

The German Healthreform and IQWiG Update

Friedhelm Leverkus

May, 10 2011



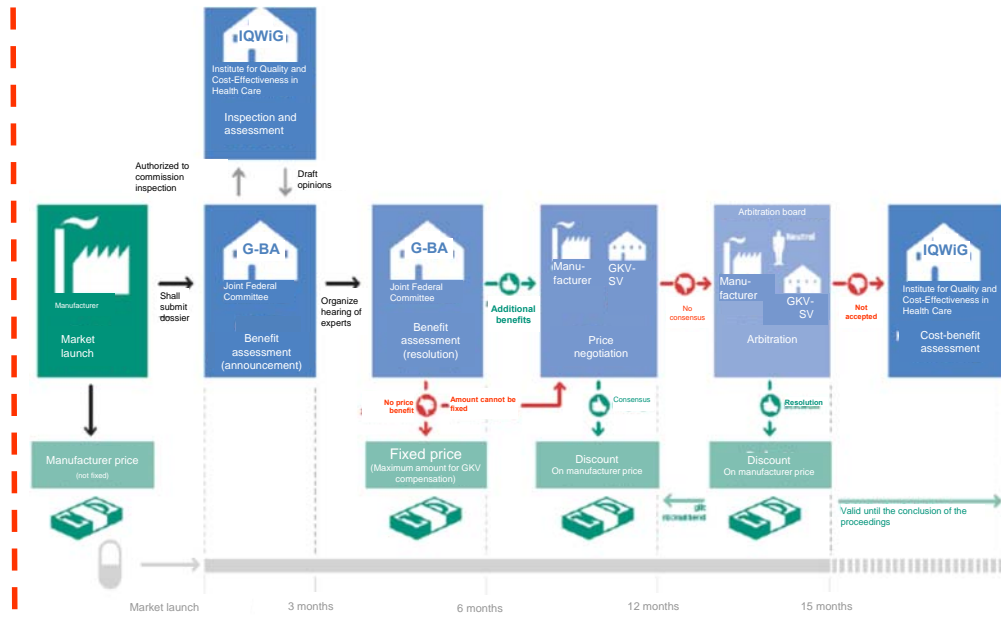
- **The New AMNOG Process**
- **Key Elements of the Law**
- **The Industry Dossier**
- **IQWiG Methods 4.0 Draft**



Optional Prefiling consultation of JC



- Before start of phase III possible
- Studies Design
- Comparator
- Endpoints
- Before Submission
- Time until Submission remains untouched
- Comparator
- Format and Content of Dossier



Source: BMG 2011, Pfizer Germany



AM-NutzenVO: Regulations for benefit assessment

Overview for value dossier



- Approved therapeutic indication
- Medical benefit & additional medical benefit compared to appropriate comparative therapy
- Number of patients and patient groups who benefits
- Costs of therapy for SHI
- Requirements for quality assured application



Scope of benefit assessment, § 35a SGB V



- **For each innovative agent:**

- Launch (Lauer-Taxe) = Value dossier
- Extension of therapeutic indication

- **In-line products:**

- Only, if requested by JC
- Extension of therapeutic indication for evaluated pharmaceuticals
- Focus on pharmaceuticals competing with evaluated pharmaceuticals

- **Exception:**

- Expected SHI Volume le 1 mio € /year
- Orphan-drugs
 - Additional benefit proved by marketing authorization, but magnitude of effect and costs for the SHI
 - Dossier and benefit assessment by more than 50 mio € / year SHI-volume

