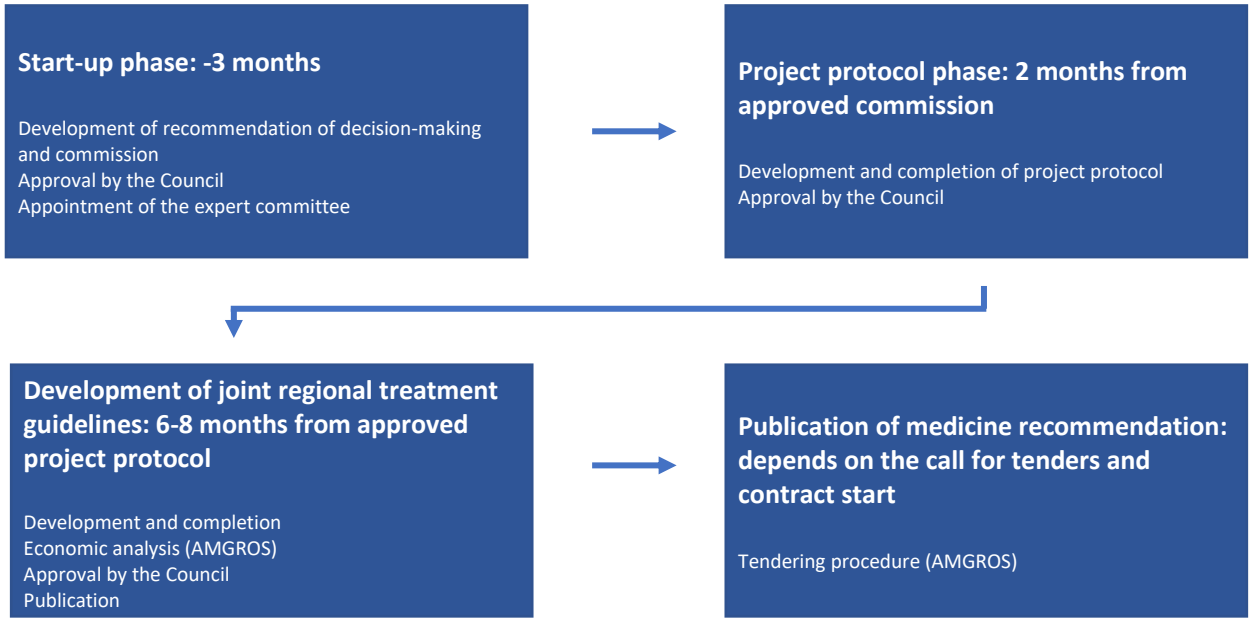
Generally speaking, these are the steps followed by the Danish Medicines Council when it assesses several medicines within the same therapeutic area:

- The Danish Medicines Council develops recommendations for decision-making and commissions for the expert committees.
- The Danish Medicines Council develops a project protocol.
- The Danish Medicines Council develops the joint regional treatment guidelines.
- Amgros develops an economic analysis.
- Amgros calls for tenders.
- The Danish Medicines Council develops the medicine recommendation.
- The regions implement the medicine recommendation [lægemiddelrekommendation].
- Amgros monitors the use of the medicine.

The project protocol and the joint regional treatment guidelines are developed according to the GRADE approach. The GRADE approach (Grading of Recommendations Assessment, Development and Evaluation system) is an internationally applied system used to assess quality of evidence and make recommendations. Generally, the approach comprises the following components:

1. Development of clinical questions and structured questions (PICO) (see section 3.1)
2. Systematic literature search
3. Selecting literature
4. Assessment of the risk of bias
5. Summary of results
6. Assessment of confidence in the estimates
7. Production of a medicine recommendation

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



Development of joint regional treatment guidelines

The following section describes the development of joint regional treatment guidelines. You can read about the preparations, the project protocol, the process of development and finalisation of the development process. You can also read about the players involved and all processes, step by step.

2 Preparing the work

2.0 Who can propose and initiate an assessment of a therapeutic area?

Everybody (the regions, professional bodies, patient associations, the pharmaceutical industry or citizens) can propose that a therapeutic area should be assessed. The secretariat considers the proposal, and employs external expertise if needed, to determine whether the proposal meets the specified criteria (see section 1.3) and how to delimit the therapeutic area, if applicable. The secretariat then makes a recommendation for decision-making and presents it to the Council. The Council makes the final decision: Whether to develop joint regional treatment guidelines within the therapeutic area and whether to establish an expert committee.

