ROeS 2013, Dornbirn, 10.09.2013

Biometrical Issues in Health Technology Assessment

Ralf Bender

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

Outline

- IQWiG and the German system
- Benefit assessment before and according to AMNOG
- Biometrical topics
  - Assessment of added benefit
  - Extent of added benefit
  - Surrogate endpoints
  - Indirect comparisons
  - Subpopulations
- Examples
- 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.

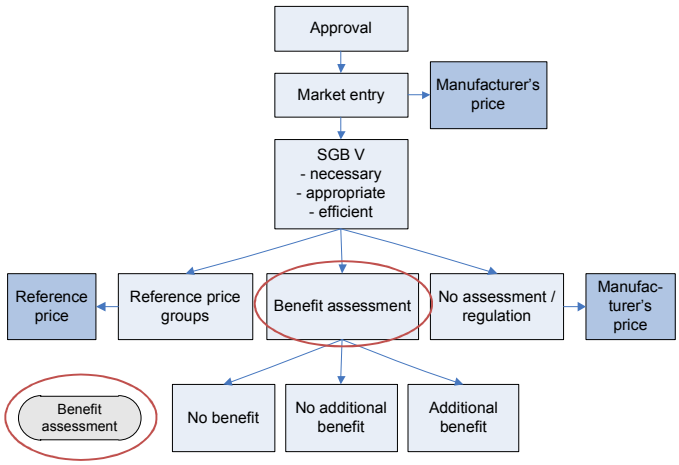
Legal supervision

IQWiG ← Commissions ← G-BA

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.

Benefit assessment before AMNOG



Benefit assessment

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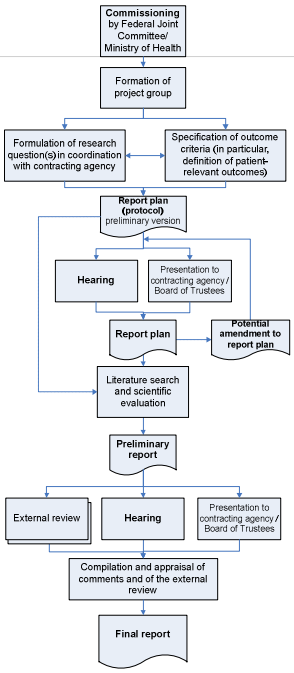
Procedure of a benefit assessment at IQWiG



Benefit assessment

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General Methods[a]

Version 4.0 of 23.09.2011

https://www.iqwig.de/download/General_Methods_4-0.pdf

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

IQWiG:

Update of General Methods

More Details →

Aktualisierung einiger Abschnitte der Allgemeinen Methoden Version 4.0 sowie neue Abschnitte zur Erstellung der Allgemeinen Methoden Version 4.1

Entwurf vom 18.04.2013

Requirements of IQWiG

Conclusion	No. of studies	Qualitative certainty	Effect(s)
Proof	≥ 2	high	homogeneous meta-analysis statistically significant
	≥ 2	high	heterogeneous effects clearly in the same direction
Indication	≥ 2	moderate	homogeneous meta-analysis statistically significant
	≥ 2	moderate	heterogeneous effects clearly in the same direction
	≥ 2	high	heterogeneous effects moderately in the same direction
	1	high	statistically significant
Hint	≥ 2	low	homogeneous meta-analysis statistically significant
	≥ 2	low	heterogeneous effects clearly in the same direction
	≥ 2	moderate	heterogeneous effects moderately in the same direction
	1	moderate	statistically significant

Prediction intervals

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

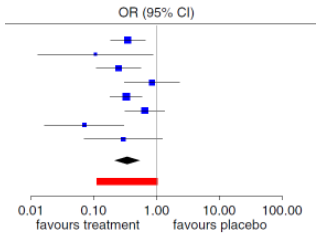
SYSTEMATIC REVIEWS

METHODOLOGY Open Access

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

Charlotte Guddat[1*], Ulrich Grouven[1,2], Ralf Bender[1,3] and Guido Skipka[1]

- 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)"