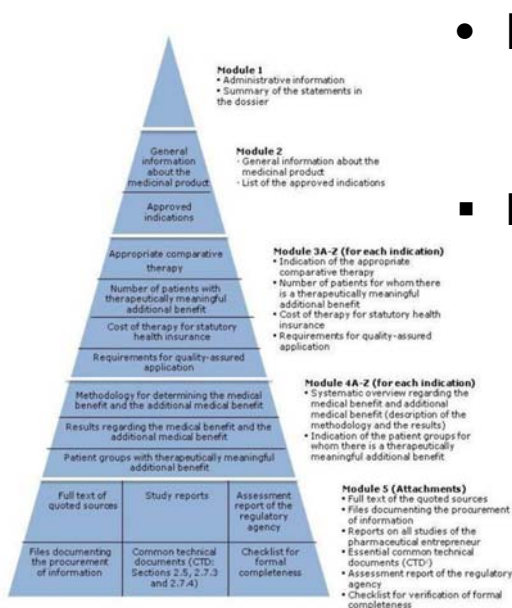
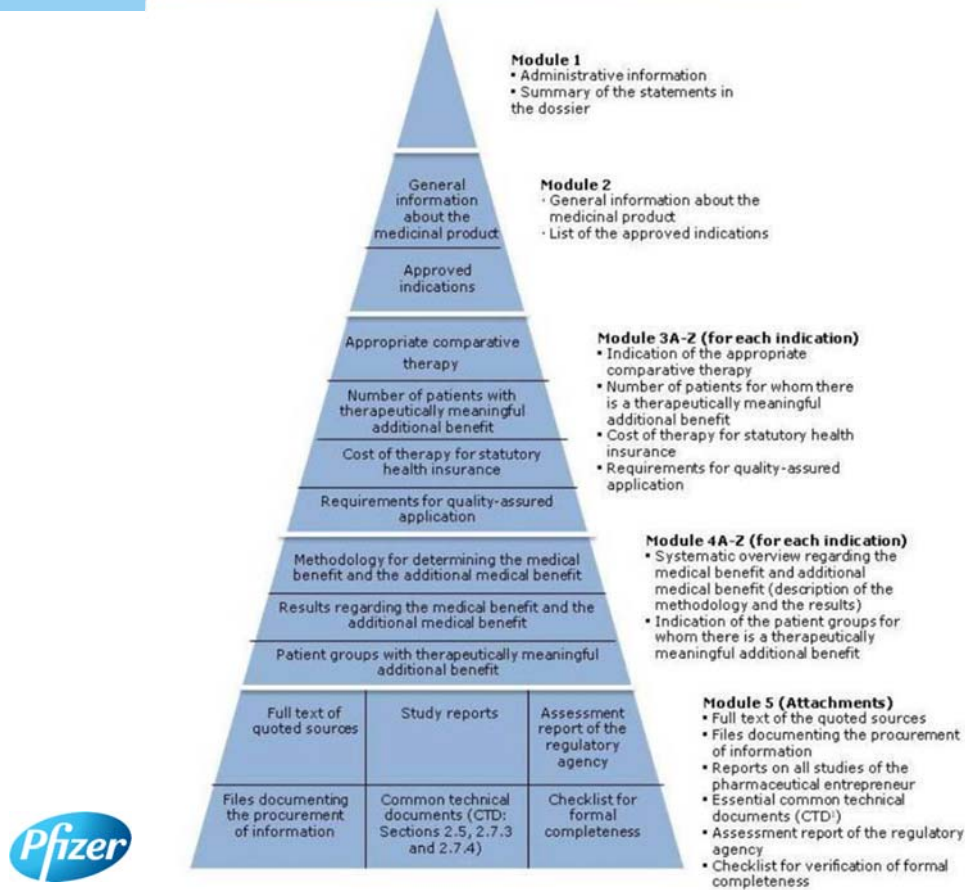


- **Additional Benefit**



- Industrie has to prove additional benefits against the comparator
- Comparator will be determined by JC
 - FRP Drug
 - Endpoint studies
 - EBM
- Additional benefit based on SPMC and clinical studies with patient relevant endpoints according to EBM
- Patient relevant endpoints (Mortality , Morbidity QoL)
- Preferable H2H RCT
- Indirect comparison are an option
- If no studies are available JC can ask for new studies





- **Modul 1**
 - Summary
 - Foundation of the Negotiations
- **Modul 2**
 - Active agent, ATC code, PZN, packaging size, etc.
 - Mode of action
 - Authorized areas of application
 - Other authorized areas of application in Germany
 - Status of authorization internationally