2.1 The responsibilities of the expert committee

During the process, the expert committee is to:

- Select and formulate the clinical and PICO questions (see section 3.1) in the project protocol that will be used to produce the treatment guidelines.
- Provide search terms for the literature search strategy to ensure relevant literature is not overlooked. An information specialist develops the search strategy together with the secretariat project group.
- Validate the literature to ensure that all relevant aspects are covered. This takes place after the secretariat project group has made an initial sorting of the identified literature.
- Validate the AGREE II assessment (see section 4.2.1) of relevant existing guidelines developed by the secretariat project group.
- Validate the AMSTAR assessment (see section 4.2.2) of relevant systematic reviews developed by the members of the secretariat project group.
- Validate the risk of bias assessment of the primary literature developed by the secretariat project group.
- Critically read the draft and final version of the joint regional treatment guidelines.
- Provide input to an introduction and background section for the therapeutic area, including patient populations and patient basis.
- Provide input to a description of the characteristics of the medicines assessed and input to the management of the medicines concerned.
- Produce guideline recommendations and a clinical basis of comparison [klinisk sammenligningsgrundlag] that forms the basis of the medicine recommendation [lægemiddelrekommendation].

- Provide input on how to monitor use of the medicine.

The expert committee typically convenes between four and six times. The Chair of the expert committee heads the work of the committee. The members of the expert committee must expect having to undertake the comprehensive task of reviewing and validating the efforts of the secretariat regarding existing relevant literature between meetings. Typically, the deadline for commenting on the draft of the treatment guidelines will be short – especially towards the end of the process.

2.2 The responsibilities of the secretariat

The Danish Medicines Council provides a project group in the secretariat to support the expert committee. This project group consists of a project and method manager, health sciences officers and a coordinator. The project and method manager is the primary contact for the expert committee members and is responsible for ensuring that all processes follow a systematic approach according to the prescribed methods and that the process adheres to the given timeframe and deadlines. The coordinator books meetings and is responsible of proofreading and publication of documents.

2.3 The role of the pharmaceutical companies

After publication of the approved protocol, the Danish Medicines Council invites the relevant pharmaceutical companies to submit relevant literature. At a later stage of the process, individual companies and the expert committee may convene giving the company an opportunity to answer specific questions from the expert committee regarding the company's medicine. In case of such meeting the expert committee provides the individual companies with the questions in writing at least 15 working days before the actual meeting.

3. The project protocol

3.0 Development of the project protocol

Assisted by the secretariat, the expert committee develops a project protocol. The purpose of developing and publishing a project protocol is to facilitate a stringent and transparent process.

The following components must be included in the project protocol:

- A concise description of the disease and the current clinical management of the disease
- A concise description of the characteristics of the medicines
- Reasons why joint regional treatment guidelines should be developed
- The clinical questions with detailed PICO descriptions (see section 3.2)
- Weighting of outcomes (critical vs important)
- A preliminary definition of the minimal clinically important differences for individual outcomes
- A general list of criteria for the selection of evidence, including which study designs are to be included (inclusion and exclusion criteria)
- Reasons whether a specific literature search on patient values and preferences is included or excluded.
- A preliminary search strategy including which databases are to be searched
- A description of which data will be extracted and how

The protocol must be approved by the Council. The approved project protocol will be published at the website of the Danish Medicines Council.

In the following sections, you can read more about clinical questions and the relevant PICO descriptions and about the definition of the minimal clinically important differences.

3.1 The clinical questions and relevant PICO

Joint regional treatment guidelines contain selected and carefully defined clinical questions concerning aspects of the use of medicines. Often the most important aspect is the choice between medicines within the same therapeutic area, including whether the medicine should be used at all for a given group of patients. However, the aspect could also concern whether to use the medicine for various severities or stages of a disease, deciding on initiation of treatment, discontinuation of treatment and change of treatment, including change of medicines for patients already undergoing treatment.

The intended group of patients, the interventions (the medicines under concern), the comparators (the medicines compared with) and the outcomes will be defined for each of the

clinical questions. 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. If relevant, there must also be a preliminary definition of subgroups.

Intervention: Definition of the interventions, that is the medicines within the therapeutic area. The different variations of the interventions (such as dose, form of administration etc.) are described under this heading and it is specifically stated which variations of each medicine the assessment entails. If medicines exist that have been approved for a group of patients but are not included in the treatment guidelines (for example because they are regarded to be outdated), the expert committee must provide a description and reasons for this exclusion.