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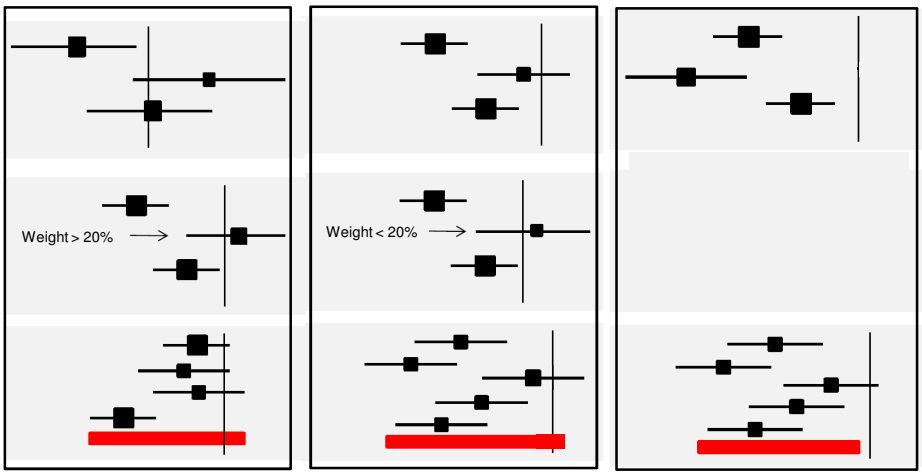
Examples for different "i.s.d." situations



Not i.s.d. **Moderately i.s.d** **Clearly i.s.d.**

Benefit assessment (before AMNOG)

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Issues regarding assessment of added benefit:

- Certainty of results (high, moderate, low)
- RCTs: Risk of bias
- Homogeneity: Statistically significant meta-analysis
- Heterogeneity: Effects clearly, moderately or not i.s.d.
- Prediction intervals
- Derivation of proof, indication or hint of added benefit

Drug assessment according to AMNOG

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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)

Drug assessment according to AMNOG

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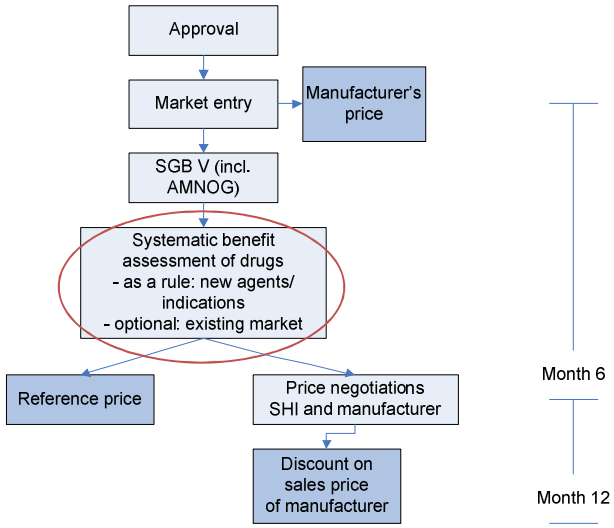
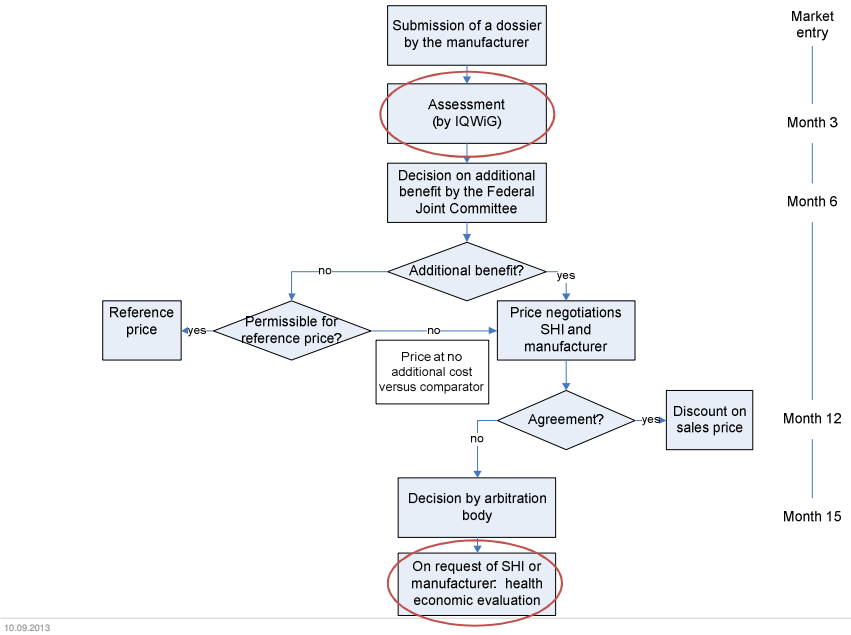


