Gemeinsamer Bundesausschuss
Relevance of Core Outcome Sets for Health Technology Assessment of Pharmaceuticals

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Who is the G-BA

The AMNOG process (early benefit assessment)

What endpoints are relevant for early benefit assessment

Influence of Core outcome sets on usefulness of clinical trials for HTA assessment
The Federal Joint Committee (GBA)

Highest decision-making body of the statutory health insurance (SHI) system

- Established in 2004
- Binding decisions for healthcare providers and sickness funds
- Ministry of Health: control of legality
- One of the tasks: early benefit assessment of pharmaceuticals
The Federal Joint Committee (GBA)

Impartial members appointed by Parliament (Bundestag)

GKV-SV: sickness funds umbrella organization
DKG: German hospital organization
KBV: German doctor association
KZBV: German dentist association

Subcommittees (total 9)
Office / Academic Staff
Academic & Methodological Institutes (IQWIG, IQTIQ)
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Early Benefit Assessment

Fair prices for medicinal products
Pricing in the Statutory Health Insurance pursuant to the Act on the Reform of the Market for Medicinal Products (AMNOG)

1. Market launch
   - Manufacturer
   - Manufacturers' price (草案)

2. Benefit assessment (publication)
   - Federal Joint Committee
   - Hearing manufacturers/experts

3. Benefit assessment (decision)
   - Federal Joint Committee
   - No additional benefits
   - Not eligible for reference price

4. Price negotiations
   - Manufacturer
   - Central Federal Institution for the Health Insurance Funds

5. Decision
   - Board of arbitration consisting of:
     - Central Federal Association of the Health Insurance Funds
     - Arbitrators' decision
     - Decision

6. Cost-benefit assessment
   - Institute for Quality and Efficiency in Health Care

Timeline:
- Market launch: 3 months
- 6 months
- 12 months
- 15 months

G-BA (Gemeinsamer Bundessausschuss)
The Early Benefit Assessment: Timeline

1. Submission of the dossier
2. Publication of the dossier and the assessment
3. Resolution on the benefit

6 months

3 months

Benefit assessment (proposal by the IQWiG)

3 months

Hearing procedure and resolution

* IQWiG: Institute for Quality and Efficiency in Health Care
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Relevant Endpoints for Early Benefit Assessment

- Mortality
- Adverse Events
- Morbidity
- Quality of Life

• Outcomes based exclusively on histological/haematological/laboratory measures not per se patient relevant
• Patient-reported outcomes preferred: Validated measuring instrument available?
• What direct clinical relevance has the outcome for the patient?
# Relevant Endpoints for Early Benefit Assessment

<table>
<thead>
<tr>
<th>Not Relevant</th>
<th>Relevant</th>
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</thead>
<tbody>
<tr>
<td>Progression-free survival based on RECIST 1.1</td>
<td>Overall survival</td>
</tr>
<tr>
<td></td>
<td>Reduction of symptoms</td>
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<tr>
<td></td>
<td>Improvement of Quality of Life</td>
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<tr>
<td>Change in HbA1c</td>
<td>Prevention of cardiovascular events (e.g. stroke, Myocardial infarction)</td>
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<tr>
<td>LDL-C</td>
<td></td>
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<tr>
<td>Change in body weight</td>
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<tr>
<td>Forced Expiratory Pressure in 1 Second (FEV1)</td>
<td>Exacerbations of COPD</td>
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<td></td>
<td>exercise capacity</td>
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<tr>
<td>Virological response (viral load)</td>
<td>HIV symptoms (Symptom Distress Module)</td>
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<tr>
<td>Resistance to HIV Integrase Inhibitors</td>
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Assessment of Quality of Life

• Has a high relevance especially for better interpretation of the impact of symptoms and adverse events for the patient

• Generic instrument (f.e. SF-36) and a disease-specific measuring instrument recommended

• Possible obstacles:
  • Missing evidence of appropriate measurement properties for the respective population/indication covering reliability, validity and ability to detect change
  • Responder analysis preferred → validated MID/response criteria?
  • Compliance of ≥ 70 % necessary
  • Longitudinal data collection should proceed beyond end of treatment
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Conceptual framework of core areas for outcome measurement in clinical trials

Core areas

- Mortality
- Quality of Life
- Resource Use/Economical impact
- Pathophysiological manifestations

Domains

- Concepts
- Death
- Life Impact
- Morbidity

Examples of specific domains within areas

- Disease
- Intervention
- ICF domains: activity and participation
- Quality of life
- Patient perception of health
- Loss of ability to work
- Psychosocial impact
- Impact on family, caregivers
- Utility

Adverse events

- Are measured within the core areas, but are labeled separately to allow assessment of benefit and harm.

Choices influenced by context
Future work should focus on how the COS should be defined and measured in practice, incorporating elements such as standardising outcome definitions and thresholds, identifying the most appropriate measurement instruments, and time points for outcome assessment.¹

The existence of heterogeneity in the definition of progression among clinical trials and a lack of clear information in clinical trial reports as to how disease progression was evaluated indicate that there is a need to standardize clinical trials protocols to provide comparability between trials for the same cancer type.²

1: MacLennan S. et al, 2017: A core outcome set for localised prostate cancer effectiveness trials, BJU Int. 120:E64-E79
Relevance of Core Outcome Sets for HTA of pharmaceuticals

• A core outcome set is not a guarantee that the clinical trial is useful for early benefit assessment

• Relevant outcomes for the patient must be implemented in a meaningful way → if necessary, further endpoints beyond the core outcome set must be defined for a study

• Core outcome sets should include patient-reported outcomes with proven reliability, validity and ability to detect change for the relevant population/indication → Clarification of uncertainties and further research needs could foster improvement

• Health-economic outcomes less important in the german HTA procedure
Conclusion

- Valuable contribution for improving clinical trial comparability
  - Improve quality of meta-analysis and systematic reviews
  - Improve feasibility of patient-reported outcome assessment
  - Indirect comparisons for benefit assessment facilitated

- Very early stage of development
  - Information of definition and measuring instruments is crucial for evaluation of patient relevance
  - Use of standardised patient-reported measuring instruments as PROMIS and core outcome sets by pharmaceutical manufacturers currently not widespread
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