Comparison: Definition of the alternatives to the concerned interventions. Since the Danish Medicines Council will often compare all the interventions listed, these same medicines comprise the comparators too. The expert committee may include placebo treatment as a comparator when the effect of the intervention is uncertain or if no direct comparisons of the interventions exist (that is through indirect comparisons). If there is wide agreement that the intervention works, the expert committee should compare with the standard treatment or another form of intervention.

Outcome: Definition and weighting of the outcomes used to assess the medicines and the definition of the minimal clinically important differences.

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.

In addition to this, it is essential to determine the relevant time periods of the intervention. This is critical, since both efficacy and adverse effects can vary considerably over time. Thus, it can be of great importance whether the medicines are evaluated over a period of six weeks, months or years. The Danish Medicines Council does not model effects in time periods that extend beyond 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 effect observed during the follow-up period and not future effects 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 assessment of the medicines.

The weight of specific outcomes varies from one disease area to another (for example, prolonged survival time are critical in some instances and quality of life in others, whereas

mitigation of non-severe although very frequent adverse effects are 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 guideline recommendations.

3.1.1 Health-related quality of life as outcome

In the assessment of medicines, The Danish Medicines Council preferably uses data from generic instruments and only makes use of disease-specific instruments in very specific cases.

3.1.2 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). The reason for this is that 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.

3.2 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. The 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, for example, on 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 in 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.

4. Joint regional treatment guidelines

4.0 Development of joint regional treatment guidelines

After approval and publication of the protocol, the development of the joint regional guidelines starts.

As mentioned before, the process follows the GRADE approach, which generally comprises the following components:

1. Formulating clinical questions and relevant PICO descriptions
2. Systematic literature search
3. Selecting literature
4. Assessment of the risk of bias
5. Summary of results
6. Assessment of confidence in the estimates
7. Development of guideline recommendations.

4.1 Systematic literature searches

The secretariat search specialist, the project and method manager and the expert committee conduct and validate the literature search as described in the protocol.

4.1.1 Effect and adverse effects

Generally, the Danish Medicines Council only considers randomised controlled trials when describing the differences in effect of various treatments. The reason for this is that randomised controlled trials are regarded as the most valid method when it comes to assessing the differences in the effect of various treatments. The randomised studies can be included either in the form of primary literature or systematic review articles and if possible from guidelines. If there is an insufficient selection of randomised controlled trials to answer the clinical questions, observational studies are considered (database studies).

The search for evidence is an iterative 3-step process: To begin with, the search aims to identify existing guidelines, which should undergo a quality assessment, and which can be included if of high quality. If existing guidelines are of a low quality, the secretariat will do a systematic search to identify review articles and primary literature. If the guidelines and systematic review articles included are not updated, the secretariat will update the search.

For each clinical question, the literature search will usually go back five years to identify guidelines and systematic review articles, unless the period has to be delimited or further extended. This might for example happen in case of significant technological developments within the area. If the identified guidelines do not answer the clinical questions, a systematic search will be carried out to identify review articles and primary literature. When searching for primary literature, the search period is delimited in accordance with the clinical questions and the development within the therapeutic area. Reasons must be given for the

delimitation. The search processes must be documented using search strings, dates and selected databases.

4.1.2 Patient values and preferences

For each joint regional treatment guideline, a search is conducted for literature that describes patient values and preferences to the medicine treatments within the therapeutic area. Evidence regarding this area is often limited and to compensate for this the searches must be broad, for example by including study designs other than randomised studies.

4.1.3 Pharmaceutical companies and expert committees can add literature

As mentioned above, the pharmaceutical companies are invited to submit literature relating to their own medicine product. Likewise, the expert committee can add supplementary literature that was not identified in the search. Literature that is relevant based on the requirements in the project protocol is then included in the assessment on equal terms with the literature found in the systematic literature search.

4.2 Selecting literature

Following each search, the secretariat sorts and assesses the identified literature with the assistance of the expert committee.

The secretariat sorts the identified references at the level of titles and abstracts. The references are then read as full texts. In consultation with the expert committee, references that are considered relevant are included for the critical appraisal process. Below is outlined how the secretariat and the expert committee critically appraise guidelines, systematic review articles and primary literature.

After completion of the literature search and sorting process, a flow diagram (PRISMA) is produced to show the number of references identified and which ones were excluded for what reason.

