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Basel, 25.09.2012

IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Institute for Quality and Efficiency in Health Care

Biometrical Requirements in (Early) Benefit Assessments

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Outline

- IQWiG and the German system
- Benefit assessment before and according to AMNOG
- The dossier – content and challenges
  - Surrogate endpoints
  - Indirect comparisons
  - Extent of added benefit
- Ongoing preparations at IQWiG
- 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.

German Social Code, Book V

§ 12 (cost-effectiveness principle*)

(1) "[Health] services must be sufficient, appropriate and cost-effective* and must not exceed the extent of what is necessary. Services that are not necessary or not cost-effective* may not be utilized by the insured persons, may not be rendered by the service providers and may not be granted by the [statutory] health insurance funds."

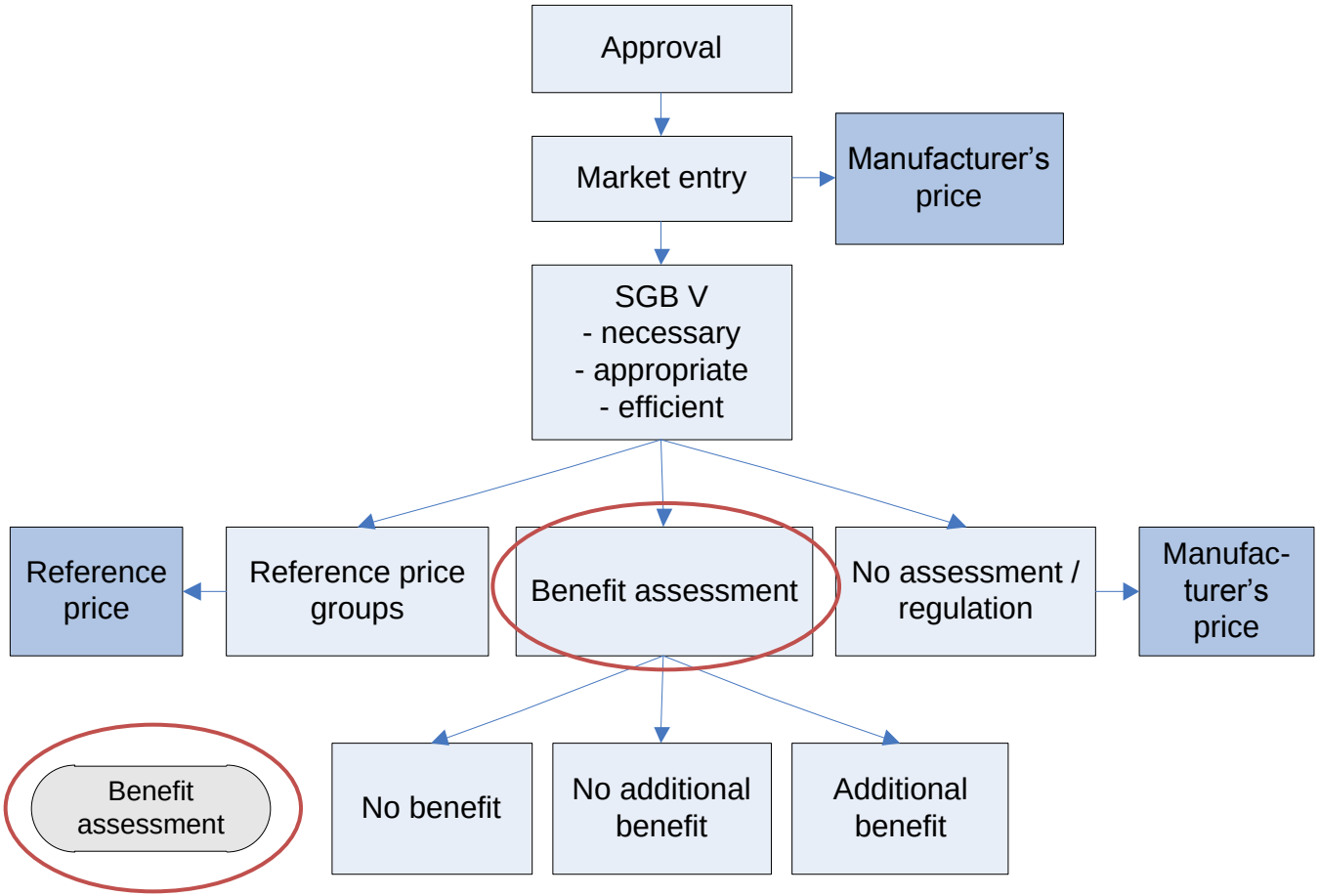
*Cost-minimization approach in the past

German Social Code, Book V

§ 139a (IQWiG)

(4) “The Institute must ensure that the assessment of medical benefit is carried out according to the internationally accepted standards of evidence-based medicine.”

