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

[1]

- § 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)

IQWiG Methods Paper (v 5.0)

[2]

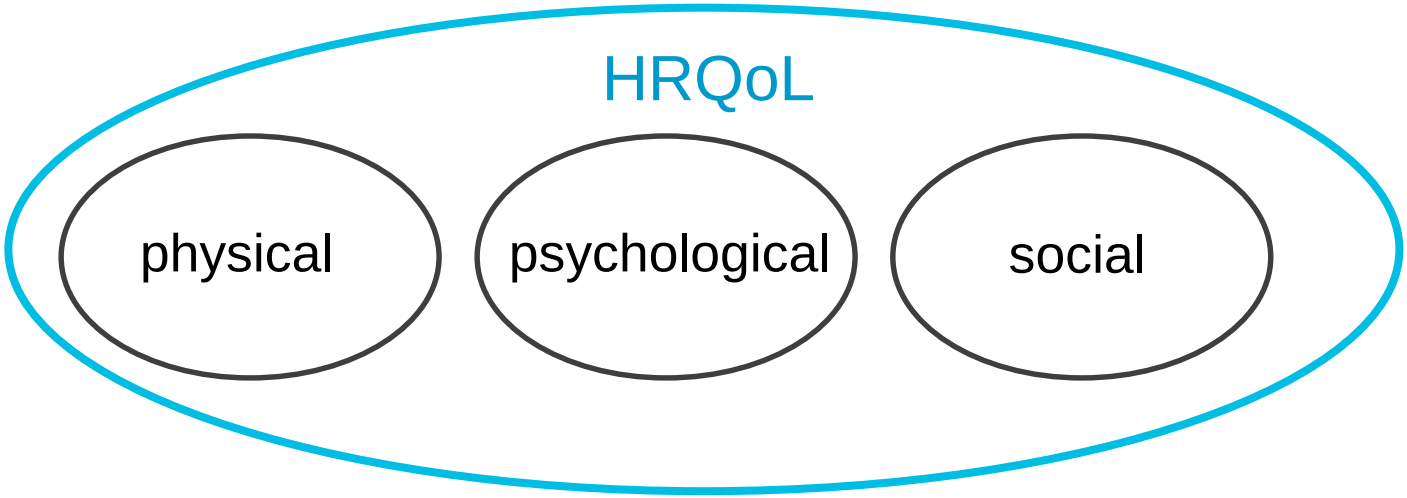
- HRQoL assessment not to replace that of other endpoints

- 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

[2,3]



- HRQoL encompassess 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

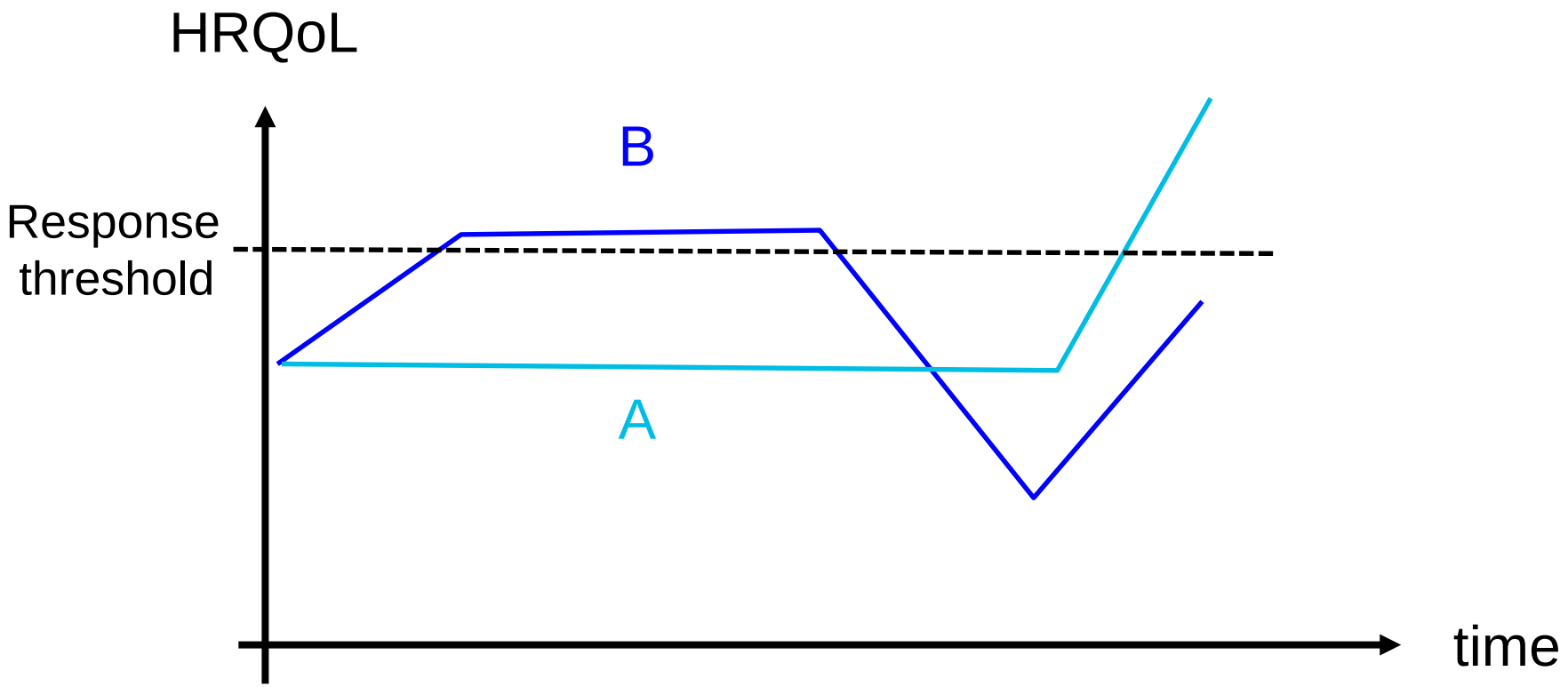
- Validated MID as threshold? (but see challenges…)