Drug assessment according to AMNOG



The dossier – challenges

New: *Extent* of added benefit

General steps from formulating question to decision on therapeutic value

- Identify/PICO
- Reflect benefits & harms!
- Determine treatment effects
- Consider uncertainty/risk of bias
- Aggregate information on various outcomes

Specific methods to ascertain "added benefit" in accordance with law (AMNOG)

- Criteria for appropriate comparator (licensed, therapeutic standard based on evidence)
- Choice and assessment of outcomes following EbM methods (clinical relevance)
- Extent of added benefit categories
  - **AM-NutzenV*: Designates categories (minor, considerable, major)**
  - IQWiG: Developed approach to operationalize extent of added benefit

*Regulation for Early Benefit Assessment of New Pharmaceuticals

AMNOG – Extent of 'added benefit'

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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'

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Criteria in accordance with AM-NutzenV*

- Major added benefit
- Considerable 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, important avoidance of other adverse 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'

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Criteria in accordance with AM-NutzenV*

- Major added benefit — sustained and great improvement# (cure, major increase in survival
- Considerable added benefit — marked improvement# (perceptible alleviation of the disease, moderate increase in survival time, alleviation of serious symptoms, relevant
- Minor added benefit → moderate and not only marginal improvement# (reduction in non-serious symptoms, relevant avoidance of side effects)
- 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'

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Criteria in accordance with AM-NutzenV*

- Major added benefit — sustained and great improvement# (cure, major increase in survival
- Considerable added benefit — marked improvement# (perceptible alleviation of the disease, moderate increase in survival time, alleviation of serious symptoms, relevant
- Added benefit not quantifiable
- Minor added benefit — moderate and not only marginal improvement# (reduction in non-serious symptoms, relevant avoidance of side effects)
- 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'

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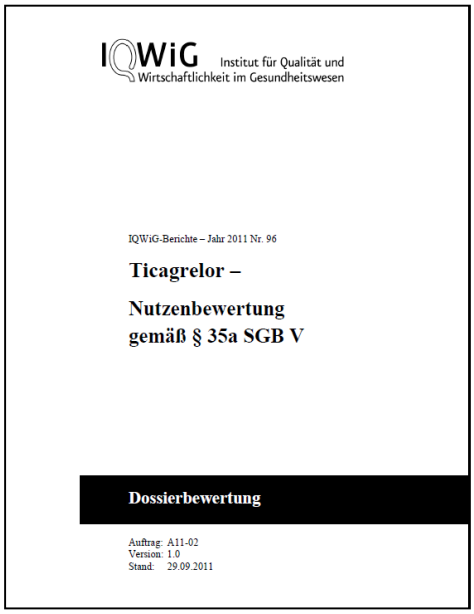
IQWiG:

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

Details →


IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG-Berichte – Jahr 2011 Nr. 96

Ticagrelor –

Nutzenbewertung gemäß § 35a SGB V

Dossierbewertung

Auftrag: A11-02
Version: 1.0
Stand: 29.09.2011

AMNOG – Extent of 'added benefit'

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IQWiG:

Update of General Methods

More Details →


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Institute for Quality and Efficiency in Health Care

Aktualisierung einiger Abschnitte der Allgemeinen Methoden Version 4.0 sowie neue Abschnitte zur Erstellung der Allgemeinen Methoden Version 4.1

Entwurf vom 18.04.2013

AMNOG – Extent of 'added benefit'

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

Extent category	Outcome category		
	Overall mortality	Serious (or severe) symptoms (or late complications) and adverse events, as well as health-related quality of life[a]	Non-serious (or non-severe) symptoms (or late complications) and adverse events
Major	**0.85**	**0.75** and risk ≥ 5%[b]	n.a.
Considerable	**0.95**	**0.90**	**0.80**
Minor	**1.00**	**1.00**	**0.90**

a: Precondition: use of a validated or established instrument and a validated or established response criterion
b: Risk must be at least 5 % for at least one of the two groups being compared