4.2.1 Tools used to assess guidelines

The secretariat project group conducts a critical appraisal of all selected guidelines, and the expert committee validates the appraisal. The guidelines are appraised using domain 3 ”Rigour of development” in the AGREE II tool (http://www.agreetrust.org).

Source of supplementary references
The guideline can be used if it covers the relevant clinical questions.

Source of searches
The guidelines can be used, if:

- Systematic methods were used to search for evidence.

- The criteria for selecting the evidence are clearly described.

Source of evidence assessments
The guidelines can be used, if:

- Systematic methods were used to search for evidence.
- The criteria for selecting the evidence are clearly described.
- The strengths and limitations of the body of evidence are clearly described.
- There is an explicit link between the recommendations and the supporting evidence.

Source of estimates
The guidelines can be used, if:

- Meta-analyses have been conducted.
- Systematic methods were used to search for evidence.
- The criteria for selecting the evidence are clearly described.
- The strengths and limitations of the body of evidence are clearly described.
- There is an explicit link between the recommendations and the supporting evidence.

4.2.2 Tools used to assess systematic review articles

The project group conducts a critical appraisal of selected systematic review articles, and the expert committee validates the critical appraisal. Systematic review articles are appraised using the AMSTAR tool (http://amstar.ca/).

Source of supplementary references
The review article can be used provided it covers the relevant clinical questions.

Source of searches
The review article can be used, if:

- A comprehensive literature search was performed.
- The selection criteria are clearly described.

Source of evidence assessments
The review article can be used, if:

- A comprehensive literature search was performed.
- The quality of the included studies was assessed and the assessment documented.
- The selection criteria are clearly described.

Source of estimates
The review article can be used, if:

- A comprehensive literature search was performed.
- Meta-analyses have been conducted.
- The methods chosen for data synthesis were appropriate.

4.2.3 Tools used to assess primary studies

The risk of bias in randomised controlled trials as well as observational studies is assessed using the Cochrane Risk of Bias Tool (http://handbook.cochrane.org/).

4.3 Summarizing the evidence

The sections above describe how to identify and critically appraise the references to be included in the evidence that forms the basis for the joint regional recommendations. In the next section, we outline how the evidence is extracted and summarized.

4.3.1 Data extraction

The purpose of data extraction is to collect relevant information from the references included.

The project group extracts data and the expert committee validates it. Data is presented in overviews containing:

- study characteristics
- baseline characteristics for the patients
- results for individual outcomes.

4.3.2 Comparative analysis

If more than one comparative study exists, a meta-analysis is conducted of the outcomes if methodologically appropriate. The principles for meta-analyses are given in the Cochrane Handbook for Systematic Reviews of Interventions.(http://handbook.cochrane.org/). If there are no available comparative studies, data can be synthesized indirectly (for example by a network meta-analyses).

Indirect comparisons from randomised studies are not randomised comparisons but, in reality, observational results across studies and as such should be assessed carefully in terms of bias. Whenever the Danish Medicines Council has both indirect and direct evidence for a comparison, the expert committee should primarily rely on the results from the direct comparisons. One exception could be if the study design of the direct evidence is extremely flawed.

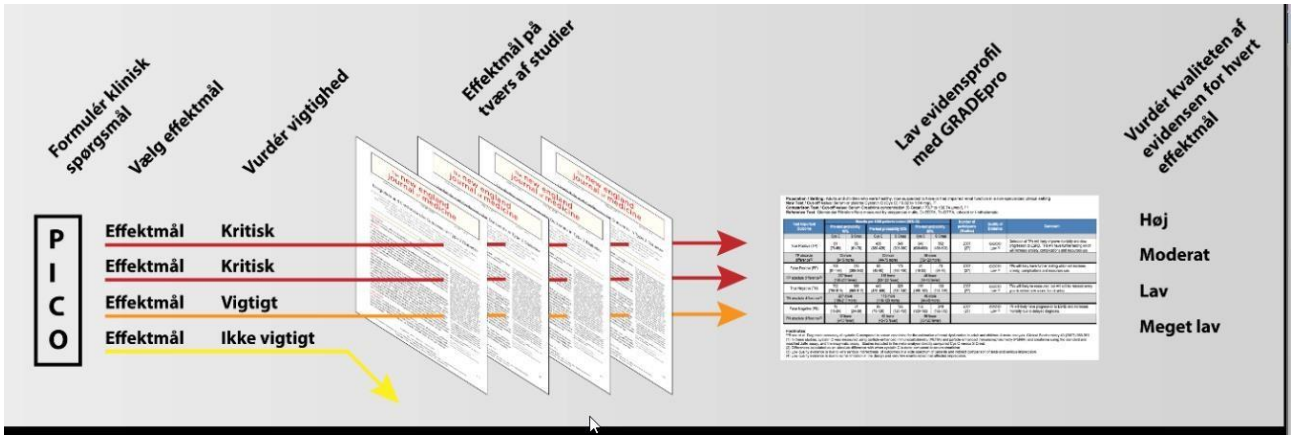
If meta-analyses cannot be conducted (including network meta-analyses), the data is synthesized in a narrative manner. Reasons must be given for the choice of synthesis method.