Benefit assessment before AMNOG



Benefit assessment

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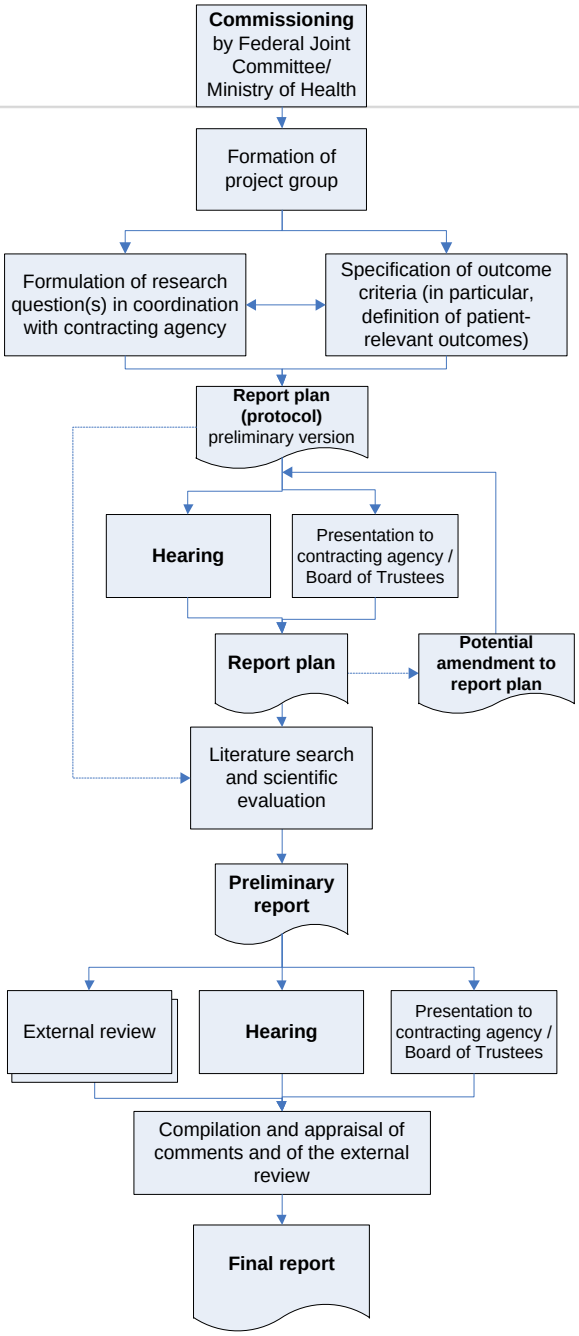
Procedure of a benefit assessment at IQWiG



Benefit assessment before AMNOG

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

Reliable results – Hierarchy of evidence

Systematic reviews (of RCTs)

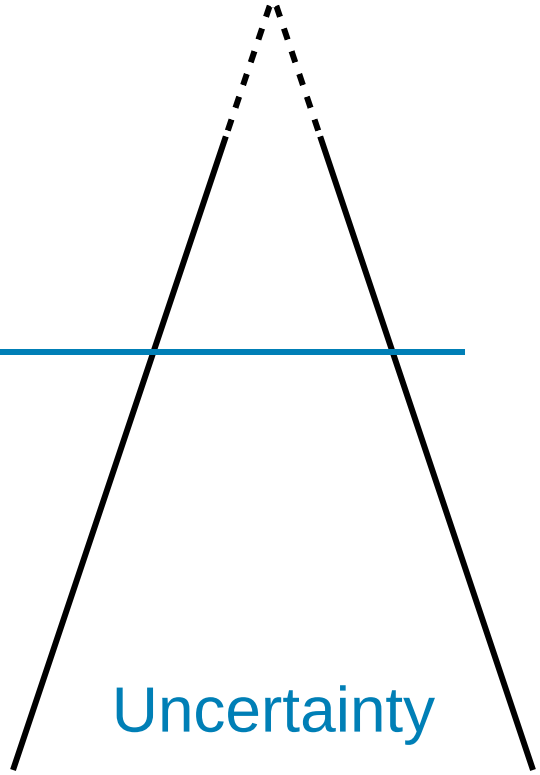
Randomized controlled trials

Controlled trials (non-RCTs)

