Biometrical Issues in the Framework of Benefit Assessment

Ralf Bender

Institute for Quality and Efficiency in Health Care (IQWiG)
Cologne, Germany
Outline

- IQWiG and the German system
- Benefit assessment and requirements of IQWiG
- Biometrical issues
  - Assessment of added benefit
  - Proof of benefit from 1 study
  - Benefit assessment in case of heterogeneity
  - Extent of added benefit
  - Indirect comparisons
- Example
- Outlook
- Summary
IQWiG and the German system

IQWiG and G-BA were founded during the 2004 health care reform.

The legal foundation of IQWiG and G-BA is Social Code Book V (SGB V).

IQWiG is solely commissioned by the Federal Joint Committee (G-BA) and the Federal Ministry of Health (BMG), but can also cover topics on its own initiative under a general commission.

Assessment of benefits and harms of medical interventions and production of independent, evidence-based reports.

Decision-making body of the self-governing health care system in Germany.
Requirements of IQWiG

- **Proof (“Beleg”):**
  - Meta-analysis of studies with high certainty of results
  - At least 2 significant studies with high certainty of results

- **Indication (“Hinweis”):**
  - Meta-analysis of studies with moderate certainty of results
  - One significant study with high certainty of results

- **Hint (“Anhaltspunkt”):**
  - Meta-analysis of studies with low certainty of results
  - One significant study with moderate certainty of results
Benefit assessment

Certainty of results:
- High: RCT with low risk of bias
- Moderate: RCT with high of bias
- Low: Non-randomized controlled trial

Risk of bias (key aspects):
- Adequate concealment
- Blinding
- Appropriate application of ITT
- In general: Good clinical practice (GCP) …
Benefit assessment

IQWiG:
Update of General Methods

More Details →

General Methods

Version 4.1 of 28 November 2013

Table: Certainty of conclusions regularly inferred for different evidence situations if studies with the same qualitative certainty of results are available

<table>
<thead>
<tr>
<th>Qualitative certainty of results</th>
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<sup>a</sup> Effects in the same direction: Clear, Moderate, No
Criteria for 1 study:

- All usual criteria for a proof of benefit are fulfilled
- Clinical study report according to the International Conference on Harmonization (ICH) guidelines is available
- The study is a multi-centre study with at least 10 centres
- The effect estimate observed has a very small corresponding $p$-value ($p < 0.001$)
- The result is consistent within the study
- The analyses are available for all relevant outcomes, i.e. these analyses are not restricted to individual selected outcomes
Requirements of IQWiG

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### Requirements of IQWiG

IQWiG, short for Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, is an institute for quality and efficiency in health care.
Prediction intervals

Guddat et al. *Systematic Reviews* 2012, 1:34
http://www.systematicreviewsjournal.com/content/1/1/34

METHODOLOGY

A note on the graphical presentation of prediction intervals in random-effects meta-analyses

Charlotte Guddat¹⁺, Ulrich Grouven¹,², Ralf Bender¹,³ and Guido Skipka¹

- Predicted range for the true treatment effect in an individual study
- Illustration of the degree of heterogeneity in forests plots of RE meta-analyses
"In the same direction (i.s.d)"

Examples for different "i.s.d." situations

- Not i.s.d.
- Moderately i.s.d.
- Clearly i.s.d.

- Weight > 20%
- Weight < 20%
Application of Prediction Intervals
in Meta-Analyses with Random Effects
Joint Statement from IQWiG, GMDS and IBS-DR

Authors: Ralf Bender, Oliver Kuß, Armin Koch, Carsten Schwenke & Dieter Hauschke

Joint statement of IQWiG, GMDS and IBS-DR (07.03.2014):

Application of prediction intervals is a valuable supplement to the present methods for meta-analyses with random effects, especially in the case of marked heterogeneity

Issues regarding assessment of added benefit:

- Certainty of results (high, moderate, low)
- RCTs: Risk of bias
- Homogeneity: Significant meta-analysis
- Heterogeneity: Effects clearly, moderately or not i.s.d.
- Prediction intervals
- Derivation of proof, indication or hint of added benefit
AMNOG – new legislation, new HTA products