• **Modul 3**

▪ **Therapy cost for the GKV**

- Costs in pharmacy sales prices
- Costs of additional GKV payments according to SPCM
 - (e.g. only monitoring costs which are mentioned in SPCM will be counted)
- Calculation of the annual costs of therapy

▪ **No Modeling**

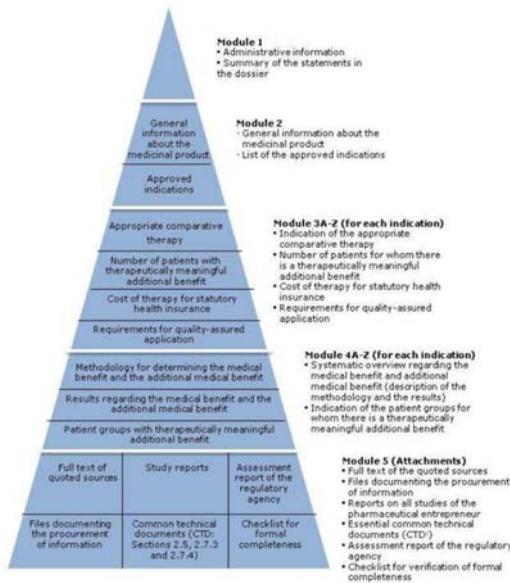
- No QUALY
- No Cost Effectiveness Analysis
- No Budget Impact Model

▪ **Paper and Pencil Analysis based on SPMC and direct Costs**

▪ **Foundation for negotiations**

▪ **no influence on additional benefit**

- Is reviewed by IQWiG



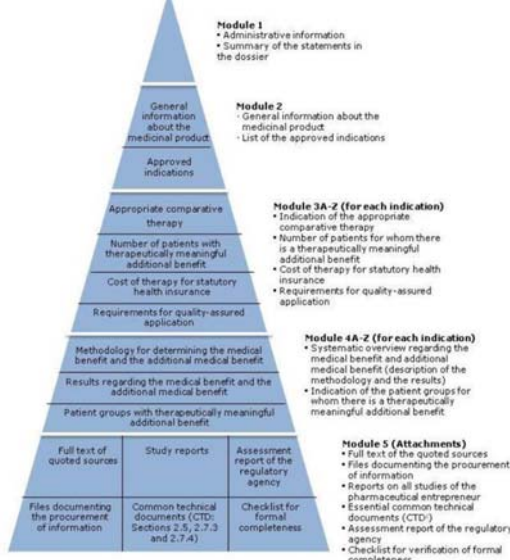
• **Modul 3**

▪ **Comparative treatment**

- appropriate comparative treatment
 - EBM based, with Endpoint Studies, FRP
- Reason for the choice:
 - Minutes of the advice of GBA
 - Reason

▪ **Epidmiology**

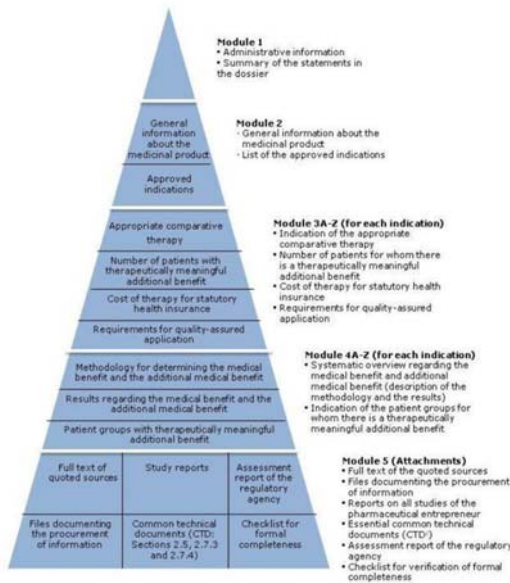
- Description of the disease, characterization of the target population
- Unmet need
- Prevalence and incidence in Germany
- **Number of patients with significant additional benefits**