Uncontrolled studies

Case series / case reports

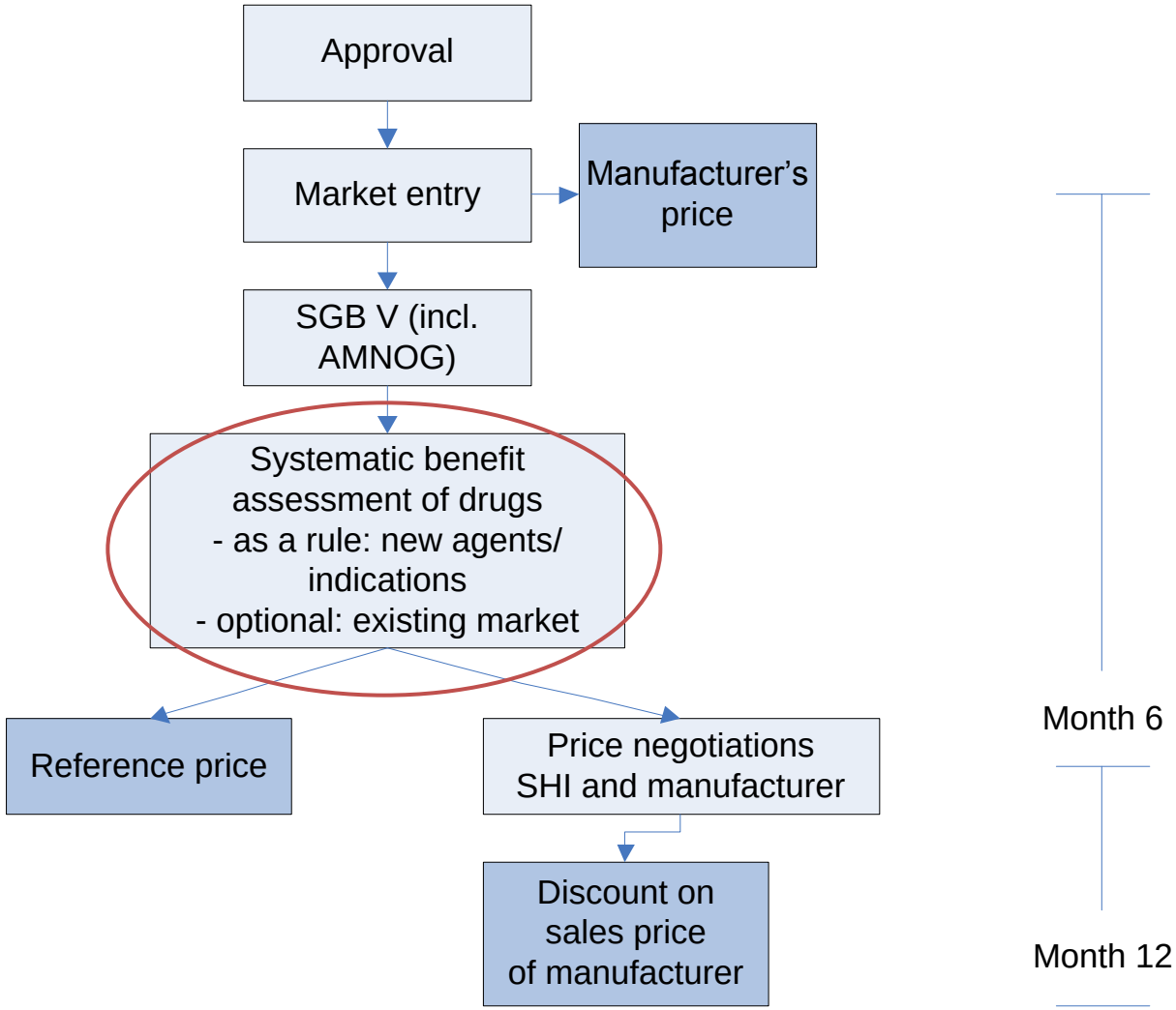
Opinions



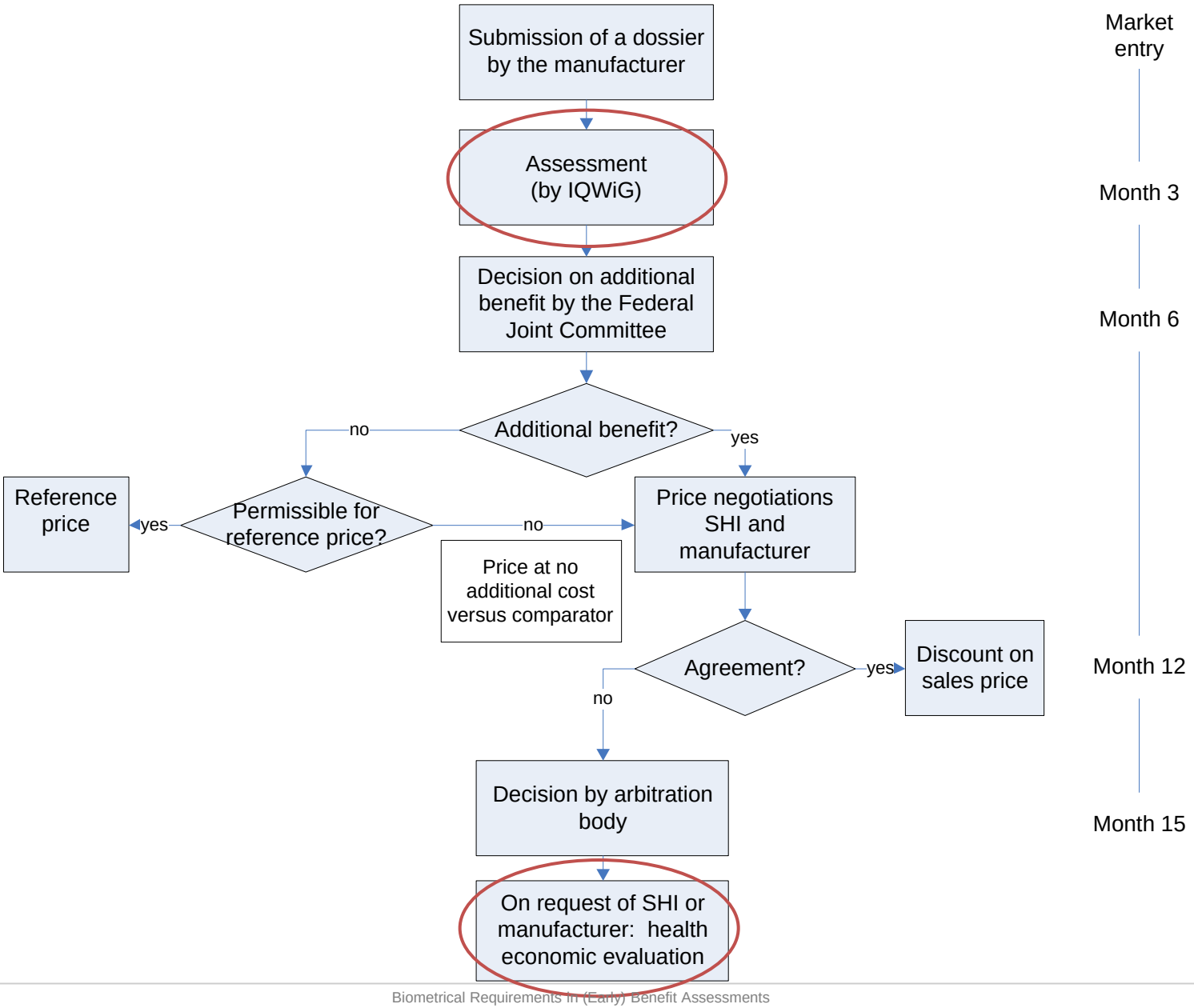
AMNOG – new legislation, new HTA products

