Health-related quality of life endpoints in benefit assessments: Demands and challenges as seen by IQWiG

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Demands

- Legal requirements
- Validity of scales and response thresholds
- Assessment periods
- Missing data issues
Challenges

- Which is the effect of interest, conceptually and technically?
- What is a relevant effect, what is a suitable response threshold?
- How to interpret continuous data?
I.

HRQoL in benefit assessments
Legislation

- § 139a, SGB V:
  IQWiG to assess benefit ... of drugs
  according to Internationally acknowledged standards of
  evidence based medicine

- § 35, § 35a, § 35b SGB V:
  Improvement in mortality, morbidity, quality of life,
  adverse events (frequency or severity)
HRQoL assessment not to replace that of other endpoints

- Instruments suited for application in clinical trials if
  - validated
    OR
  - established

Relevance of effects and extent of added benefit: Same level as serious symptoms / adverse events
HRQoL ↔ Morbidity

- HRQoL encompasses all dimensions
- Single dimensions: morbidity
II.

Validity of scales
Face validity

- Relevant items given the indication / population
- Patient relevance
- Time-specific
- Sensitive to changes
- Preferably measured as PRO
Validation studies

- Scale development to involve patients (qualitative interviews, focus groups, item reviews)
  Patient perspective: relevant, comprehensible, complete?

- Reliability (ICC ≥ 0.7)

- Responsiveness

- Construct validity (factor analysis)
Multi-dimensional scales / constructs

- Analyse total score if possible, but also present sub-scales / dimensions

- Evaluate single dimensions only if prespecified

- Generally accepted (examples):
  SF-36, EORTC QLQ C30
  or otherwise approved in previous assessments
II. Data collection and assessment requirements
Repeated Measurements

- Assess HRQoL repeatedly
- Until End of Study
- Collect data as completely as possible
Dealing with missing data

- In terms of estimands framework: apply treatment policy approach

- Avoid missing data strategies that are likely to result in biased effects (e.g. LOCF)

- Back results by sensitivity analyses, also by varying effect measures
Response criteria (thresholds)

- Prior specification of analysis, including response thresholds

- Validated MID as threshold? (but see challenges…)

- Sensitivity analyses for multiple thresholds and/or analysis of continuous data
III.

Challenges
Points of view in repeated measurements

HRQoL

Response threshold

B

A

time

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Time to improvement

HRQoL

Response threshold

early:
B better than A
Effect at end of study

HRQoL

Response threshold

B

A

late:
A better than B

time
Mean effect during study period

HRQoL

B better than A
Responder analyses

- Thresholds to describe patient relevant changes

- Need suitable criteria, e.g. MID
  → but conflicting and varying MIDs exist.

- Setting specific: Patient characteristics, disease severity, analytical tools, observational periods …

- Lack of standard for assessing quality of validation studies.
Proposal for discussion

- Prefer: MID pre-specified and > 15 % of range of scale
- Otherwise: Apply threshold of 15 % of range of scale
- Otherwise: Analyze continuous outcomes by standardised effect measures
Continuous data analysis

- Significance ↔ Patient relevance

- Use standardised effect measure and threshold of irrelevance of 0.20

- How to standardise in case of repeated measurements?
Missing data issues

- Missing data due to study design:
  - Incomplete data collection (prior to end of study)
  - Repeated measurements end with intercurrent event

- Missing data due to other (patient-related) reasons

- Analysing data and assessing impact of missings
  - choosing suitable methods
  - interpreting results w.r.t. risk of bias
  - how many missing data can be tolerated?
SISAQoL Initiative

- International collaboration to develop and propose standards for analysing quality of life in cancer trials

- Methodological work:
  - Minimum standards on the design, analysis and interpretation of PRO data from randomized cancer trials

- Terminology for clinically meaningful change and related concepts and recommendations on how to define them
III.

Conclusions
Conclusions

- HRQoL as regular part of benefit assessment
- Validated instruments
- Response criteria defined a priori
- Repeated assessment of HRQoL until end of study
- Proper handling of missing data
Comments – Questions – Suggestions

Thank you!
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References

- [1] Social Code Book V, § 35 a, § 35 b, § 139a