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Relevance of Core Outcome Sets for Health Technology Assessment of Pharmaceuticals

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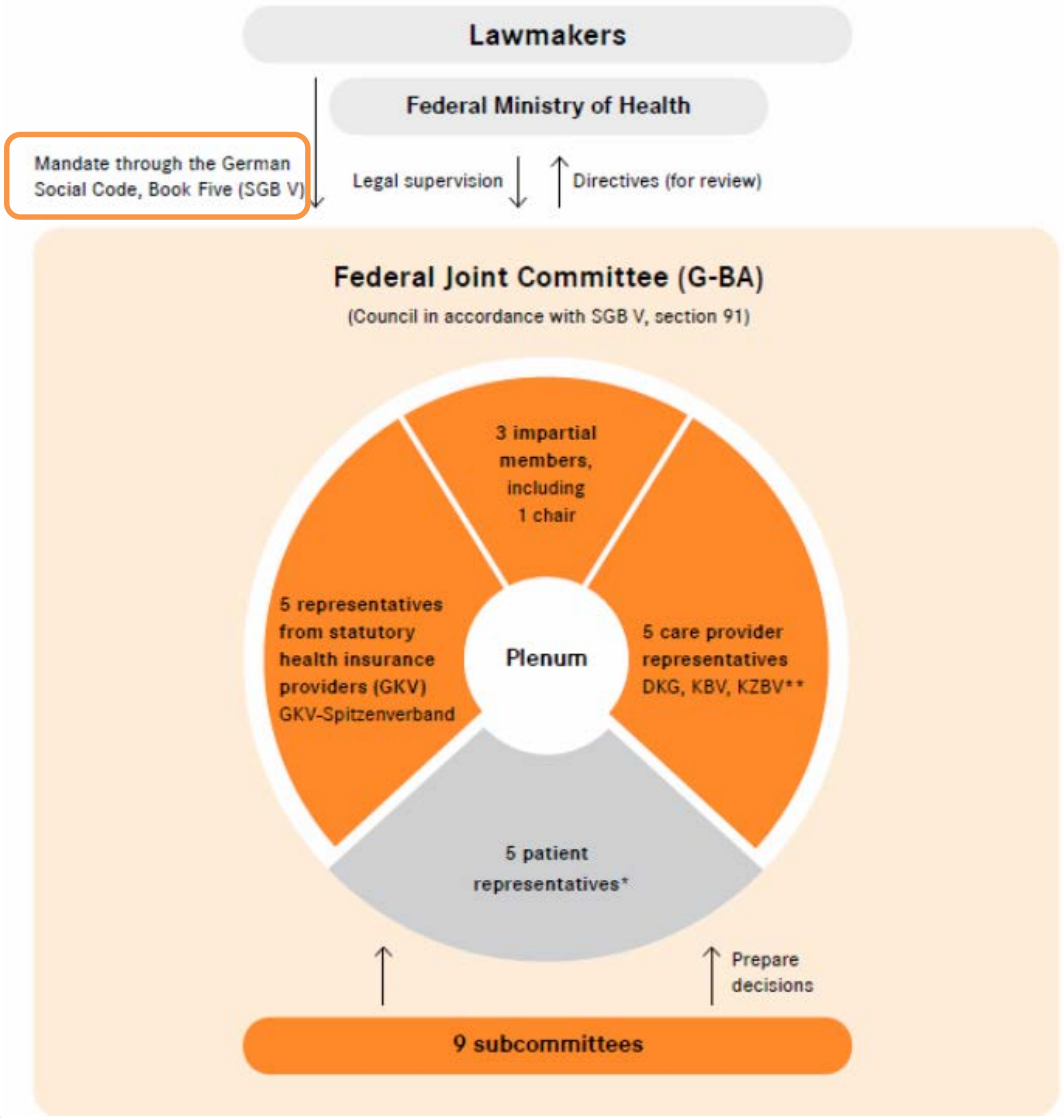
- **Who is the G-BA**
- **The AMNOG process (early benefit assessment)**
- **What endpoints are relevant for early benefit assessment**
- **Influence of Core outcome sets on usefulness of clinical trials for HTA assessment**