- 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)

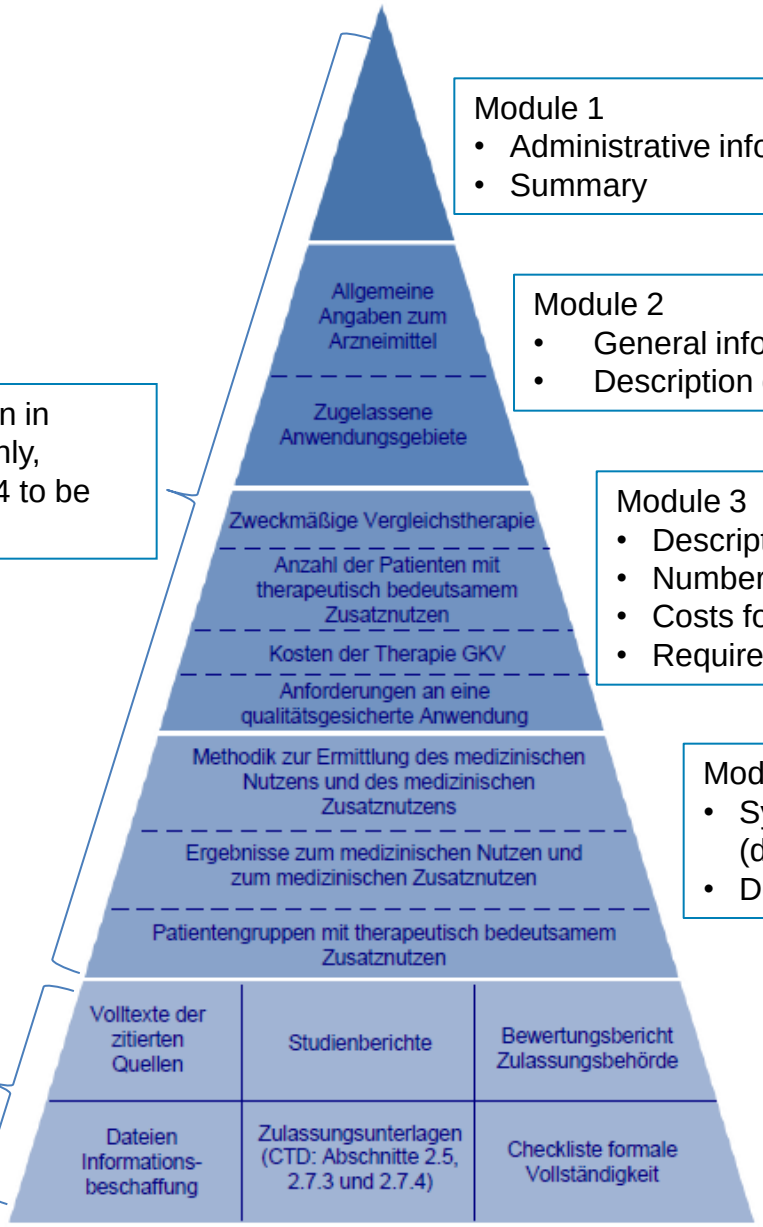
Drug assessment according to AMNOG



Drug assessment according to AMNOG



The dossier – content



Module 1
- Administrative information
- Summary

Module 2
- General information on the drug
- Description of approved indication

Module 3
- Description of appropriate comparator
- Number of patients with relevant additional benefit
- Costs for the SHI
- Requirements for quality-assured application

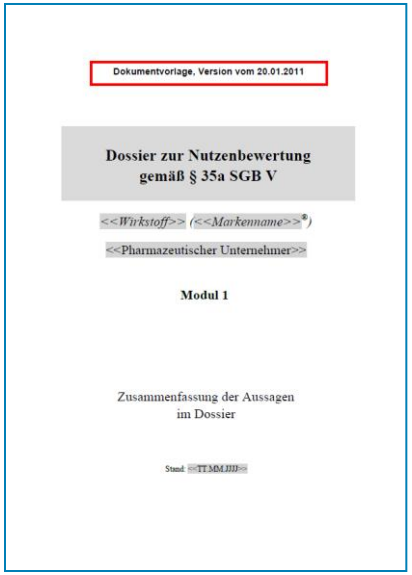
Module 4
- Systematic review of the benefit and additional benefit (description of methods and results)
- Description of patient groups with a relevant additional benefit

Module 5
- Full texts of references
- Data on the documentation of information retrieval
- Study reports for all manufacturer-sponsored trials
- Approval documents (CTD 2.5, 2.7.3, 2.7.4)
- Evaluation report of the regulatory authority
- Checklist for the review of formal completeness

Submission in German only, Module 1-4 to be published

Submission in English possible, not to be published

The dossier – content


Dokumentvorlage, Version vom 20.01.2011

Dossier zur Nutzenbewertung gemäß § 35a SGB V

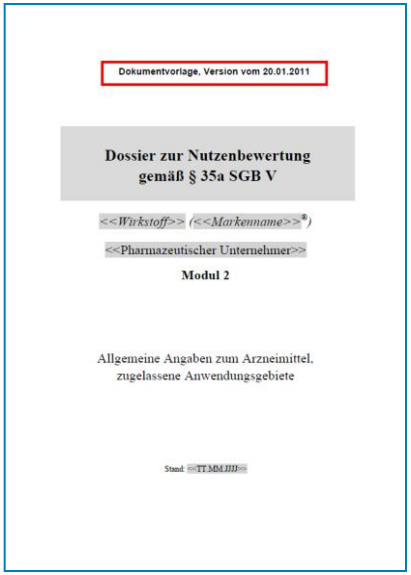
<<Wirkstoff>> (<<Markenname>>®)

