Medicinrådet

Population, intervention, comparator(s) and outcomes

Guideline

Version 1.0

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1. Background

The PICO approach (population, intervention, comparator and outcomes) is applied to ensure a systematic and transparent approach to evidence assessment when new drugs are evaluated.

2. Patient population

The patient population must fall within the indication of the new drug, but narrowing of the population may be necessary to reflect Danish clinical practice. Applicants should consult Danish clinical guidelines and previous assessments by the Danish Medicines Council in the therapeutic area, including any treatment initiation criteria in earlier recommendations.

If there are subgroups of patients who will have different treatment pathways in Danish clinical practice or who respond differently to the drug, the applicant must describe and present subgroup data. The applicant must also describe relevant diagnostic tests and examinations required to select patients for treatment.

3. Intervention

The applicant must describe the drug (the intervention) based on the study or studies informing the health economic analysis. If the intervention deviates from the summary of product characteristics (e.g., lower dose or earlier discontinuation), this must be described.

4. Comparator

Information on the current standard treatment in Danish clinical practice may be described in guidance from the Danish Medicines Council, guidelines from the relevant medical societies, clinical departments, and/or other sources. If there is no treatment alternative for the disease in Danish clinical practice, the comparator will typically be supportive care or no treatment.

If the available studies of the new drug's effectiveness and safety do not use a comparator relevant to Danish clinical practice, the applicant must perform an indirect comparison; see the Danish Medicines Council's guidance on clinical effectiveness and safety. If the introduction of the new drug leads to changes in the overall treatment pathway (e.g., subsequent lines of therapy), the applicant must describe the expected changes. In some cases, the comparator and/or the intervention may be a sequence of treatments.

As a general principle, the submission must include all comparators relevant to Danish clinical practice. If the applicant chooses not to compare with one or more relevant comparators, this must be described and justified.

Each comparator must be included individually. This means that, as a general rule, the applicant should not combine data for two or more treatment alternatives and report, for example, average effect or average costs in the health economic analysis.

In cases where the Danish Medicines Council has determined that several treatments are equivalent, it may be sufficient to compare the intervention with only one of the equivalent comparators.

In cases where the comparator in the study of the new drug's effectiveness consists of one of several treatment alternatives (e.g., "investigator's choice"), it will not always be possible or appropriate to present the alternatives individually. If such treatment alternatives are used as individual comparators, the applicant must describe and justify this.

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

If the comparator has not previously been assessed and recommended by the Danish Medicines Council, the applicant must conduct two health economic analyses: one using the comparator that reflects current Danish clinical practice, and one using a comparator that can reasonably be assumed to be cost-effective. This may, for example, be supportive care or no treatment.

This applies, for example, when the comparator is a drug that entered clinical use in Denmark before the establishment of the Danish Medicines Council on 1 January 2017. The supplementary analysis is required because the existing comparator is not necessarily a cost-effective treatment. If the comparator is not cost-effective, a comparison between the new drug and the comparator will not provide a valid estimate of the new drug's cost-effectiveness.

If the comparator can be considered established Danish treatment practice and the costs associated with the comparator are low, the applicant may omit the supplementary analysis using another comparator. The applicant may consult the Danish Medicines Council to obtain guidance prior to submission of the application.

5. Outcomes

The primary outcome in the study or studies on which regulatory approval is based must always be included in the submission. Health-related quality of life and safety are also always relevant outcomes. Results must be presented for all outcomes used in the health economic model. As a general principle, outcome data must be presented with the longest possible follow-up.

In indirect comparisons, clearly state any differences in the definition of outcomes across studies. Indicate how such differences are handled in the comparison and their implications for interpreting the results.

5.1 Surrogate outcomes

A surrogate outcome can be defined as a substitute for a direct measure of the patient's physical and/or mental well-being, functioning, or survival. In general, the use of surrogate outcomes in assessing an intervention's effect is associated with considerable uncertainty, as the relationship between the treatment effect on the surrogate outcome and the patient-relevant outcome of primary interest may be difficult to demonstrate [1], and the use of surrogate outcomes is often associated with overestimated effect sizes [2].

The applicant must present evidence for the validity of the surrogate outcomes used. The Danish Medicines Council assesses whether a surrogate outcome can be used based on an overall judgement using the evidence hierarchy below (inspired by Ciani et al. 2017 [3]).

- Level 1: A relationship between effect on the surrogate outcome and effect on the patient-relevant outcome is demonstrated in a meta-analysis of RCTs in the population under assessment.
    - 1a: RCTs of drugs in the same pharmacological class as the drug under assessment.
    - 1b: RCTs of drugs in a different pharmacological class.
- Level 2: Observational studies of the surrogate outcome in relation to the patient-relevant outcome.
    - 2a: Evidence for an effect of the surrogate outcome on the patient-relevant outcome (e.g., Mendelian randomisation studies).
    - 2b: Evidence of an association between the surrogate outcome and the patient-relevant outcome.
- Level 3: Only evidence of a biologically plausible relationship between the surrogate outcome and the patient-relevant outcome (e.g., pathophysiological studies or understanding of the disease process).

6. References

1. Guidance on outcomes for joint clinical assessments. Member State Coordination Group on HTA; 2024.

2. Ciani O, Buyse M, Garside R, Pavey T, Stein K, Sterne JAC, et al. Comparison of treatment effect sizes associated with surrogate and final patient relevant outcomes in randomised controlled trials: meta-epidemiological study. BMJ. 2013;346(jan29 1):f457–f457.

3. Ciani O, Buyse M, Drummond M, Rasi G, Saad ED, Taylor RS. Time to Review the Role of Surrogate End Points in Health Policy: State of the Art and the Way Forward. Value Health. 2017;20(3):487–95.

7. Version log

Version	Date	Revision
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