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

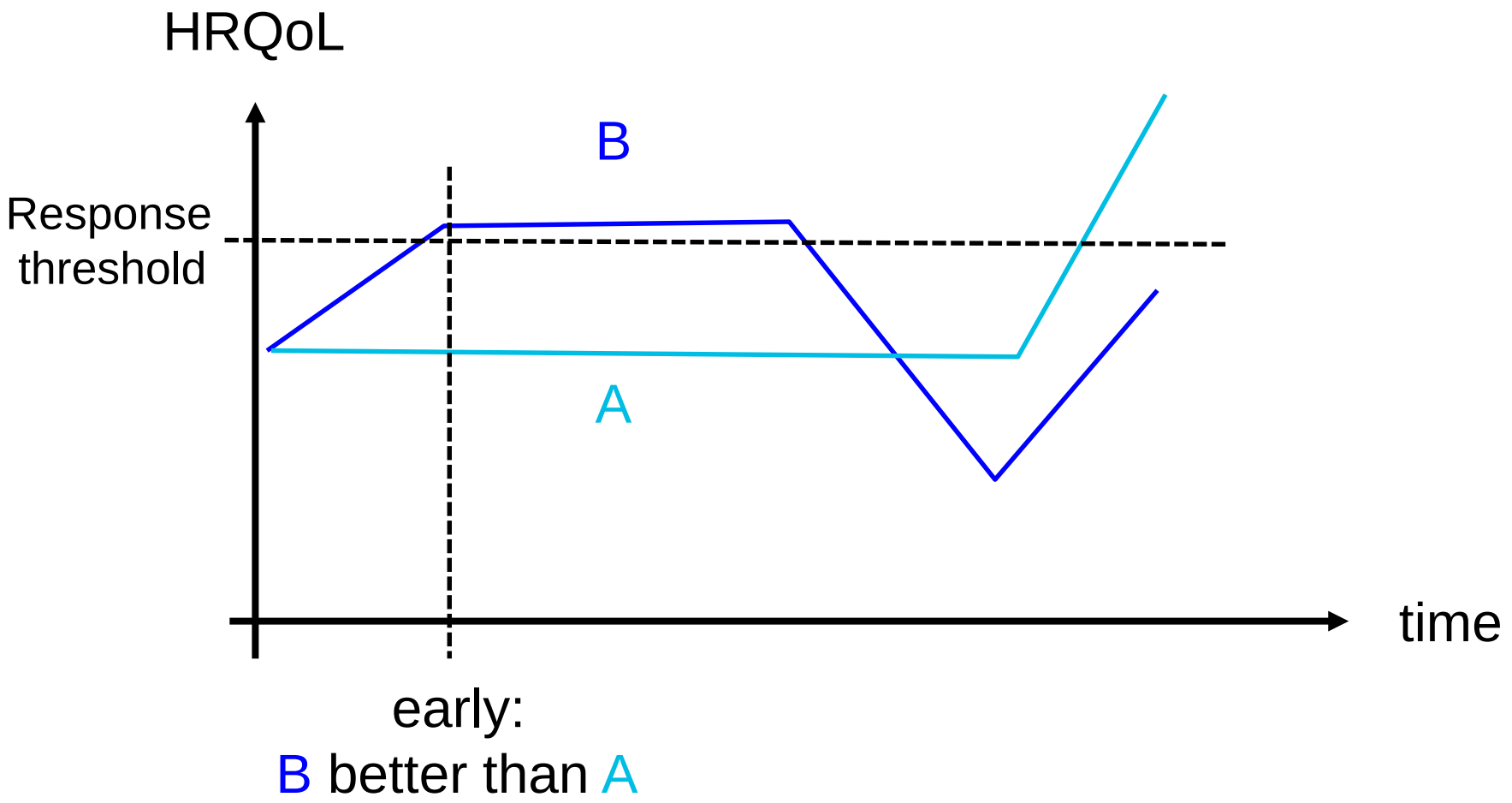
III.