<<Pharmazeutischer Unternehmer>>

Modul 1

Zusammenfassung der Aussagen im Dossier

Stand: <<TT.MM.JJJJ>>


Dokumentvorlage, Version vom 20.01.2011

Dossier zur Nutzenbewertung gemäß § 35a SGB V

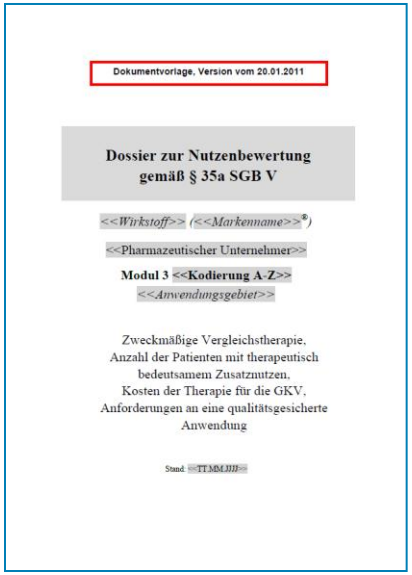
<<Wirkstoff>> (<<Markenname>>®)

<<Pharmazeutischer Unternehmer>>

Modul 2

Allgemeine Angaben zum Arzneimittel, zugelassene Anwendungsgebiete

Stand: <<TT.MM.JJJJ>>


Dokumentvorlage, Version vom 20.01.2011

Dossier zur Nutzenbewertung gemäß § 35a SGB V

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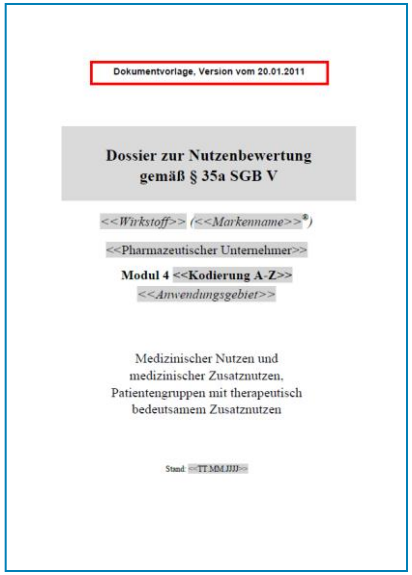
<<Pharmazeutischer Unternehmer>>

Modul 3 <<Kodierung A-Z>>

<<Anwendungsgebiet>>

Zweckmäßige Vergleichstherapie, Anzahl der Patienten mit therapeutisch bedeutsamem Zusatznutzen, Kosten der Therapie für die GKV, Anforderungen an eine qualitätsgesicherte Anwendung

Stand: <<TT.MM.JJJJ>>


Dokumentvorlage, Version vom 20.01.2011

Dossier zur Nutzenbewertung gemäß § 35a SGB V

<<Wirkstoff>> (<<Markenname>>®)

<<Pharmazeutischer Unternehmer>>

Modul 4 <<Kodierung A-Z>>

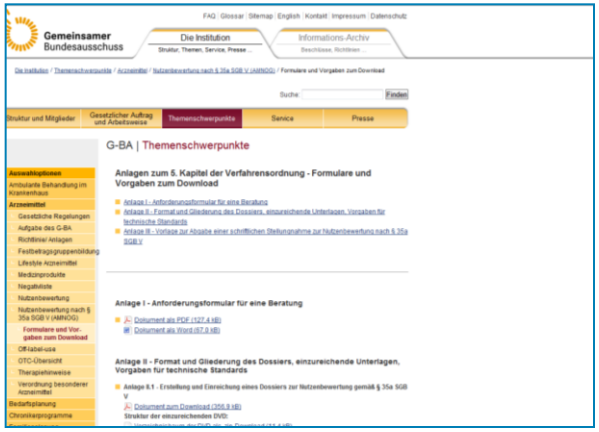
<<Anwendungsgebiet>>

Medizinischer Nutzen und medizinischer Zusatznutzen, Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen

Stand: <<TT.MM.JJJJ>>

Comprehensive German-language templates (including methodological advice) available from: http://www.g-ba.de

- Dossier submission in German only (except for study reports)



The dossier – challenges

"Just because everything is different doesn't mean anything has changed." Irene Peter

Wanted: The "added therapeutic value"

- "A new medicinal product can be said to have added therapeutic value if sound clinical data show that it offers patients better efficacy, and/or better safety and/or simpler administration, than existing alternatives"*

Still the same challenges?

- Patient-relevant outcomes
- Reliable results
- Appropriate comparators

*Eichler H-G, Bloechl-Daum B, Abadie E, Barnett D, Konig F, Pearson S. Relative efficacy of drugs: an emerging issue between regulatory agencies and third-party payers. Nat Rev Drug Discov 2010; 9(4): 277-291.