AMNOG – Extent of 'added benefit'

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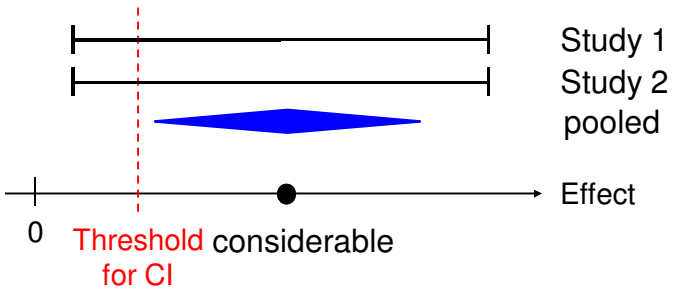
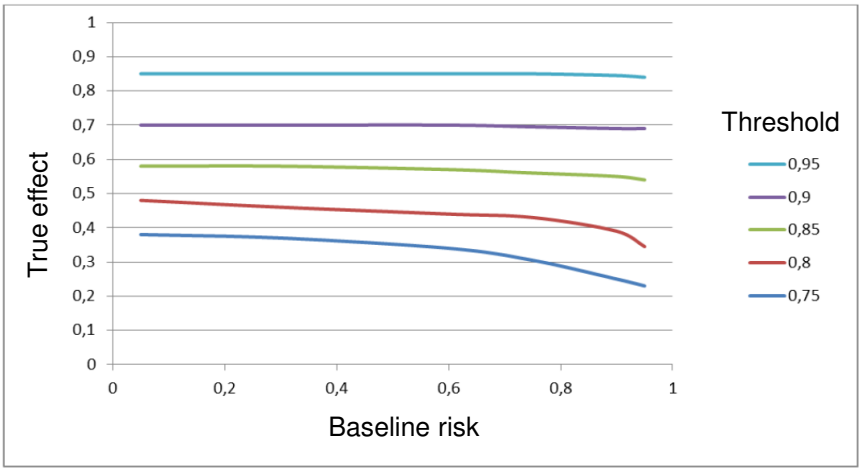
Main idea



If you have 2 studies each with power of 1-β for the usual test of superiority, then the threshold is chosen so that the pooled analysis also has a power of 1-β for the for the shifted hypothesis

AMNOG – Extent of 'added benefit'

True effects (RRs) in dependence on baseline risk



AMNOG – Extent of 'added benefit'

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

Extent category	Outcome category		
	Overall mortality	Serious (or severe) symptoms (or late complications) and adverse events, as well as health-related quality of life	Non-serious (or non-severe) symptoms (or late complications) and adverse events
Major	**0.53 – 0.58**	**0.24 – 0.38**	n.a.
Considerable	**0.84 – 0.85**	**0.69 – 0.71**	**0.34 – 0.48**
Minor	n.a.	n.a.	**0.69 – 0.71**

AMNOG – Extent of 'added benefit'

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 can be extended and refined

Surrogate endpoints

Requirements for validation of surrogates

- High correlation
- Biological plausibility
- Intervention specificity
- Indication specificity
- Generalizability / robustness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IQWiG-Berichte – Jahr: 2011 Nr. 80

Aussagekraft von Surrogatendpunkten in der Onkologie

Rapid Report

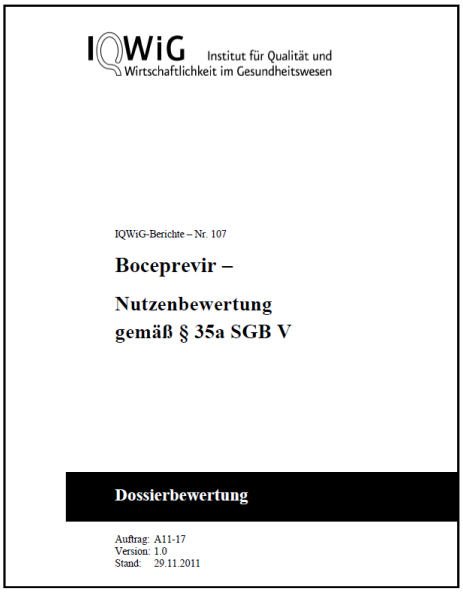
Auftrag: A10-05
Version: 1.1
Stand: 21.11.2011

