Statistical Issues in the Benefit Assessment acc. to the German AMNOG

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Overview

Part 1
- The AMNOG process
- Some definitions
- Studies acceptable for the dossier

Part 2
- Endpoints
- Subgroup analyses
- Surrogates

Part 3
- Metaanalyses
- Indirect comparisons
  - Adjusted ITCs
  - Historical comparisons
Overview

- **Part 1**
  - The AMNOG process
  - Some definitions
  - Studies acceptable for the dossier

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  - Endpoints
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PART 1
The players for the benefit assessment...

- G-BA = Joint Federal Committee (Gemeinsamer Bundesausschuss)  
  => Decision making body

- IQWiG = Institute for quality and efficiency in health care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)  
  => assesses the dossier from a methodological view (suggests a benefit)
Submission of a dossier by the company

Benefit assessment by G-BA (Usually order to IQWiG)

- Additional benefit shown
  - Price negotiations of company with board of health insurance institutions
    - Price negotiated = reimbursed price
    - Cost-benefit assessment
  - No agreement: Arbitration board
- No additional benefit
  - Reference price group
G-BA

- Consists of 13 voting members
  - 5 members from the board of the statutory health insurances
  - 5 members of care givers (hospital association (DKG), association of physicians (KBV), association of dentists (KZBV))
  - 3 independent members including Prof. Hecken (chairperson)
- Makes decisions on every aspect of reimbursement in the German health care system
  - e.g. new pharmaceuticals, reimbursement of medical devices
IQWiG

- Institute to assess the benefit dossiers by order of the G-BA
- Participate in the oral hearings to defend their dossier assessment
- Assessments are based on the methods paper (actual version 5.0)
Timelines

- Advice meeting: ca. 10 weeks after submission of request
- Dossier preparation: ca. 6-12 months
- Dossier submission: at day of report in Lauer Taxe (ca. 4 weeks after approval)
- IQWiG (or G-BA) Dossier Assessment: 3 months after submission
- Written response: 21 days after publication of assessment
- Oral hearing: ca. 2-3 weeks after submission date for written response

- No clock-stop
- No delays allowed
Definitions

- **Effect size**
  - Size of an treatment effect (should be provided as relative effect, e.g. odds ratio, relative risk, hazard ratio).

- **Confidence in benefit**
  - Provides the confidence, that the results of the study (-ies) or metaanalyses is close to the truth.
  - Will be assessed based on the potential for bias and the size of the statistical uncertainty.
Definitions

§ 3 Benefit

(1) The benefit of a new drug is the patient relevant therapeutic effect with regard to an increased health status, reduction of duration of disease, prolongation of survival, reduction of adverse events or increased QoL.

=> Shown by marketing authorization by EMA

Approval

- Authority decides on the benefit-risk-ratio
- Dichotomized decision
Definitions

- § 3 Additional benefit
  - (2) The additional benefit of a new drug is a benefit acc. to (1) and the benefit is higher with regard to quality or quantity compared to a G-BA-defined comparator.
  
  => Early benefit assessment

- Benefit assessment
  - G-BA assesses additional benefit of approved drugs
  - Determination of effect size and confidence in benefit
  - Assessment of size of evidence
§ 5 (7) Size of additional benefit

- **Major**
  - Healing, major prolongation of survival, long-lasting absence of serious symptoms, mostly avoiding serious adverse events

- **Considerable**
  - Moderate prolongation of survival, attenuation of serious symptoms, remarkable relief of disease, relevant prevention from serious adverse events, major prevention from other adverse events

- **Minor**
  - Reduction of non-serious symptoms, relevant prevention from adverse events

- **Not quantifiable**
- **No additional benefit**
- **Benefit lower than benefit of FJC-defined comparator**
Assessment is based on relative effect measures below 1

<table>
<thead>
<tr>
<th></th>
<th>Mortality</th>
<th>Serious symptoms or AEs and QoL</th>
<th>Non-serious symptoms or AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>0.85</td>
<td>0.75 and Risk ≥ 5%</td>
<td>-</td>
</tr>
<tr>
<td>Considerable</td>
<td>0.95</td>
<td>0.90</td>
<td>0.80</td>
</tr>
<tr>
<td>Minor</td>
<td>1.00</td>
<td>1.00</td>
<td>0.90</td>
</tr>
</tbody>
</table>

95% CI must be below the limits shown in the table

Source: IQWiG methods paper, Version 5.0
Evidence level

- I a systematic Reviews of studies of level Ib
- I b randomised, controlled, clinical study (RCT)
- II a systematic Reviews of studies of level IIb
- II b prospective cohort studies
- III retrospective studies to compare treatments
- IV Case series and other non-comparing studies (e.g. single-arm clinical studies)
- V Case reports, consensus papers, etc.
Definition confidence in benefit

- IQWiG uses three categories for the grading based on the study and the endpoints:
  - **High confidence**: RCT with low potential for bias.
  - **Moderate confidence**: RCT with high potential for bias.
  - **Low confidence**: Results of non-randomized studies.