- New law to reorganize pharmaceutical market for the statutory health insurance
- Came into force on 01/01/2011
- § 35a SGB V directly concerns early benefit assessment of drugs:
  - For new chemical entities / new indications
  - Requirement linked to market entry
  - Now onus of proof on manufacturer to demonstrate added benefit (vs. an appropriate comparator) – submission of a dossier
  - Results used for price negotiations
    (Not for the decision: reimbursement yes/no)
AMNOG – Extent of ‘added benefit’

Criteria in accordance with AM-NutzenV*

- **Major added benefit**
  - Sustained and great improvement# (cure, major increase in survival time, long-term freedom from serious symptoms, extensive avoidance of serious side effects)

- **Considerable added benefit**

- **Minor added benefit**

- **No added benefit has been proven**

- **Less benefit**

*Regulation for Early Benefit Assessment of New Pharmaceuticals

# in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator
# AMNOG – Extent of ‘added benefit’

## Criteria in accordance with AM-NutzenV*

<table>
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<tr>
<th>Added Benefit Level</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td><strong>Major added benefit</strong></td>
<td>Sustained and great improvement# (cure, major increase in survival time)</td>
</tr>
<tr>
<td><strong>Considerable added benefit</strong></td>
<td>Marked improvement# (perceptible alleviation of the disease, moderate increase in survival time, alleviation of serious symptoms, relevant avoidance of serious adverse effects)</td>
</tr>
<tr>
<td><strong>Minor added benefit</strong></td>
<td></td>
</tr>
<tr>
<td><strong>No added benefit has been proven</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Less benefit</strong></td>
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AMNOG – Extent of ‘added benefit’

Criteria in accordance with AM-NutzenV*

Major added benefit
- Sustained and great improvement# (cure, major increase in survival)
- Marked improvement# (perceptible alleviation of the disease, moderate increase in survival time, alleviation of serious symptoms, relevant avoidance of serious adverse effects)

Considerable added benefit
- Moderate and not only marginal improvement# (reduction in non-serious symptoms, relevant avoidance of side effects)

Minor added benefit
- No added benefit has been proven

Less benefit

*Regulation for Early Benefit Assessment of New Pharmaceuticals

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AMNOG – Extent of ‘added benefit’

Criteria in accordance with AM-NutzenV*

- **Major added benefit**
  - Sustained and great improvement# (cure, major increase in survival, great improvement)
  - Marked improvement# (perceptible alleviation of the disease, moderate increase in survival time, alleviation of serious symptoms, relevant avoidance of serious adverse effects)

- **Considerable added benefit**
  - Moderate and not only marginal improvement# (reduction in non-serious symptoms, relevant avoidance of side effects)

- **Minor added benefit**

- **No added benefit has been proven**

- **Less benefit**

*Regulation for Early Benefit Assessment of New Pharmaceuticals

# in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator
AMNOG – Extent of ‘added benefit’

IQWiG:
First proposal to operationalize extent of added benefit based upon shifted null hypotheses

Details →
AMNOG – Extent of ‘added benefit’

IQWiG:
Update of General Methods

More Details →

General Methods
Version 4.1 of 28 November 2013

AMNOG – Extent of ‘added benefit’

Threshold values for determination of the extent of an effect
Effect measure: RR

<table>
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<th>Extent category</th>
<th>Outcome category</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Overall mortality</td>
</tr>
<tr>
<td>Major</td>
<td>0.85</td>
</tr>
<tr>
<td>Considerable</td>
<td>0.95</td>
</tr>
<tr>
<td>Minor</td>
<td>1.00</td>
</tr>
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<sup>a</sup>: Precondition: use of a validated or established instrument and a validated or established response criterion
<sup>b</sup>: Risk must be at least 5 % for at least one of the two groups being compared
Main idea

If you have 2 studies each with power of $1-\beta$ for the usual test of superiority, then the threshold is chosen so that the pooled analysis also has a power of $1-\beta$ for the shifted hypothesis.
AMNOG – Extent of ‘added benefit’

