Medicinrådet

Analyses of Clinical Effectiveness and Safety

Guideline

Version 1.0

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1. Comparative analyses of effectiveness and safety

Where possible, the intention-to-treat estimand [1] should be used for effectiveness analyses unless another estimand is necessary to ensure relevance to Danish clinical practice. When alternative estimands are applied, these must be justified and described — for example, adjustment for crossover from placebo to the new drug may be relevant if the new drug is not used in Danish clinical practice.

Analyses should, wherever possible, be based on a randomised controlled trial (RCT) that directly compares the company's drug with the relevant comparator used in Danish clinical practice (head-to-head). If no RCT with a direct comparison exists, the applicant may conduct an indirect comparison through a common comparator (anchored analysis). If no RCT data with a common comparator — or no RCT data at all — are available, the company may conduct an unanchored indirect comparison or a naive indirect comparison. The applicant must describe and justify the assumptions underpinning the chosen method.

1.1 Meta-analyses with direct comparison

If several RCTs include direct comparisons, the applicant must aggregate the results in a meta-analysis, provided that the assumptions required for such a method are met [2]. The company must demonstrate in the submission that the included studies are sufficiently comparable to be combined in a meta-analysis.

1.2 Indirect comparisons

If no RCT data with a direct comparison between the intervention and the relevant comparator(s) are available, the company must conduct an indirect comparison. For indirect comparisons where studies for the intervention and comparator share a common comparator, anchored methods must be used, as these rely on relative effects and are therefore less dependent on strong assumptions than unanchored methods. These include Bucher's method, network meta-analyses (NMA), and anchored Matching-Adjusted Indirect Comparison (MAIC). An NMA should, as far as possible, include only studies of the company's new drug and the selected comparator(s). If the applicant performs an anchored MAIC, the applicant must demonstrate that adjusting for differences in effect modifiers reduces bias compared with indirect comparisons without adjustment (e.g., Bucher's method), by showing that effect modifiers exist and that they are sufficiently unbalanced to influence the relative treatment effect. The submission must describe how potential effect modifiers were identified and which effect modifiers were adjusted for. Any important effect modifiers that could not be

adjusted for must also be described. In situations where the intervention and comparator cannot be compared indirectly using an anchored analysis, the company may compare data from single-arm clinical studies or from individual arms of RCTs. Where possible, the company must conduct statistical analyses that adjust for all relevant between-study differences — for example, an unanchored MAIC or a simulated treatment comparison (STC). Unanchored comparisons must adjust for both effect modifiers and prognostic variables. If the evidence base for the intervention and/or comparator is too sparse, or if there are other reasons why an indirect comparison between the drugs is not appropriate, the company must provide a descriptive naive comparison between the intervention and the comparator. In all cases, the applicant must justify the chosen methods and describe the strengths and limitations of the analyses. Data, methods, and analyses must be documented in such a way that transparency is ensured at every step from raw study data to final results.

2. Subgroup and sensitivity analyses

2.1 Subgroup analyses

The applicant may submit subgroup analyses if these are considered relevant for the Danish Medicines Council's assessment — for example, if the applicant seeks assessment for a subgroup of patients within the indication. The Danish Medicines Council may also request subgroup analyses that are relevant for Danish clinical practice. In such cases, the applicant must present both patient characteristics and subgroup results. Results for subgroups must be reported as both relative and absolute differences

2.2 Sensitivity analyses

Applicants should present sensitivity analyses for the most important outcomes in cases where there is substantial doubt regarding the assumptions of the primary analysis, e.g., analyses with an alternative approach to handling missing data. For further considerations regarding multiplicity and sensitivity analyses, see the EU-HTA guidelines [3].

3. Safety

The submission must include safety data from the same studies used to document effects for both the intervention and the comparator(s). If there are data from a pooled safety population which is substantially larger than that included in the clinical effectiveness study, these data should be used as supplementary information — for example, to describe rarer serious adverse events.

The submission must include data on adverse events of significant clinical and/or economic importance. As a general rule, safety data must be presented irrespective of assumed causality with the treatment, i.e., adverse events (AE) and treatment-emergent adverse events (TEAE). For estimates concerning overall safety — for example, the proportion of serious adverse events — both the absolute and relative differences between the intervention and comparator must be reported. The submission must also include one or more tables showing the most frequently observed adverse events, including event frequency and severity. There must be consistency between the adverse event data reported in the safety section of the submission and the safety data used in the health economic analysis.

4. References

1. Hernán MA, Robins JM. Per-Protocol Analyses of Pragmatic Trials. N Engl J Med. 2017;377(14):1391–8.

2. Practical Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons. Member State Coordination Group on HTA; 2024.

3. Guidance on reporting requirements for multiplicity issues and subgroup, sensitivity and post hoc analyses in joint clinical assessments. Member State Coordination Group on HTA; 2024

5. Version log

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1.0	February 19th 2026	Approved and published.

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