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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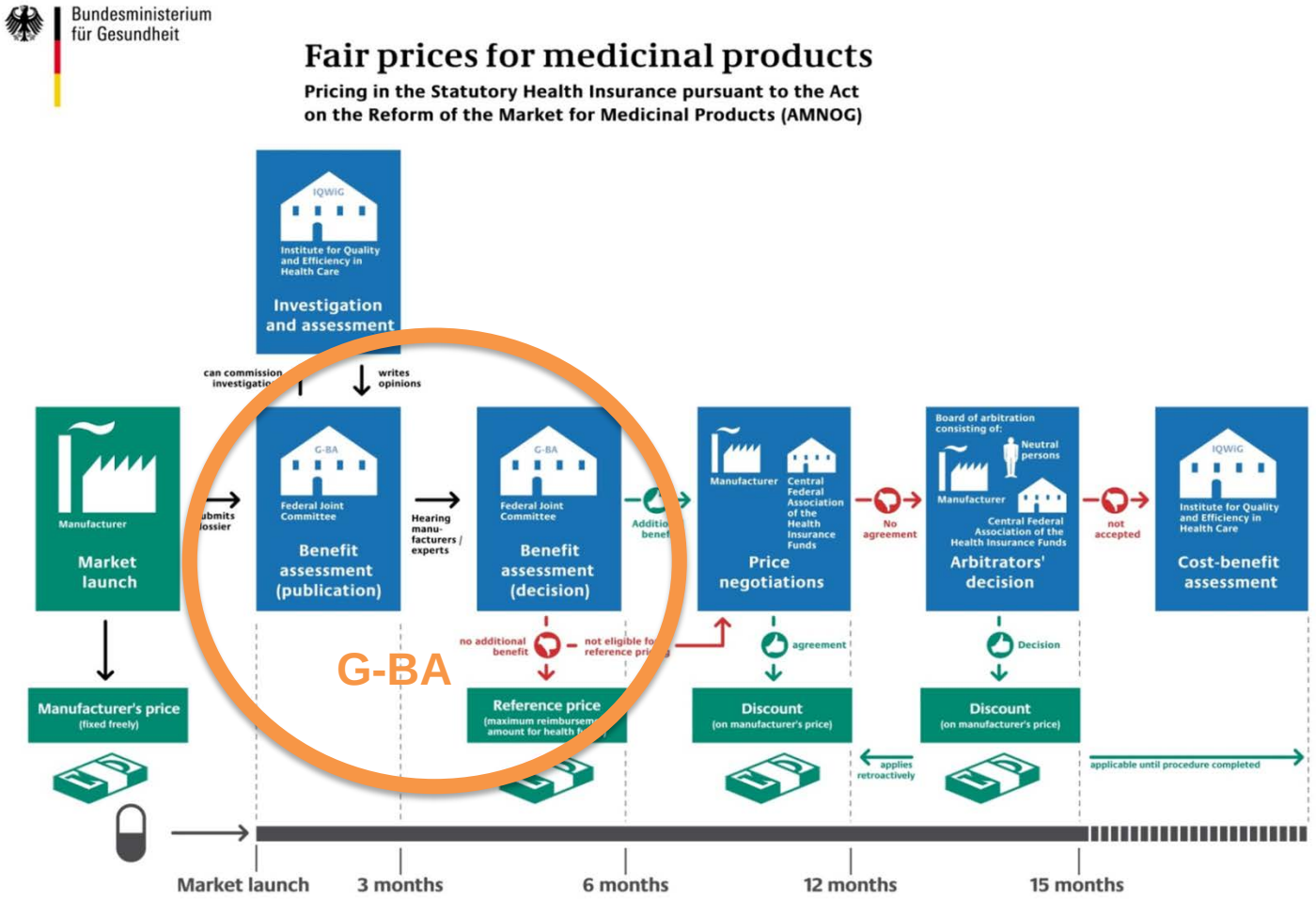
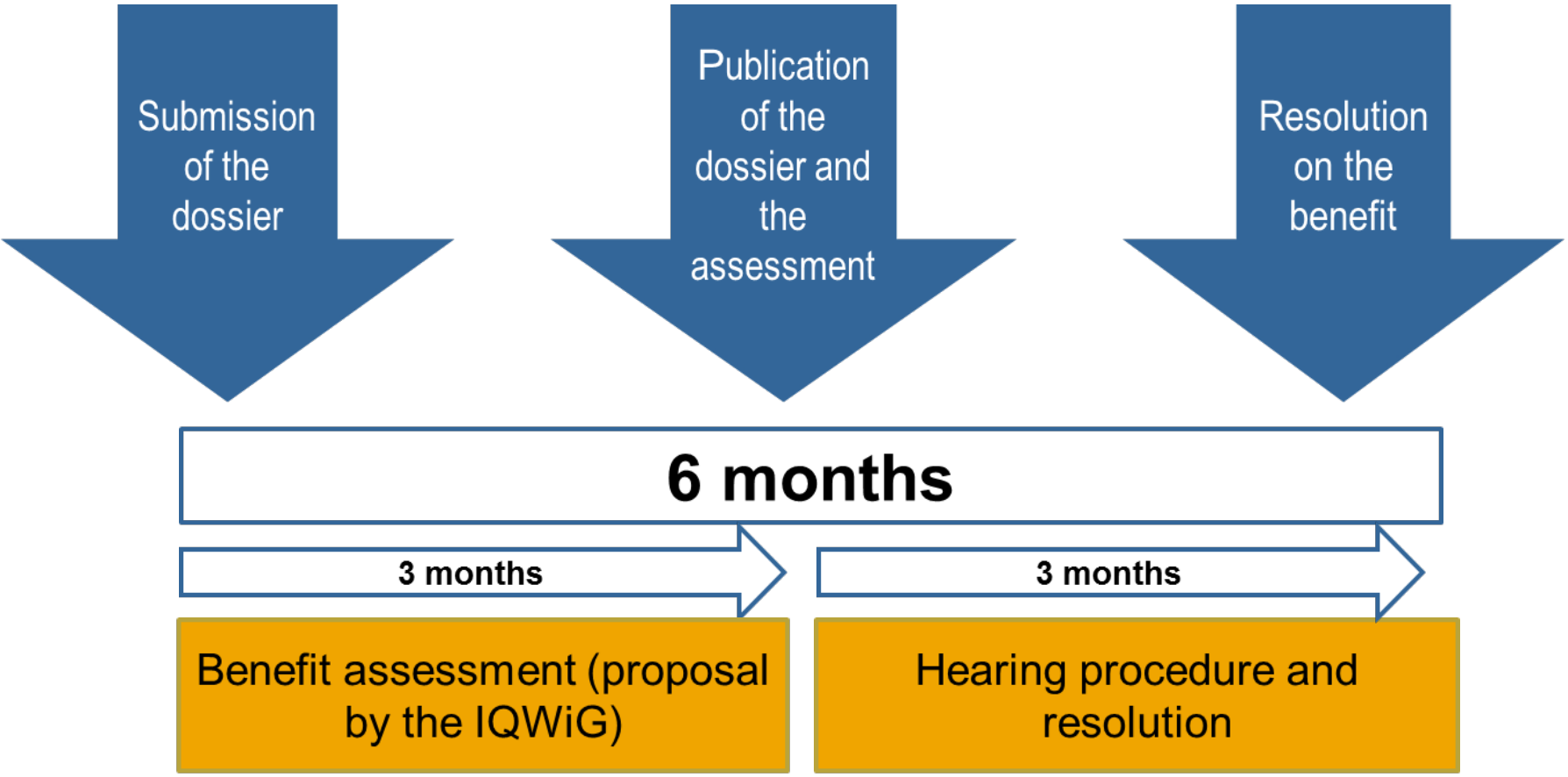
Early Benefit Assessment