• **Modul 4**

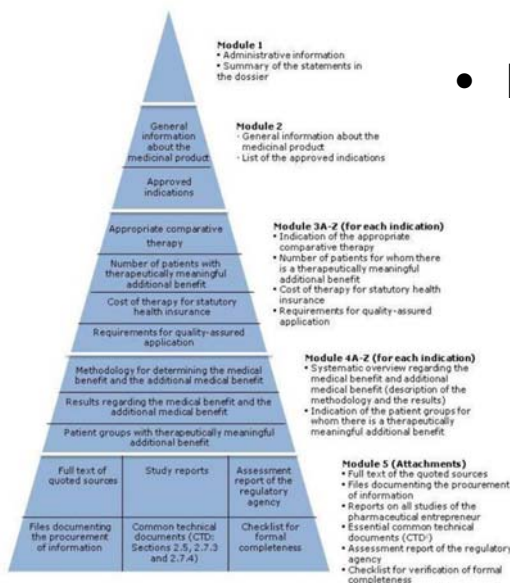
• **Benefit and Additional Benefit**


- **Systematic Review**
 - Bibliographical research+ Study register search+Industry+IIR
- **Assesment of the Evidence (biometric quality of the study)**
- **Patient relevant Endpoints, Design**
- **Summarizing the Studies in Meta-analyses**
 - Random Effect Model
 - If heterogeneity not large no pooled effect should be calculated
 - subgroups and the effect modifying variables
- **If no H2H studies available Indirect Comparison may be accepted**
- **Non Randomized studies may accepted**
 - Reason, why it is impossible or inappropriate to implement RCTs
 - Reasons why the observational study are not biased
 - Non Randomized study will have little value in the process
- **Surrogate Endpoints may not be accepted**



• **Modul 5**

- **Clinical Study Reports**
- **Common Technical documents**
 - CTD 2.5 2.73 2.74
- **EPAR**
- **Modul 4 is not confidential**
- **Modul 5 confidential parts could be flagged**



Classification (AM-NutzenV)		Description (AM-NutzenV)	Examples (AM-NutzenV) 
Level I	Extensive additional benefit	▪ Sustainable and benefit not yet achieved	<ul style="list-style-type: none"> ▪ Cure ▪ Extensive extension of life span ▪ Long lasting suppression of heavy symptoms ▪ Avoidance of severe side effects
Level II	Significant additional benefit	▪ Benefit not yet achieved	<ul style="list-style-type: none"> ▪ Soothing of severe symptoms ▪ Moderate extension of life span ▪ Perceptible relief ▪ Other significant
Level III	Marginal additional benefit	▪ Moderate or only small benefit	<ul style="list-style-type: none"> ▪ Soothing of mild symptoms
Level IV	Additional benefit not quantifiable	▪ Scientific data do not allow quantification of additional benefit	▪ Not detailed in AM-NutzenV
Level V	No additional benefit	▪ Not detailed in AM-NutzenV	▪ Not detailed in AM-NutzenV
Level VI	Less benefit than comparable therapy	▪ Not detailed in AM-NutzenV	▪ Not detailed in AM-NutzenV