Patient-relevant outcomes

- Mortality
- Morbidity
  (medical condition, complications, adverse events)
- Health-related quality of life

No (invalid) surrogate endpoints

Requirements for validation of surrogates

- High correlation
- Biological / pharmacological plausibility
- Intervention specificity
- Indication specificity
- Generalizability / robustness

- Assessment of an intervention:

Effect on surrogate endpoint

Correlation → ⇩ ← Certainty of proposition

Effect on clinical endpoint

Effect size → ⇩ ← Certainty of results

Benefit

Criteria for certainty of proposition

- Systematic data basis
- Accepted validation method
- Analyses regarding generalizability and robustness
- Consideration of intervention specificity
- Consideration of indication specificity
- Consistent endpoint definition

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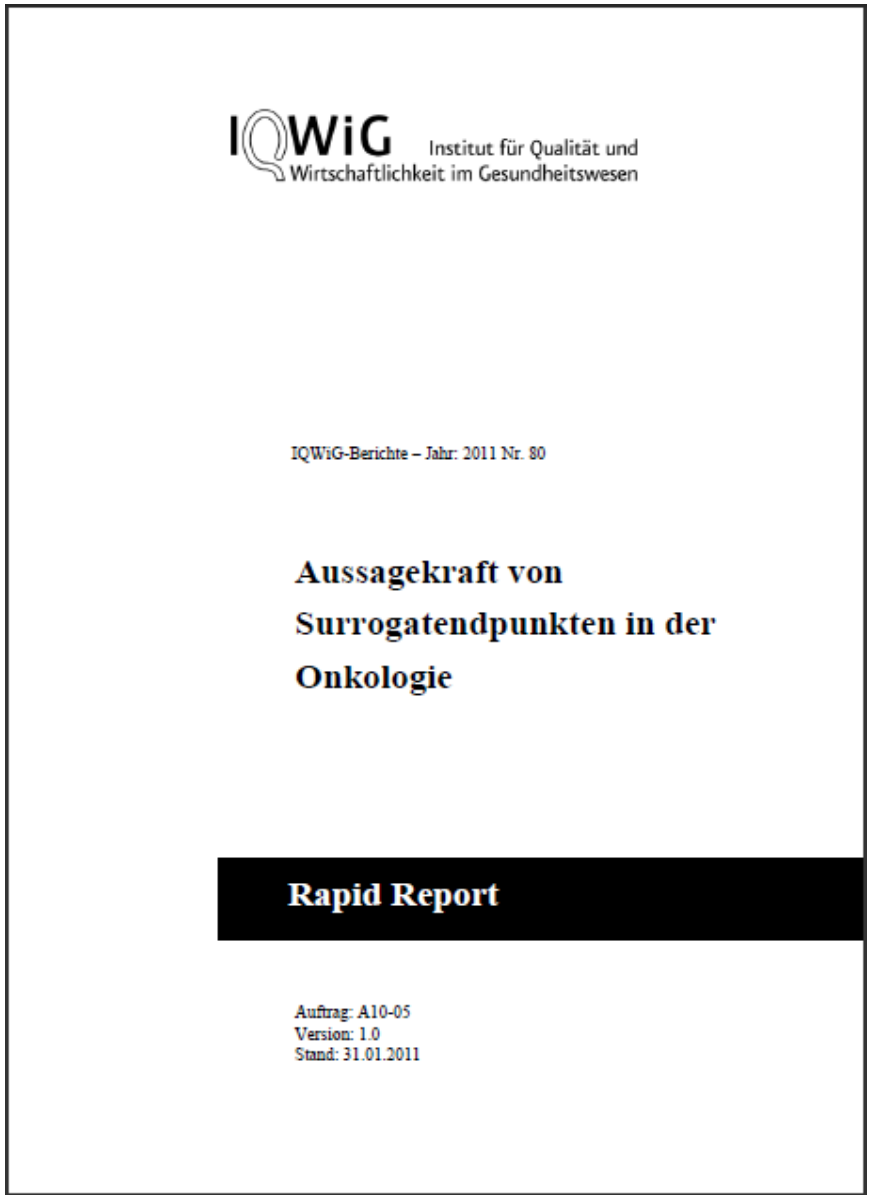
Surrogate endpoints:

Details →



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IQWiG-Berichte – Jahr: 2011 Nr. 80

Aussagekraft von Surrogatendpunkten in der Onkologie

Rapid Report

Auftrag: A10-05
Version: 1.0
Stand: 31.01.2011

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

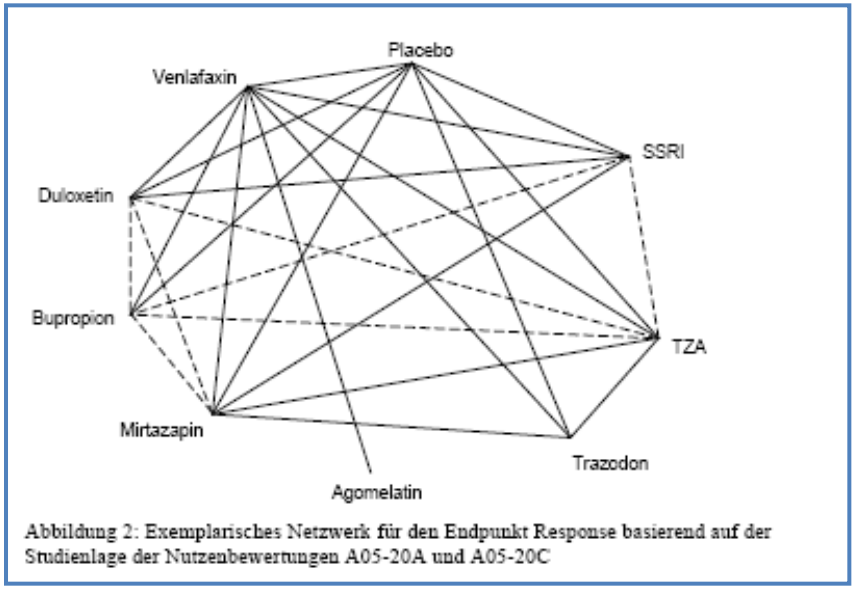

Abbildung 2: Exemplarisches Netzwerk für den Endpunkt Response basierend auf der Studienlage der Nutzenbewertungen A05-20A und A05-20C