True effects (RRs) in dependence on baseline risk

![Graph showing true effects (RRs) in dependence on baseline risk.](image-url)
## AMNOG – Extent of ‘added benefit’

### Range of true effects (RRs) for the different extent categories

<table>
<thead>
<tr>
<th>Extent category</th>
<th>Outcome category</th>
<th>Overall mortality</th>
<th>Serious (or severe) symptoms (or late complications) and adverse events, as well as health-related quality of life</th>
<th>Non-serious (or non-severe) symptoms (or late complications) and adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>0.53 – 0.58</td>
<td>0.24 – 0.38</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>Considerable</td>
<td>0.84 – 0.85</td>
<td>0.69 – 0.71</td>
<td>0.34 – 0.48</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>n.a.</td>
<td>n.a.</td>
<td>0.69 – 0.71</td>
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Issues regarding extent of added benefit:

- IQWiG proposal based upon shifted hypothesis
- Pragmatic approach considering power of 2 studies
- Based upon RR (binary data)
- Application also to HR (time-to-event data)
- No standard approach for other scales (continuous, ordinal data)
- Proposal should be extended and refined
Indirect comparisons – requirements

- Adjusted indirect comparisons ONLY
- Description of
  - Method
  - Assumptions
- In case of Bayes methods description of
  - A priori distributions
  - No. of Markov chains
  - Initial values
- Reasons for similarity
- Check of homogeneity
- Check of consistency
- Computer code
- Sensitivity analyses
Indirect comparisons: Details

Original Article

Received 28 June 2011, Revised 10 July 2012, Accepted 19 July 2012

(wileyonlinelibrary.com) DOI: 10.1002/jrsm.1057

Unsolved issues of mixed treatment comparison meta-analysis: network size and inconsistency

Sibylle Sturtz\textsuperscript{a}\textsuperscript{*}\textsuperscript{†} and Ralf Bender\textsuperscript{a,b}

Impact of network size:
Larger networks are based upon more evidence but have more potential for heterogeneity and inconsistency
Indirect comparisons

Importance of Results from Indirect Comparisons

Joint Statement from IQWiG, GMDS and IBS-DR
Authors: Ralf Bender, Carsten Schwenke, Claudia Schmoor, Dieter Hauschke

Joint statement of IQWiG, GMDS and IBS-DR (07.03.2012):

Network meta-analyses lead to lower certainty of results compared to meta-analyses of direct head-to-head studies

Unadjusted indirect comparisons are not acceptable

http://www.gmds.de/pdf/publikationen/stellungnahmen/120202_IQWIG_GMDS_IBS_DR_engl.pdf
Example: Axitinib for kidney cancer

Axitinib for kidney cancer

Example of a dossier, in which an unadjusted indirect comparison was used
Example: Axitinib for kidney cancer

- No direct head-to-head trial available
- No bridge comparator available
- No adjusted indirect comparison possible

Company used **STC**, which represents an unadjusted indirect comparison

**Assessment of IQWiG:**

In its dossier, the drug manufacturer did not present any data suitable for the comparison with everolimus … **An added benefit of axitinib for this treatment situation is therefore not proven.**
Outlook

- New Draft of IQWiG General Methods Paper Version 4.2
  - New chapter on cost-benefit assessment
  - New IQWiG product: Assessment of potential of a new examination or treatment method
  - Published 18.06.2914
  - 31 comments until 07.08.2014
  - Hearing on 01.10.2014


- Planned: Special article series on analysis of adverse events in Biopharmaceutical Statistics
Summary

- Proof of (additional) benefit requires – in general – a meta-analysis of studies with high certainty of results
- Study design and analysis according to GCP
- Criteria for a proof of benefit from 1 study
- Prediction intervals as new tool in the case of heterogeneity
- IQWiG proposal to operationalize the assessment of the extent of added benefit
- In early benefit assessment situations with lower certainty of results are expected
- IQWiG tries to solve problems to deal with situations leading to lower certainty of results