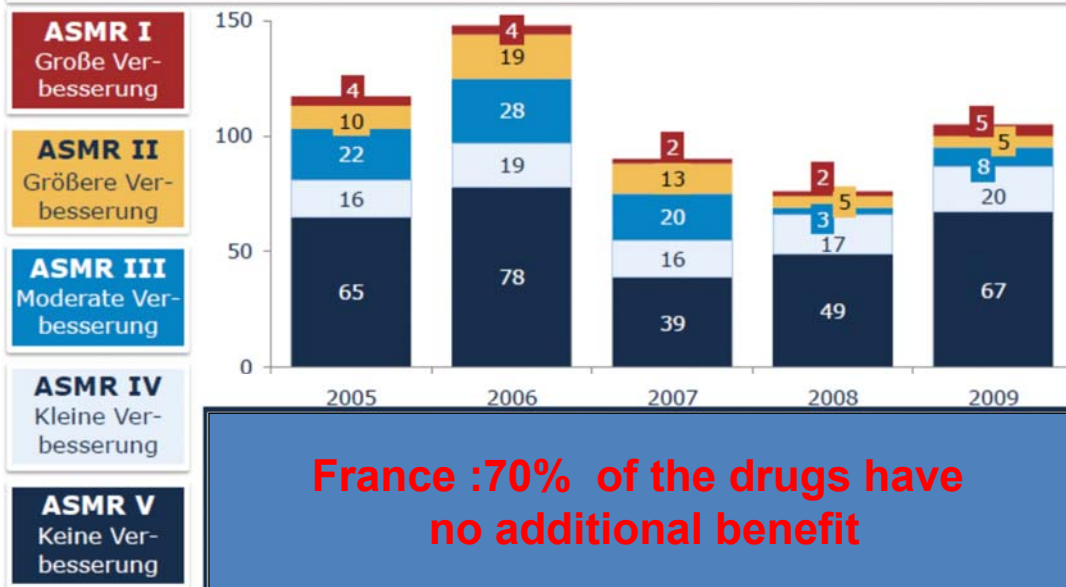
Quelle: McKinsey; AM-NutzenV (draft November 8, 2010)

