The German Healthreform and IQWiG Update

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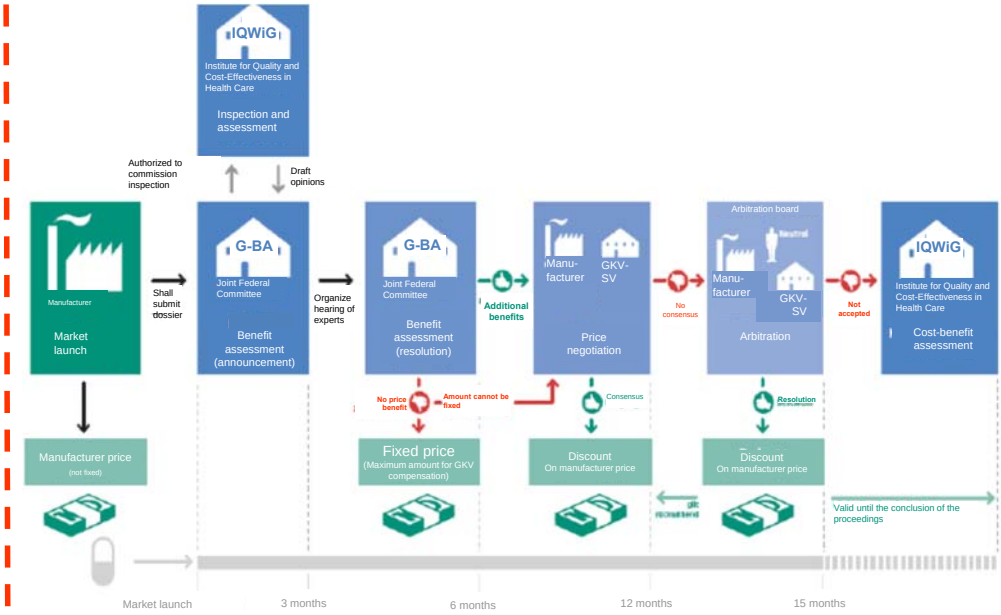
- The New AMNOG Process
- Key Elements of the Law
- The Industry Dossier
- IQWiG Methods 4.0 Draft

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

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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

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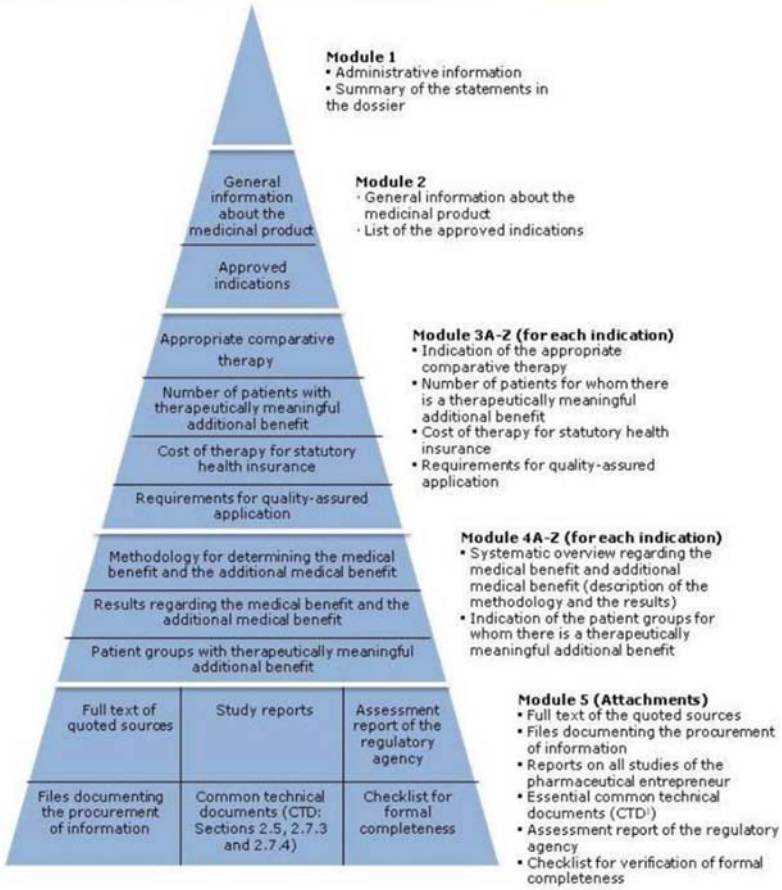
- **Additional Benefit**
  - Industrie has to prove additional benefits against the comparator
  - Comparator will be determined by JC
    - FRP Drug
    - Endpoint studies
    - EBM
  - Additional benefit based on SPMC and clinical studies with patient releavnt endpoints according to EBM
  - Patient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