4.4 Assessment of quality of evidence

When the literature has been summarized, the secretariat and the expert committee assess the quality of the evidence.

Here, quality of evidence means *the confidence in the estimated effect*. As already mentioned, the GRADE approach is used for this purpose. The following sections offer a brief presentation of GRADE and how the tool is used as part of joint regional treatment guidelines. For more 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).

The GRADE approach differs from other evidence assessment tools in that the quality of the 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 – 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 evaluating the quality for the individual outcomes considering the importance of each.



The evidence is assessed across within 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.

The evidence from well-conducted observational studies can be upgraded one or two levels if an assessment of these domains speaks in favour of it:

- Size of the effect
- Dose response
- Confounding.

The secretariat and the expert committee assess the individual domains. If the domain improves the evidence slightly, the evidence is upgraded one level (for example from low to moderate) and if it improves the evidence substantially, it is upgraded two levels (for example from low to high).

The assessments of the quality of the evidence are presented in an evidence profile.

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.

4.4.1 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 studies included.

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.

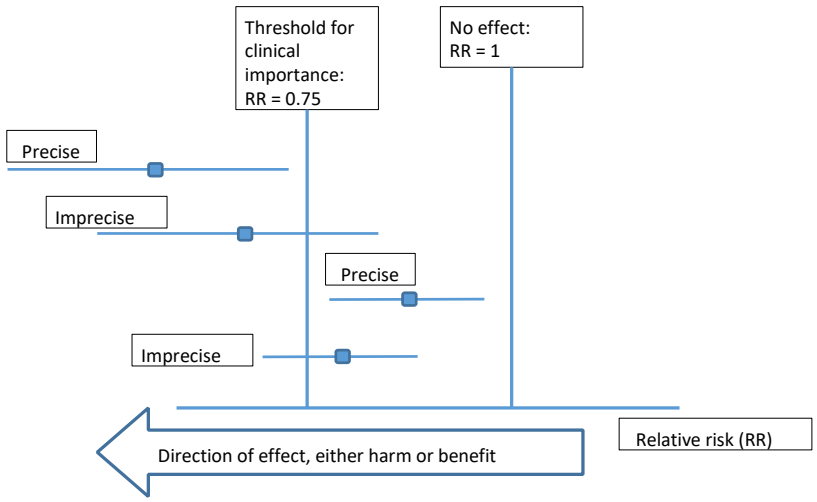
Inconsistency
An inconsistency is an inexplicable and significant difference in the effect estimate across studies. When the secretariat and the expert committee assess inconsistency, they use the relative effect measures (HR, RR or OR). Inconsistency may for instance be caused by differences in the 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 (lacking publication of entire studies) or selective reporting of effects (only the most positive effects are reported).

Size of the effect

The evidence can be upgraded one level if an observational study indicates a large effect, and two levels if the effect is very large. This is relevant in the highly extraordinary cases when the relative difference between the groups is between a factor 5 and 10.

Dose response
If an observational study indicates a clear link between dose and response, the evidence can be upgraded.

Confounding
If confounding in an observational study indicates an underestimation of the effect, the evidence can be upgraded. Confounding is a variable or a factor that may "confuse" the investigator and which may contribute to an over- or underestimation of the effect.

4.4.2 Assessment of the overall quality of evidence

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. Generally, the overall quality of evidence is determined according to the critical outcome with the lowest quality.

4.5 Writing recommendations

GRADE recommendations can be in favour (positive) or disfavour (negative) of a given intervention. The strength of the recommendation may be either strong or low. This distinction will depend on the balance between beneficial and harmful effects, the confidence in the estimates effects, patient values and preferences and, if applicable, practical matters.