Frankreich



Bewertung des Zusatznutzens (ASMR) ist wichtig für die Preisverhandlungen

Bewertung des therapeutischen Fortschritts von Zulassungen seit 2005

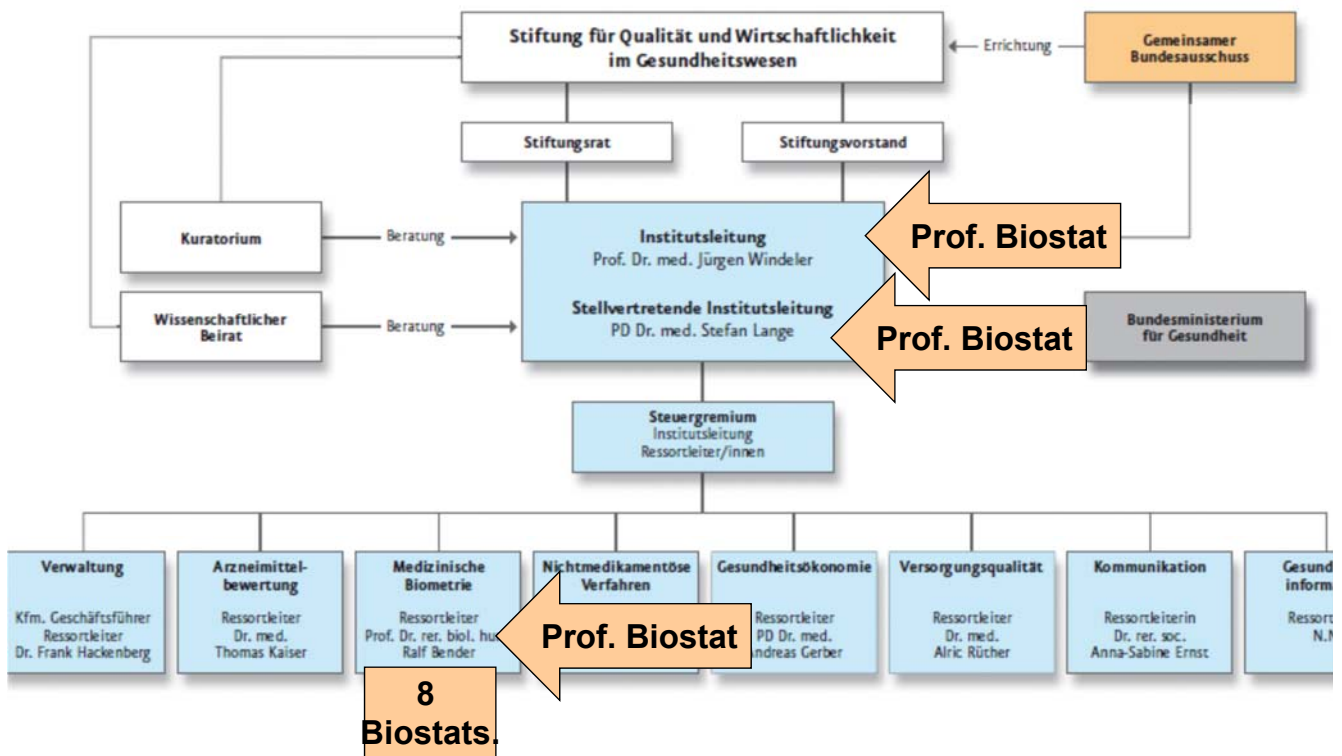


■ IQWiG will Review the dossier



- According standards of EBM and IQWiG Methodpaper
- Validity and Completeness
- Quality of Design and Analysis
- Is the additional benefit demonstrated ?
- How strong is the Evidence ?
- Certainty of the Results
- Magnitude of the Effects ?
- IQWiG Conclusion can differ from Industry conclusion





Market Access Pfizer Deutschland GmbH

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

Allgemeine Methoden

Entwurf für Version 4.0 vom 09.03.2011



Dossier Prozess is described

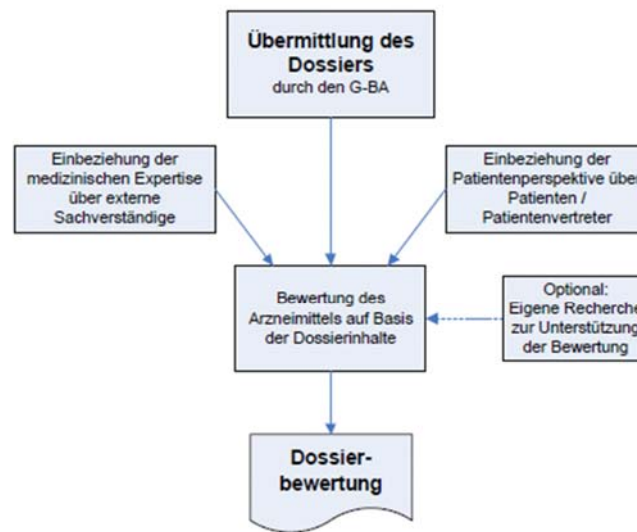


Abbildung 3: Ablauf der Erstellung einer Dossierbewertung



• Surrogate Endpoint

- (see also Rapid Report: Surrogate Endpoints in Oncology)
- Not patient relevant
- Validation through Meta Analysis of several RCTs with Surrogate and Endpoints. (Indication and Intervention)
- If no Validation possible (R to low) STE (Surrogate Treshold Effect) approach should be maintained
- STE- minimal Treatment effect to assure effect concerning the patient relevant endpoint