- Computer code
- Sensitivity analyses

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Indirect comparisons:

Details →

SPi | Journal Code: J R S M | Article ID: 1 0 5 7 | Dispatch: 10.08.12 | No. of Pages: 14 | CE: Matugas, Ma. Theresa | ME:

Original Article

Research Synthesis Methods

Received 28 June 2011, Revised 10 July 2012, Accepted 19 July 2012 Published online 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]

Indirect comparisons and mixed treatment comparison (MTC) meta-analyses are increasingly used in medical research. These methods allow a simultaneous analysis of all relevant interventions in a connected network even if direct evidence regarding two interventions is missing. The framework of MTC meta-analysis provides a flexible approach for complex networks. However, this method has yet some unsolved problems, in particular the choice of the network size and the assessment of inconsistency. In this paper, we describe the practical application of MTC meta-analysis by using a data set on antidepressants. We focus on the impact of the size of the chosen network and the assumption of consistency. A larger network is based on more evidence but may show inconsistencies, whereas a smaller network contains less evidence but may show no clear inconsistencies. A choice is required that network should be used in practice. In summary, MTC meta-analysis represents a promising approach; however, clear application standards are still lacking. Especially, standards for the identification of inconsistency and the way to deal with potential inconsistency are required. Copyright © 2012 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

Keywords: mixed treatment comparison (MTC) meta-analysis; indirect comparison; model assumptions

Research Synthesis Methods

Sturtz & Bender
***Res. Syn. Meth.* 2012 (in press)**

Still the same challenges? !

- Patient-relevant outcomes
- Reliable results
- Appropriate comparators

- A proven (additional) benefit of a medical intervention
  - Requires reliable results based on patient-relevant outcomes
  - Is the prerequisite for a sufficient, appropriate and cost-effective health service

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’

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’

Major added benefit

Considerable added benefit

Minor added benefit

No added benefit has been proven

Less benefit

Criteria in accordance with AM-NutzenV*

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)

*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’

Major added benefit

Considerable added benefit

Minor added benefit

No added benefit has been proven

Less benefit

Criteria in accordance with AM-NutzenV*

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

moderate and not only marginal improvement[#] (reduction in non-serious symptoms, relevant avoidance of side effects)

*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’

Major added benefit

Considerable added benefit

Minor added benefit

No added benefit has been proven

Less benefit

Criteria in accordance with AM-NutzenV*

Added benefit not quantifiable

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

moderate and not only marginal improvement[#] (reduction in non-serious symptoms, relevant avoidance of side effects)

*Regulation for Early Benefit Assessment of New Pharmaceuticals

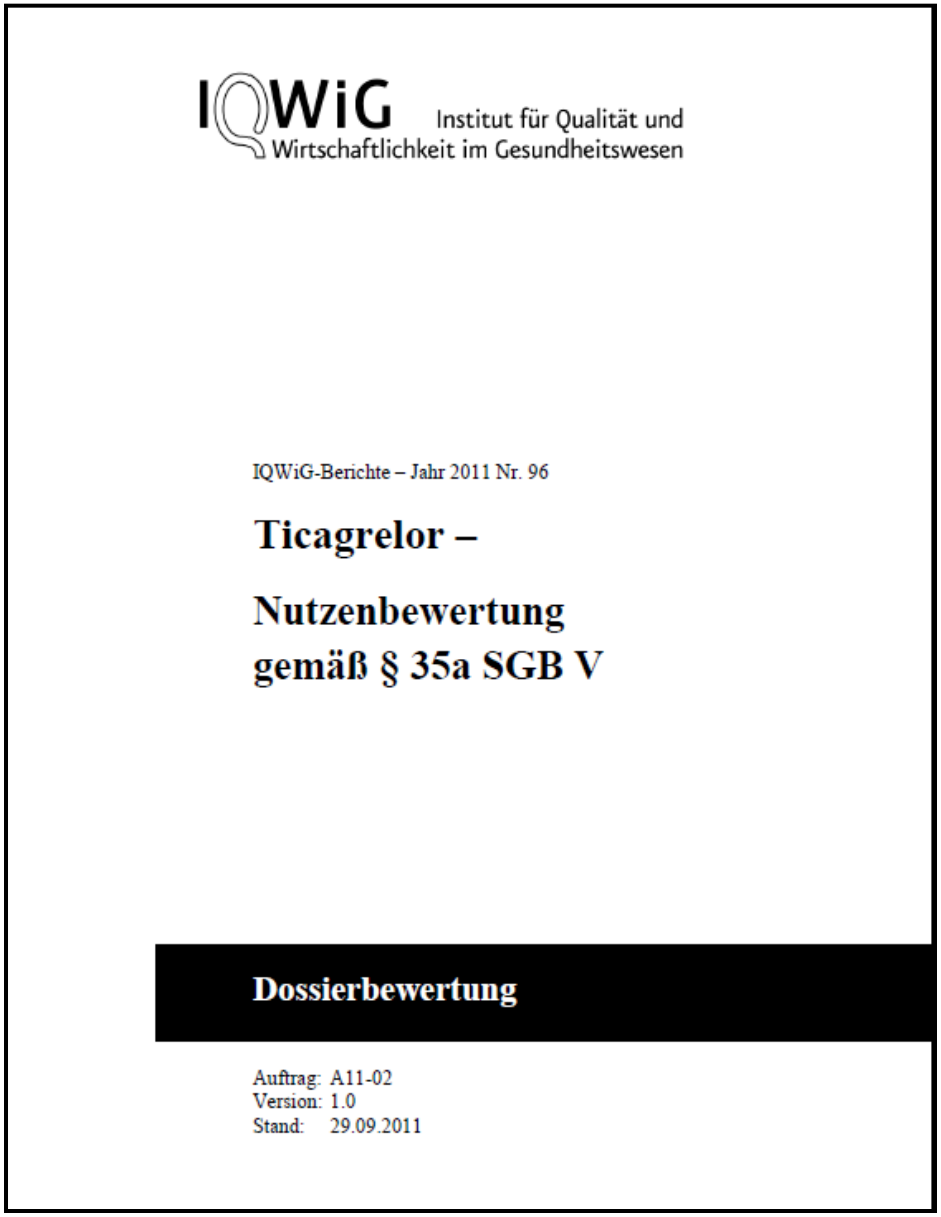
[#]in the therapy-relevant benefit, which has not previously been achieved versus the appropriate comparator