- **Alternative: Use of clearly accepted surrogates**

Example: Boceprevir for hepatitis C

Boceprevir for HCV

Example of a dossier, in which a surrogate endpoint was used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IQWiG-Berichte – Nr. 107

Boceprevir –

Nutzenbewertung gemäß § 35a SGB V

Dossierbewertung

Auftrag: A11-17
Version: 1.0
Stand: 29.11.2011

Example: Boceprevir for hepatitis C

- Adequate data available for patients who have not yet developed liver cirrhosis (but 1 study only)
- No data on patient relevant outcomes
- Endpoint: Sustained virological response (SVR)
- SVR is a surrogate endpoint which is not validated
- It is accepted that patients with no detectable hepatitis C virus in the blood are at lower risk of liver cancer
- However, it is unclear how many cases of liver cancer can in fact be prevented by boceprevir

⇨ **Assessment of IQWiG:**

IQWiG recognizes an **"indication" of a benefit for boceprevir** …
It is unclear whether the added benefit is "minor", "considerable" or "major“ … the corresponding legal ordinance specifies the assessment category of **"unquantifiable"**

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
- Check of homogeneity
- Check of consistency
- Computer code
- Sensitivity analyses

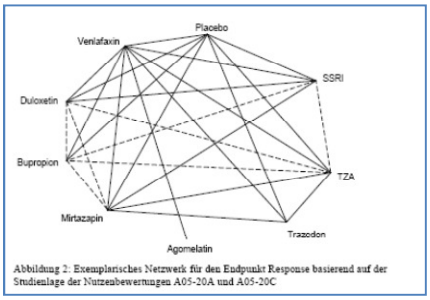

Abbildung 2: Exemplarisches Netzwerk für den Endpunkt Response basierend auf der Studienlage der Nutzenbewertungen A05-20A und A05-20C

Original Article

Research Synthesis Methods

Received 28 June 2011, Revised 10 July 2012, Accepted 19 July 2012 Published online 27 September 2012 in Wiley Online Library

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

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

Sibylle Sturtz[a]*† and Ralf Bender[a,b]

Res. Syn. Meth. **2012**, 3 300–311

Impact of network size:

Larger networks are based upon more evidence but have more potential for heterogeneity and inconsistency

Indirect comparisons

INTERNATIONAL BIOMETRIC SOCIETY

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Institute for Quality and Efficiency in Health Care

gmds Deutsche Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie e.V.

Stellenwert von Ergebnissen aus indirekten Vergleichen
Gemeinsame Stellungnahme von IQWiG, GMDS und IBS-DR
Autoren: Ralf Bender, Carsten Schwenke, Claudia Schmoor, Dieter Hauschke

GMDS Geschäftsstelle
Beatrix Behrendt
Industriestraße 154
D-50996 Köln

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

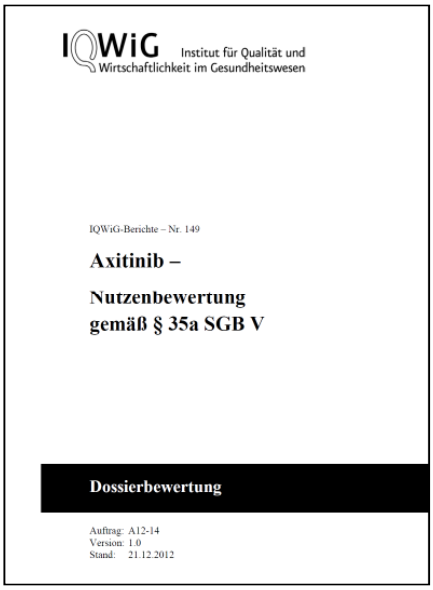
Unadjusted indirect comparisons are not acceptable

http://www.gmds.de/pdf/publikationen/stellungnahmen/120202_IQWIG_GMDS_IBS_DR.pdf

Example: Axitinib for kidney cancer

Axitinib for kidney cancer

Example of a dossier, in which an unadjusted indirect comparison was used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IQWiG-Berichte – Nr. 149