The Early Benefit Assessment: Timeline



* IQWiG: Institute for Quality and Efficiency in Health Care

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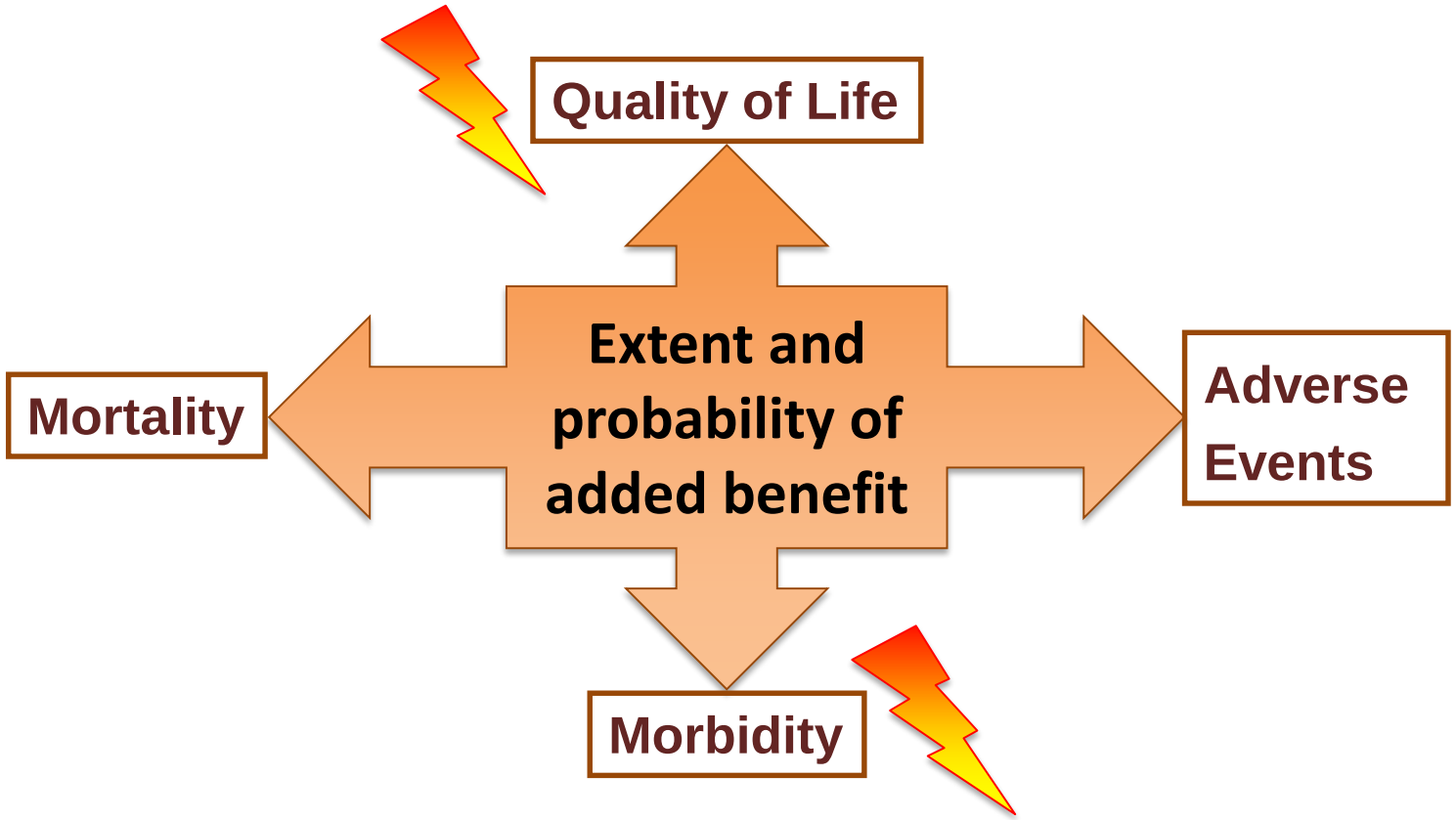
Relevant Endpoints for Early Benefit Assessment



