MSR160

Optimizing Patient-Reported Outcomes in German HTA: Addressing Key Challenges and Methodological Requirements

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Background

Patient-reported outcomes (PRO), particularly those related to health-related quality of life (HRQoL), are essential in the German benefit assessment (AMNOG process). The Federal Joint Committee (G-BA) mandates the inclusion of HRQoL data in benefit dossiers and frequently criticizes its absence in pivotal clinical trials. Without robust PRO data, the overall impact of efficacy gains and adverse events may be misinterpreted, weakening the perceived value of a new treatment.

Key Requirements

Validated Instruments

- Use of psychometrically validated instruments is mandatory.
- Instruments should demonstrate reliability, validity, sensitivity to change, interpretability, and acceptability.
- Both disease-specific and generic instruments are expected.

Continuous Analysis

- A standardized mean difference (Hedges‘g) should be used to assess clinical relevance of mean differences.
- Thresholds for added benefit (based on 95% CI for Hedges’g): 0.2 (minor added benefit) to 0.5 (major added benefit)
- Note: If both responder analyses (meeting the methodological requirements) and continuous analyses are submitted in the dossier, typically only the responder analysis are considered for the benefit assessment by the G-BA.

Responder Analysis

- Different mean observation periods between treatment arms: HR for Time-to-event analyses (deterioration / improvement).
- Similar mean observation periods between treatment arms: Relative Risk (RR), Odds Ratio (OR) and Risk Difference (RD) or HR for Time-to-event analyses (deterioration / improvement).

Clinical Relevance Thresholds

- Pre-specified MIDs are only accepted, if they are ≥15% of scale range, alternatively, a threshold of exactly 15% of scale range is accepted even without pre-specification.
- Exceptions: EORTC QLQ C30 incl. disease specific modules: ≥10-point change required and accepted.

Missing Data and Estimands

- G-BA and IQWiG strongly recommend the use of a treatment policy estimand, which requires that PRO data be collected regardless of intercurrent events such as treatment discontinuation, disease progression, or treatment switching.
- Strict data quality thresholds apply: If less than 70% of patients are considered in the analysis of a PRO endpoint due to missingness, the endpoint will be disregarded. The same holds if the difference between treatment arms exceeds 15 percentage points, this is assumed to indicate non-random exclusion. Return rates must be reported per timepoint and should include all randomized or treated patients in the denominator.

Special Considerations

Special methodological considerations apply when a relevant number of patients die during follow-up. In such cases, the use of competing risk methods (e.g. Aalen-Johansen estimators) is recommended over traditional Kaplan-Meier estimates, which may overestimate the incidence of events such as PRO deterioration. In the presence of competing risk, the IQWiG General Methods Version 7, Chapter 9.3 provides specific guidance on appropriate survival analysis techniques in the context of benefit assessment.

Indirect Treatment Comparisons (ITC)

Indirect treatment comparisons (ITC) are increasingly used in HTA submissions. PRO, however, are often not included in ITC due to challenges related to heterogeneity in measurement, timing, and reporting across trials. This applies particularly to the German benefit assessment, where formal acceptance of PRO-based ITC results remains limited.

If PRO are used in ITC, they are expected to meet the same methodological standards as other outcomes. This includes the use of validated instruments, pre-defined responder thresholds, appropriate handling of missing data, and alignment of estimands and analysis timepoints.

Given the evolving methodological landscape, early advice with G-BA may help clarify expectations. Further experience and methodological refinement will likely inform the future role of PRO in ITC-based benefit assessments.

EU HTA Outlook

The implementation of EU HTA through the Joint Clinical Assessment (JCA) process has initiated a stronger focus on the standardized use of PRO across Europe. While there is substantial methodological alignment between EU-level guidance and German HTA bodies (IQWiG, G-BA), important differences remain, particularly regarding estimand strategy, choice of instruments, data completeness thresholds, MIDs and interpretation of responder analyses.

These differences are not only observed between Member States but also between EU-level guidance and national HTA requirements. To ensure that evidence generated for the JCA can also support national decisions in AMNOG, early planning and methodological harmonization, especially for PRO, are strongly recommended.

Are PRO data accepted in the German HTA?

- Was a validated PRO instrument used?
  - NO → Exclusion of PRO Data
  - YES
- Has a relevant MID been defined?
  - NO → Application of 15% threshold or Exclusion of PRO Data
  - YES
- Was an acceptable estimate used?
  - NO → Critical / Risk of rejection
  - YES
- Completion rate ≥70% at baseline?
  - NO → Exclusion of PRO Data
  - YES
- Difference in missing data between groups >15%?
  - YES → Risk for MNAR → exclusion likely
  - NO

PRO data is accepted and considered

Recommendations

- Plan PRO strategy early in the clinical development process.
- Early G-BA Advice Meetings are recommended.
- Use psychometrically validated and indication-appropriate instruments.
- Align analysis strategy with HTA, not just regulatory, objectives.
- Ensure sufficiently high return rates.
- Use MID-based responder analyses or continuous (Hedges‘g) analyses where appropriate.
- Design trials to capture PROs even after intercurrent events (e.g. progression, discontinuation).

Take-Home Message

Validated, high-quality and interpretable PRO are essential to demonstrate an added benefit in the German benefit assessment and will become increasingly relevant for the EU HTA system. Treatment-policy estimands, early planning and strict adherence to data quality requirements are crucial for success.

This poster summarizes key content from Chapter 5 (“Patient-Reported Outcomes”) of the German Benefit Assessment, White Paper 2025, a cross-company methodological guidance document for the German AMNOG process.

Full details and additional chapters, scan the QR code below to access the complete White Paper.

Disclaimer
The methodological criteria outlined in this poster are based on a synthesis of published guidance and observed G-BA / IQWiG assessment practices. However, each HTA assessment remains subject to individual interpretation by the relevant authorities. The recommendations and thresholds presented here should be understood as indicative rather than perspective. They are intended to support early planning and methodological alignment but do not guarantee acceptance in a specific HTA context.