Axitinib –

Nutzenbewertung gemäß § 35a SGB V

Dossierbewertung

Auftrag: A12-14
Version: 1.0
Stand: 21.12.2012

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 <u>unadjusted indirect comparison</u>

METHODOLOGICAL CONSIDERATIONS

Pharmacoeconomics 2010; 28 (10): 957-967
1170-7690/10/0010-0957/$49.95/0

No Head-to-Head Trial? Simulate the Missing Arms

J. Jaime Caro[1,2] and *K. Jack Ishak*[3]

1 Division of General Internal Medicine and Department of Epidemiology, Biostatistics and Occupational Health, Faculty of Medicine, McGill University, Montreal, Quebec, Canada
2 United BioSource Corporation, Lexington, Massachusetts, USA
3 United BioSource Corporation, Dorval, Quebec, Canada

⇨ **<u>Assessment of IQWiG:</u>**

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**.

Subpopulation problem

Frequent problem in dossiers:

- PICO (mainly) chosen by G-BA leads to different populations than in the RCTs performed for drug approval
- Population of RCT subdivided into subpopulations
- Low power (within single subpopulations)
- Similar but not identical to subgroup analyses
- In usual subgroup analyses a *p*-value ≥ 0.2 for a heterogeneity or interaction test may be sufficient to rely on the overall effect estimate
- This is not the case for the transferability of effects between different subpopulations

Subpopulation problem

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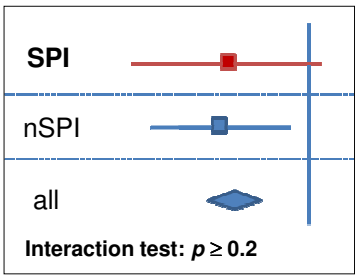
Data situation:



← Subpopulation of interest

Questions:

- Is it justified to transfer the overall (statistically significant) effect on the subpopulation of interest (SPI)?
- What is the extent of added benefit in the subpopulation?

Subpopulation problem

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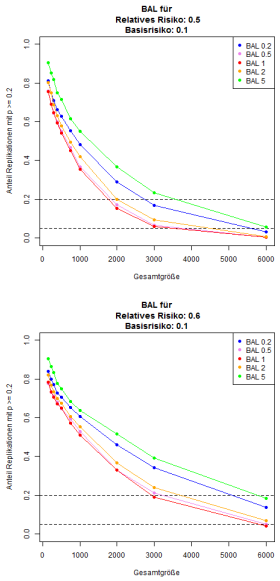
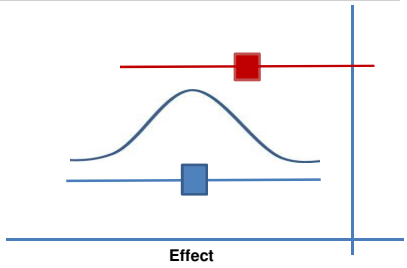
- Due to low power of interaction tests, a *p*-value ≥ 0.2 is in general insufficient as proof of homogeneity
- In the case of a low baseline risk and a null effect in one subpopulation, the probability of a *p*-value ≥ 0.2 for the interaction test may be 60% or higher
- With low baseline risk a very large sample size (e.g. n ≥ 6000) is required to exclude a null effect in the SPI from a *p*-value ≥ 0.2 for the interaction test
- The transferability of effects between different subpopulations or from the overall effect on the SPI cannot automatically assumed



Subpopulation problem

Possible approach:



- Simulation study for specific data situation
- Fixed:
  Sample size, baseline risk, null effect in SPI
- Calculate the probability of the observed (or more extreme) result (RR in SPI and interaction test)
- If this probability is small (< 2.5%) an **added benefit** in the SPI can be assumed
- However, the extent of the added benefit in the SPI is **non-quantifiable**

Summary

- Principal requirements of IQWiG in benefit and early benefit assessments are the same
- Proof of (additional) benefit requires – in general – a meta-analysis of studies with high certainty of results
- 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
- IQWiG proposal to operationalize the assessment of the extent of added benefit
- Improved new methods for specific situations desirable (indirect comparisons, subpopulation problem)