- 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

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

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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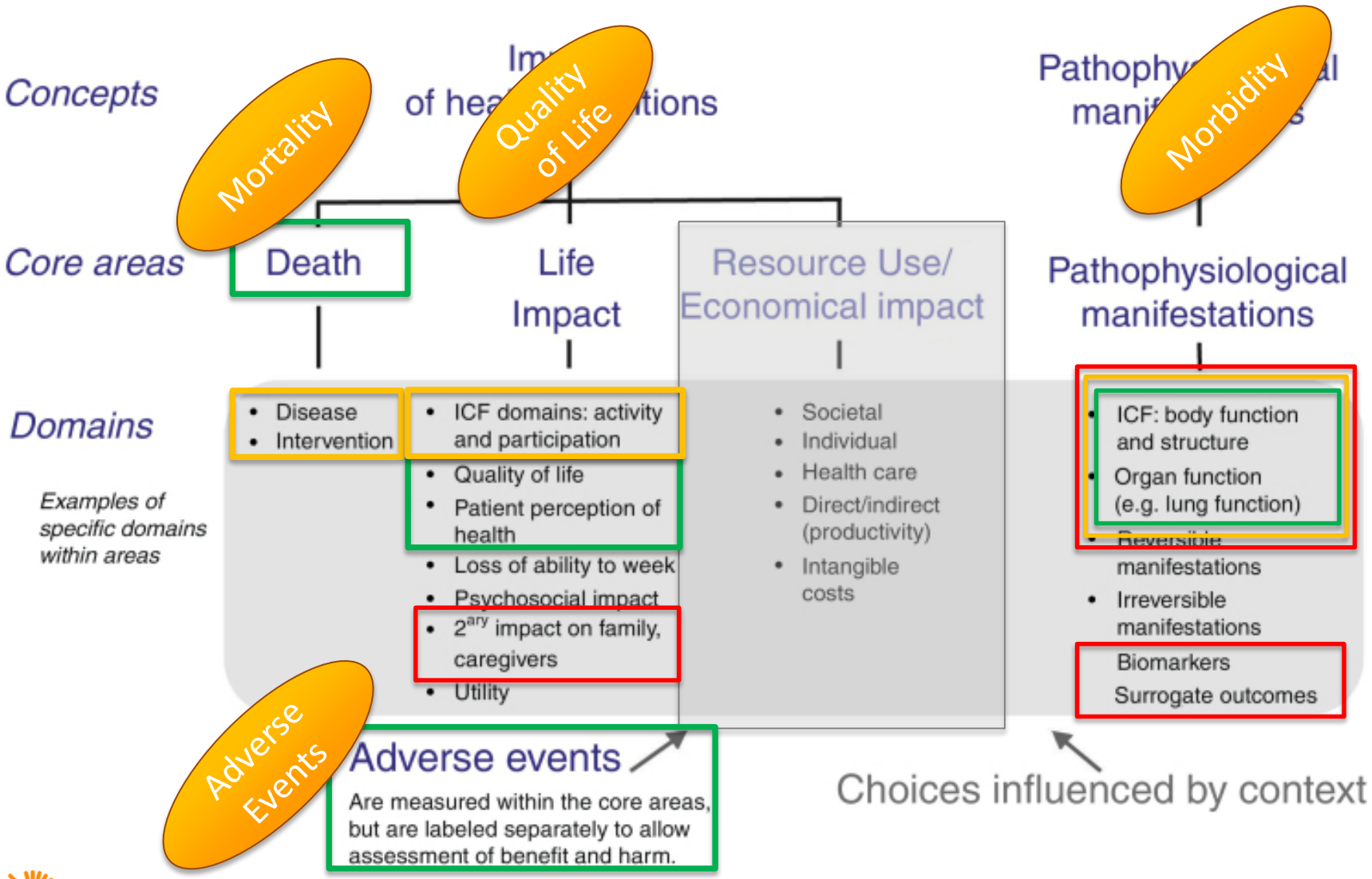
Conceptual framework of core areas for outcome measurement in clinical trials



Relevance of Core Outcome Sets for HTA of pharmaceuticals

Table 4 Final COS for trials of interventions for localised prostate cancer.

Domain		Outcome
Universal (i.e. applicable to all interventions)		
Cancer/survival		Death from prostate cancer
Cancer/survival	√	Death from any cause
Cancer/survival		Local disease recurrence
Cancer/survival		Distant disease recurrence/metastases
Cancer/survival		Disease progression
Cancer/survival		Need for salvage therapy
Bowel function		Faecal incontinence
Bowel function	√	Bowel function (including diarrhoea, faecal urgency, rectal bleeding, rectal itch, constipation, bowel frequency, and painful bowel movements)
Urinary function		Stress incontinence
Urinary function		Urinary function (including urge incontinence, weak urine stream, nocturia, haematuria, dysuria, frequency, urgency, need for temporary catheter, and catheter related problems)
Sexual function		Sexual function (including erectile dysfunction, reduced or loss of libido, frequency of intercourse, ejaculatory function, orgasmic function, and sexual function,)
Quality of life	√	Overall quality of life (including anxiety, depression, lack of confidence, feeling less masculine, feeling tired or fatigued, overall quality of life, quality of life relating to urinary function, quality of life relating to sexual function, quality of life relating to bowel function and quality of life impact on immediate family)

?

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
2: Hernandez-Villafuerte K. et al, 2018: Challenges and methodologies in using progression free survival as a surrogate for overall survival in oncology, International Journal of Technology Assessment in Health Care, 34:3, 300-316

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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