The dossier – challenges

IQWiG:

Proposal to operationalize extent of added benefit based upon shifted null hypotheses

Details →



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IQWiG-Berichte – Jahr 2011 Nr. 96

Ticagrelor –

Nutzenbewertung gemäß § 35a SGB V

Dossierbewertung

Auftrag: A11-02
Version: 1.0
Stand: 29.09.2011

The dossier – challenges

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Tabelle 32: Feststellung des Ausmaßes des Zusatznutzens - quantitative Operationalisierungen

		Zielgrößenkategorie			
		Überlebenszeit (Mortalität)	**Schwerwiegende *(bzw. schwere)*** Symptome *(bzw. Folgekomplikationen)* und Nebenwirkungen	***Lebensqualität***	**Nicht schwerwiegende *(bzw. nicht schwere)*** Symptome *(bzw. Folgekomplikationen)* und Nebenwirkungen
Zusatznutzen	**Erheblich** **nachhaltige** und gegenüber der zweckmäßigen Vergleichstherapie bisher nicht erreichte **große Verbesserung** des therapierelevanten Nutzens	Erhebliche Verlängerung der Überlebensdauer **KI_S: 0,85** (RR_1 = 0,50)	Langfristige Freiheit bzw. weitgehende Vermeidung **KI_S: 0,75** (RR_1 = 0,17) **und Risiko ≥ 5%**[2]	*Erhebliche Verbesserung*[1] **KI_S: 0,75** (RR_1 = 0,17) **und Risiko ≥ 5%**[2]	Nicht besetzt
	Beträchtlich gegenüber der zweckmäßigen Vergleichstherapie bisher nicht erreichte **deutliche Verbesserung** des therapierelevanten Nutzens	Moderate Verlängerung der Überlebensdauer **KI_S: 0,95** (RR_1 = 0,83)	Abschwächung bzw. relevante Vermeidung **KI_S: 0,90** (RR_1 = 0,67)	*Bedeutsame Verbesserung*[1] **KI_S: 0,90** (RR_1 = 0,67)	Bedeutsame Vermeidung **KI_S: 0,80** (RR_1 = 0,33)
	Gering gegenüber der zweckmäßigen Vergleichstherapie bisher nicht erreichte **moderate und nicht nur geringfügige Verbesserung** des therapierelevanten Nutzens	*Jegliche (statistisch signifikante) Verlängerung der Überlebensdauer* **KI_S: 1,00**	*Jegliche (statistisch signifikante) Verringerung* **KI_S: 1,00**	*Relevante Verbesserung*[1] **KI_S: 1,00**	Relevante Vermeidung **KI_S: 0,90** (RR_1 = 0,67)

Ergänzungen gegenüber AM-NutzenV *kursiv* gesetzt

1: Voraussetzung ist die Verwendung eines validierten Instruments sowie eines validierten Responsekriteriums. Werte gelten für Non-Response.

2: für mindestens eine der beiden zu vergleichenden Gruppen.

AM-NutzenV: Arzneimittel-Nutzenbewertungsverordnung, KI_S: Schwellenwert für obere Grenze des 95%-Konfidenzintervalls, RR_1: tatsächliches Relatives Risiko

Issues regarding extent of added benefit:

- IQWiG proposal based upon shifted hypothesis
- Pragmatic approach considering power of 2 studies
- Problems in the case of 1 study and subgroups
- Based upon RR (binary data)
- No proposal for other scales (continuous, ordinal data)
- Proposal should be discussed, extended and improved

Ongoing preparations at IQWiG

- Participation in the panels of the G-BA
- Development of templates for the assessment report
- Involvement of external experts and patient representatives in assessments according to AMNOG
- Further development of methods for the assessment of dossiers (e.g., subgroups, indirect comparisons)
- Especially: Refinement of approach to operationalize extent of added benefit

Summary

- Principal requirements of IQWiG in benefit assessments remain 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 expected
- New category “hint” (*“Anhaltspunkt”*)
- New: Extent of added benefit
- Procedures are different:
  - Before AMNOG: SR performed by IQWiG
  - AMNOG: SR performed by manufacturer (assessed by IQWiG)
  - AMNOG: All new drugs will be assessed (with some exceptions)