Statistical Significance is not enough

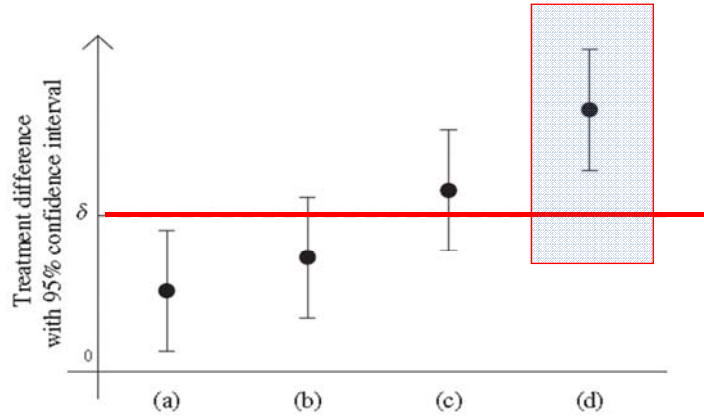
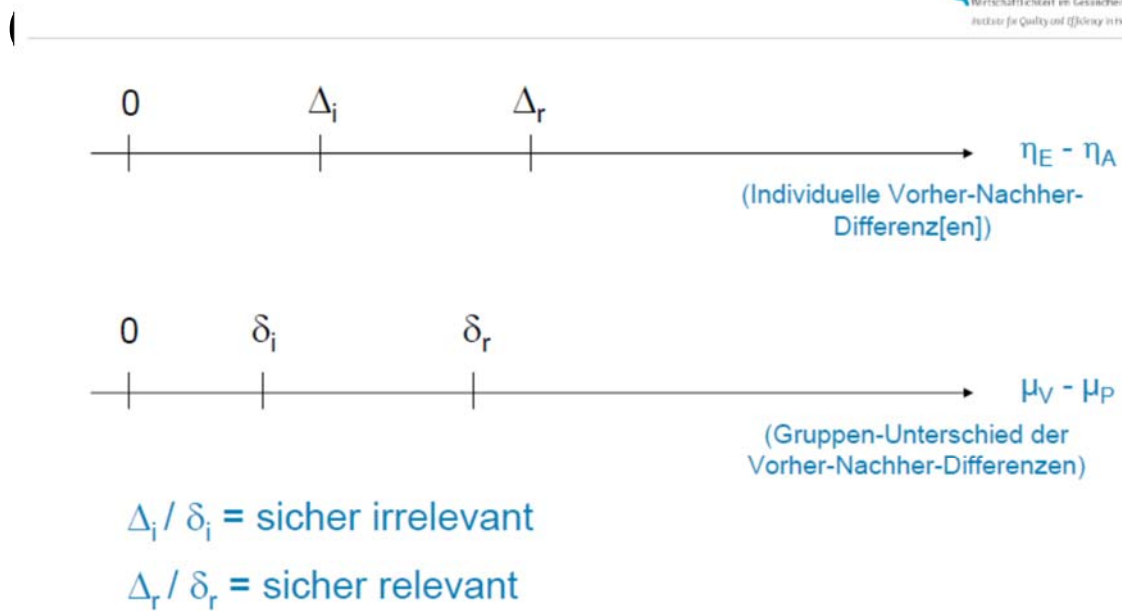


Figure 1. Criteria for a statistically significant result using the threshold δ (dashed line) that defines the minimum clinically relevant effect.



Victor



Step-procedure for Clinical Relevance

- 1) If a valid δ on for Group Level is available use this for shifted Nullhypothesis
- 2) If a valid (MID) Responder definition is available use this. Significance is sufficient
- 3.) If not Available than use SMD (Hedge G) =0.2 or adapt MID to group level



- **Combined Endpoints**
 - Individual components must all patient relevant
 - surrogates only if of Institut as valide recognition
 - Components has separately represent
 - Are the weights equal
 - Is the effect parallel?
 - Wasn't relevant endpoints point considered?
 - posthoc defines ?
- **Indirect Comparisons**
 - MTC is in Development
 - Accepted for the early Benefit Assesment and Cost-Benefit Assesment
 - Evidence of MTC is lower than H2H



Subgroup Analysis

- **Method Paper 3.0**
 - Arbitrary selection of subgroups
 - post hoc Analysis
 - Multiple testing
 - Small Power
 - SGA should not dominate(NS) the primary analysis,
- **Method 4.0**
 - exception social law implications
 - Life specific Characteristics, age sex
 - AMNOG:Identify Subgroups of patients with additional benefit
 - Difference between Studies and Meta Analysis
 - Data of Subgroups should only pooled , if there is no substantiell heterogeneity
 - Interaction Test $P < 5\%$ Proof of Subgroup Effect
 - Interaction Test $P < 20\%$ Indication of Subgroup Effect
 - **Proof: no pooled Estimator**
 - Indication: Description of Subgroups
 - More than two subgroups– $p > 20\%$ pool



- **What does this mean ?**
 - For our products
 - For our studies
 - For profession





Module 4 Benefit and Additional benefit

- **Price will be function of**
 - comparator
 - Disease area
 - Magnitude of effect
 - Evidence