In early benefit assessments only one phase III trial available.

- i.e. at most hint for benefit possible (except for Mega-trials with more than 1,000 patients (e.g. assessment of Ticagrelor))
- Downgrading, if high potential for bias for the single endpoint (e.g. QoL)
  - Unidirectional results for subgroups, but not all with significance
  - Oncology: unidirectional hazard ratio for OS for different time-cuts, but not all significant (e.g. assessment of Eribulin)
Definitions

- **Confidence in benefit (IQWiG Methods paper 5.0 chapter 3.1.4)**
  - **Proof**
    - Statistical significance in $\geq 2$ RCTs with high confidence in benefit
  - **Hint**
    - Statistical significance in one RCT with high confidence in benefit or in $\geq 2$ RCTs with moderate confidence in benefit
  - **Clue**
    - Statistical significance in one RCT with moderate confidence in benefit or in $\geq 2$ RCTs with low confidence in benefit
  - **No confidence**
Assessment Ipilimumab 2nd line

- **Dossier BMS**
  - OS: Proof for major add. benefit
  - AEs: AEs can be treated, no add. harm
  - Overall: Proof for major add. benefit

- **IQWiG**
  - OS: Hint for major add. benefit
  - AEs: Hint for major add. harm
  - Overall: Hint for considerable add. benefit

- **FJC**
  - OS: Hint for considerable add. benefit
  - AEs: AEs can be treated, no add. harm
  - Overall: Hint for considerable add. benefit
Acceptable study types

- Studies with the highest evidence to be reported
  - If RCTs available, then these are to be reported
  - If no RCT is available, the studies with next highest evidence to be reported
    - E.g. single-arm studies
    - E.g. non-randomized studies
Most wanted…

Randomized controlled Trials (RCTs)

- Blinded allocation of patients preferred
- Control group mandatory (ideally the FJC-defined comparator)
- Blinding preferred (at least single-blind, better double-blind if possible)
- Randomization mandatory (if applicable)
- Adequate statistical methods mandatory
- Subgroup analyses mandatory at least for (if applicable)
  - Gender
  - Agegroups
  - Severity of disease
  - Country / Region
- Appropriate description of loss-to-follow-up patients / drop-outs
Intent-to-Treat Analysis

- All randomized patients
  - Analyzed as randomized,
  - Not taking into account any protocol deviations
    - In- and exclusion criteria
    - Actual treatment


- Primary population for results in benefit dossier
Other populations in clin. studies

- 'Full Analysis Set' (FAS) = modified ITT (ICH E9)
  - Close to intent-to-treat principle
  - Modifications like
    - Patients with at least one dose
    - Safety analysis: analyzed as treated (not as randomized)
  - Acceptable for dossier, if deviance from ITT < 5%

- 'Per Protocol Set' (PP)
  - Patients without major protocol deviations
  - Not acceptable for dossier.
## Upcoming events

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Title</th>
<th>Date</th>
<th>Location</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>One day meeting</td>
<td>Bayesian Methods for Dose Finding and Biomarkers</td>
<td>28(^{\text{th}}) February</td>
<td>RSS, 12 Errol Street, London</td>
<td></td>
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<tr>
<td>Training Course</td>
<td>Missing data</td>
<td>6(^{\text{th}})-7(^{\text{th}}) March</td>
<td>Heathrow, UK</td>
<td>Presented by Michael O’Kelly</td>
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<tr>
<td>Webinar</td>
<td>Big Data</td>
<td>22(^{\text{nd}}) March, 3pm</td>
<td></td>
<td>What's the big deal with big data and will it have a big impact on me?</td>
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Please visit [www.psiweb.org/events](http://www.psiweb.org/events) for more information.
3-6th June 2018 : PSI Conference


Poster Abstract deadline : 28th February 2018
Early Bird Discount : 21st March 2018
Thank you for your attention!