Challenges

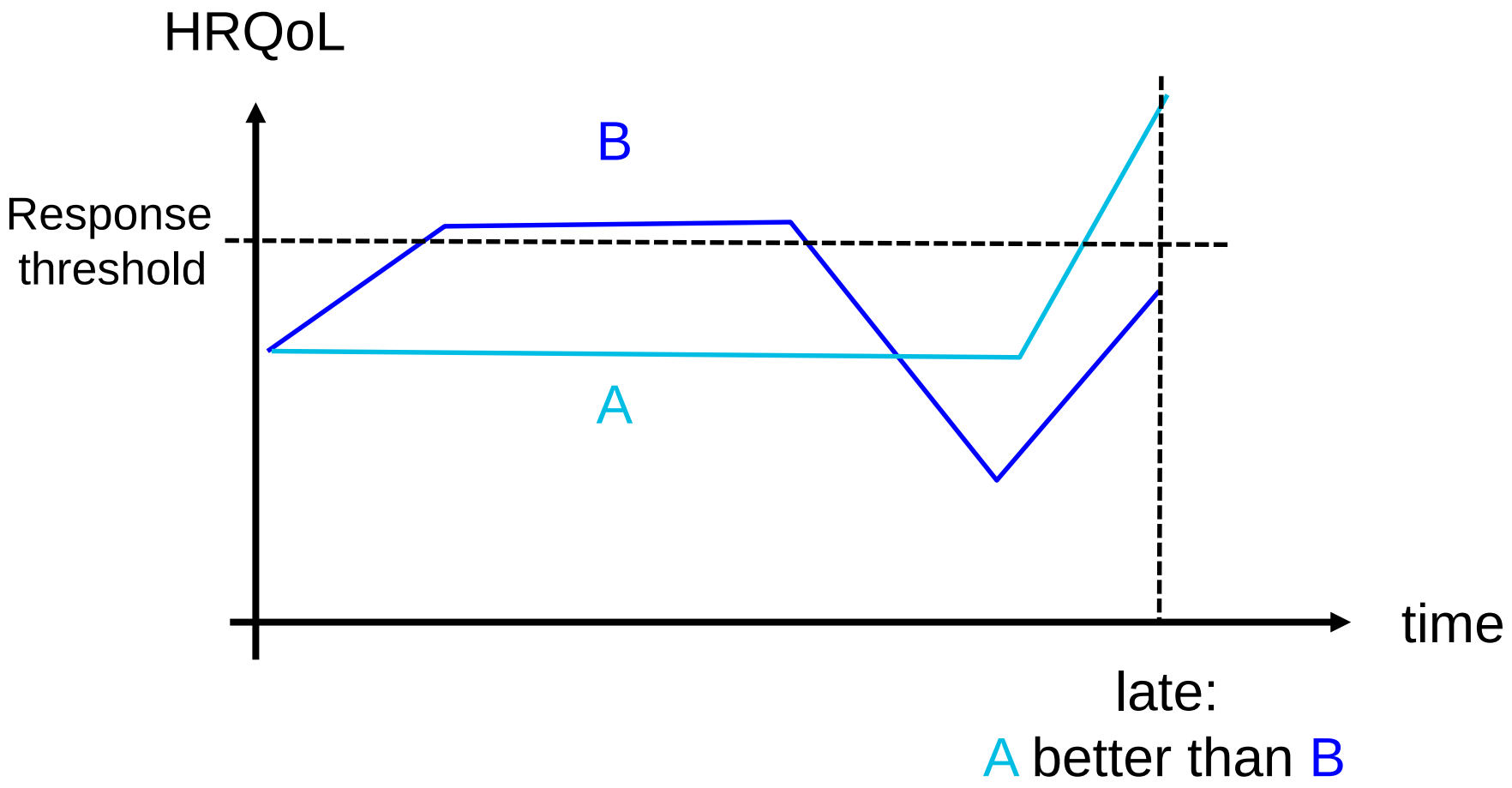
Points of view in repeated measurements



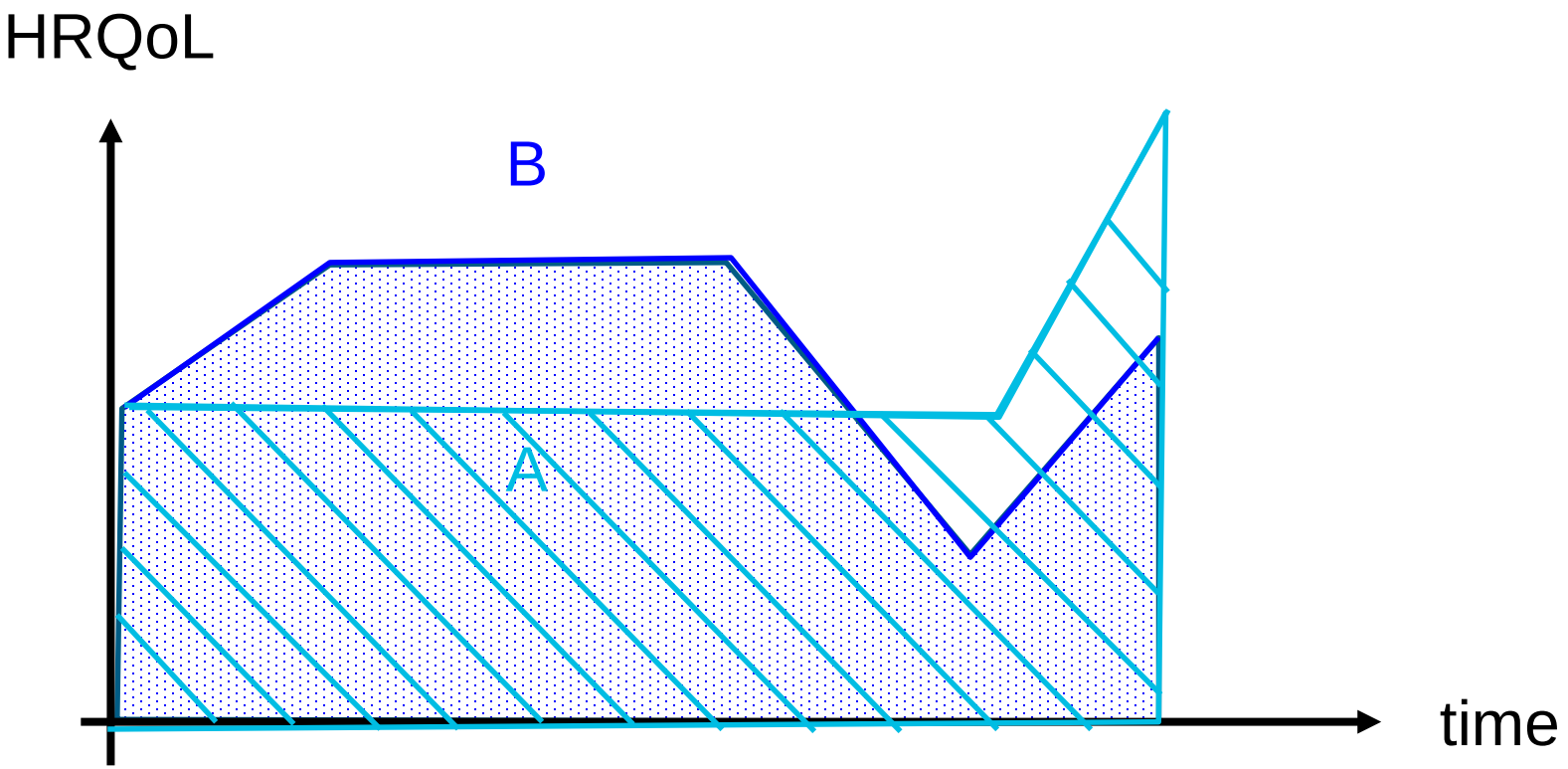
Time to improvement



Effect at end of study



Mean effect during study period



B better than A

Responder analyses

[4,5]

- 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

[6]

- 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

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- [2] IQWiG Methods Paper, https://www.iqwig.de/en/methods/methods-paper.3020.html
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- [7] IQWiG, 2018. A18-41 Dossierbewertung Pertuzumab (Mammakarzinom), https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/2018/a18-41-pertuzumab-mammakarzinom-nutzenbewertung-gemaess-35a-sgb-v.10102.html