The Danish Medicines Council uses the following wordings in the recommendations:

- A strong positive recommendation is characterised by "Use" [Anvend].
- A weak positive recommendation is characterised by "Consider" [Overvej].
- A weak negative recommendation is characterised by "Do not use on a routine basis" [Anvend ikke rutinemæssigt].
- A strong negative recommendation is characterised by "Do not use" [Anvend ikke].

If two or more interventions are given the same recommendation for the same (sub)populations, they should be considered as being clinically equivalent. Generally, the Danish Medicines Council will categorise medicines to be equivalents when there is no reasonable cause to think that there are clinically important differences between the assessed medicines.

To the extent possible, recommendations must rely on evidence; but even if the evidence is ambiguous, the expert committee must formulate a recommendation based on the other aspects used in the assessment. In such cases, the wording

used in the recommendations will be "Good clinical practice" [God klinisk praksis]. For example, a change between analogue medicines for carefully selected patients will only be recommended if it is considered safe from a medical perspective.

Use for xx% of the group of patients
This recommendation is used when the composite sum of the benefits of the intervention is thought to clearly surpass the harm for a certain percentage of the given population.

Consider
The expert committee uses this recommendation when the benefits of the medicine surpass the harms, or when available evidence cannot exclude that the medicine offers an important benefit. In parallel with this, the expert committee will assess whether the adverse effects are few or absent. This recommendation is also used when patient values and preferences vary.

Do not use on a routine basis
The expert committee uses this recommendation when the harm of the medicine, in the expert committee's opinion, surpasses the benefits, but where this cannot be supported by strong evidence.

The Danish Medicines Council also uses this recommendation when there is evidence of both beneficial and harmful effects but where the mutual balance is difficult to determine. This recommendation is also used when the patients exhibit a difference in preferences.

Do not use
The expert committee uses this recommendation if high quality evidence shows that the composite harm of treatment with the medicine clearly surpass the benefits.

The Danish Medicines Council will also formulate a strong recommendation against use when review of the evidence shows that the intervention most likely will be useless.

The quality of the evidence provided
In addition to the recommendation, the quality of evidence is illustrated as being

- High (⊕⊕⊕⊕)
- Moderate (⊕⊕⊕◯)
- Low (⊕⊕◯◯)
- Very low (⊕◯◯◯)

4.6.1 From evidence to recommendation

The expert committee must conduct a systematic discussion of the thoughts supporting the recommendations. The thoughts concerning the balance between beneficial and harmful effects, the confidence in the estimated effects, patient values and preferences and, if applicable, practical matters, must be presented in a systematic, detailed and transparent manner.

The intention is to ensure a transparent decision-making process. Therefore, interested parties must be able to study the outcomes that the expert committee chose to emphasize; which patient preferences were taking into account; etc.

If a weak recommendation is given despite strong confidence in the evidence, the expert committee must also elaborate its reasoning. The same applies for strong recommendations in the event of low confidence in the evidence.

4.6.2 Clinical comparison report

The expert committee describes equivalent medicines in clinical basis of comparison. The clinical basis of comparison must be used in the subsequent economic analysis and calls for tenders. The report must state the number of doses and the sizes required for the various medicines to be regarded as equivalents within a clinically important period of time. The description must also state how to administer the medicines. If, for example, a given tablet is available in different strengths and the Danish Medicines Council recommends use of only a single strength, the report must detail how to administer the recommended dose.

5. Conclusion of the work

The secretariat project group compiles and writes the final version of the joint regional treatment guidelines. The Chair and the rest of the expert committee members comment on, edit and approve the finished joint regional treatment guidelines, which are then approved by the Council.

The Council convenes between eight and ten times a year. At these meetings, the Chair and/or selected members of the expert committee present the joint regional treatment guidelines for its approval.

The Danish Medicines Council publishes the joint regional treatment guidelines on its website no later than ten working days after the council meeting where it was approved.

Medicine recommendations

The Danish Medicines Council makes medicine recommendations [lægemiddelrekommendationer] based on comparative economic analyses for equivalent medicines. These recommendations state the order of priority of clinically equivalent medicines based on their total costs. A medicine with a low clinical rating will never be awarded a higher priority in the medicine recommendation solely due to low total costs compared with a medicine with a higher clinical priority.

The medicine recommendations are also published at the website of the Danish Medicines Council.