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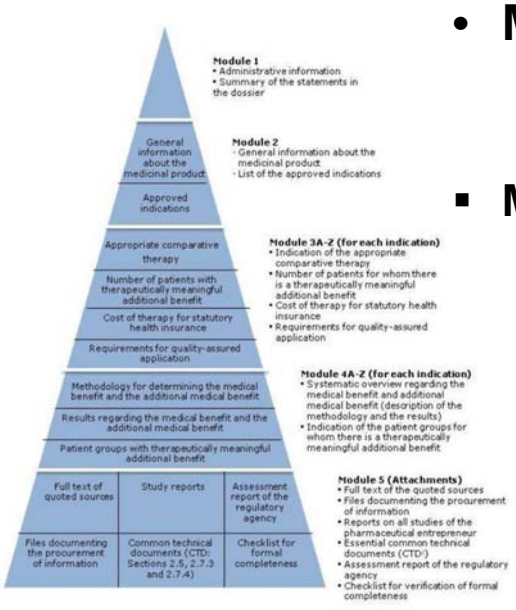
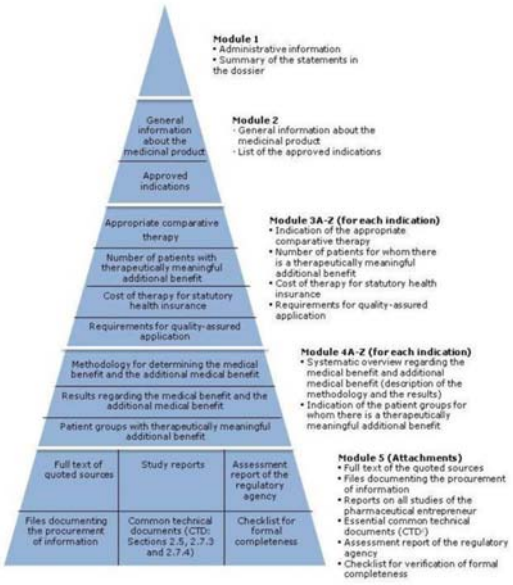


- **Modul 1**
  - Summary
    - Foundation of the Negoations
- **Modul 2**
  - Active agent, ATC code, PZN, packaging size, etc.
  - Mode of action
  - Authorized areas of application
  - Other authorized areas of application in Germany
  - Status of authorization internationally



- **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 negations
  - no influence on additional benefit
    - Is reviewed by IQWiG

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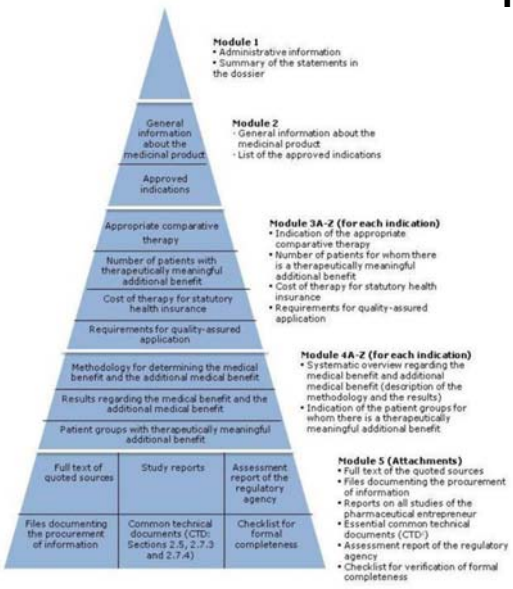
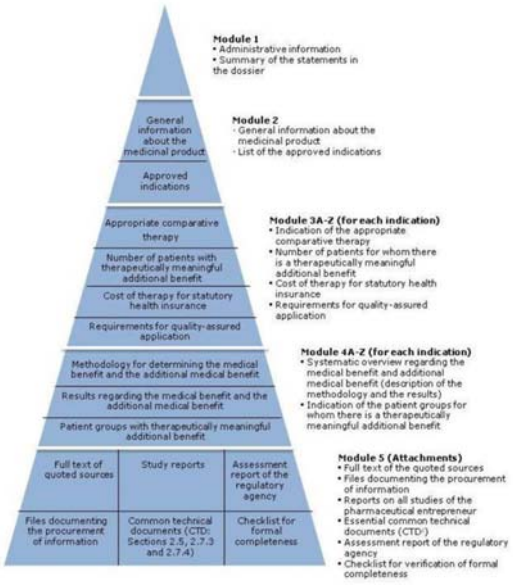


- **Modul 3**
  - Comparative treatment
    - appropriate comparative treatment
      - EBM based, with Endpoint Studies, FRP
    - Reason for the choice:
      - Minutes of the advice of GBA
      - Reason
  - **Epidmiology**
    - Description of the disease, characterization of the target population
    - 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
    - Asssement 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

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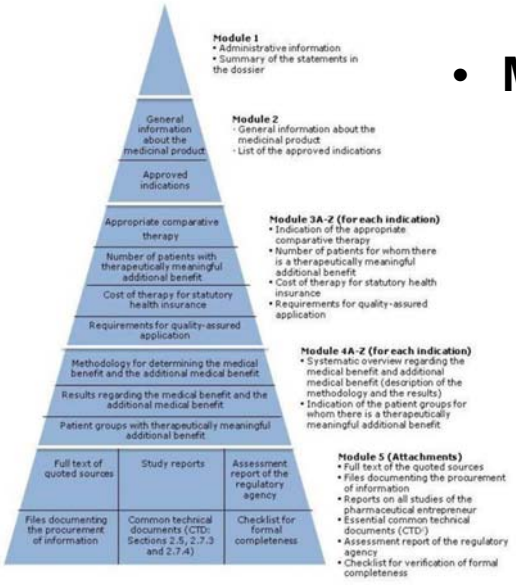

- **Modul 5**
  - Clinical Study Reports
  - Common Technical documents
    - CTD 2.5 2.73 2.74
  - EPAR
  - Modul 4 is not confidential
  - Modul 5 confidential parts could be flagged

Classification (AM-NutzenV)		Description (AM-NutzenV)	Examples (AM-NutzenV)
Level I	Extensive additional benefit	▪ Sustainable and benefit not yet achieved	▪ 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	▪ Soothing of severe symptoms ▪ Moderate extension of life span ▪ Perceptible relief ▪ Other significant
Level III	Marginal additional benefit	▪ Moderate or only small benefit	▪ 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)

vfa. Die forschenden Pharma-Unternehmen

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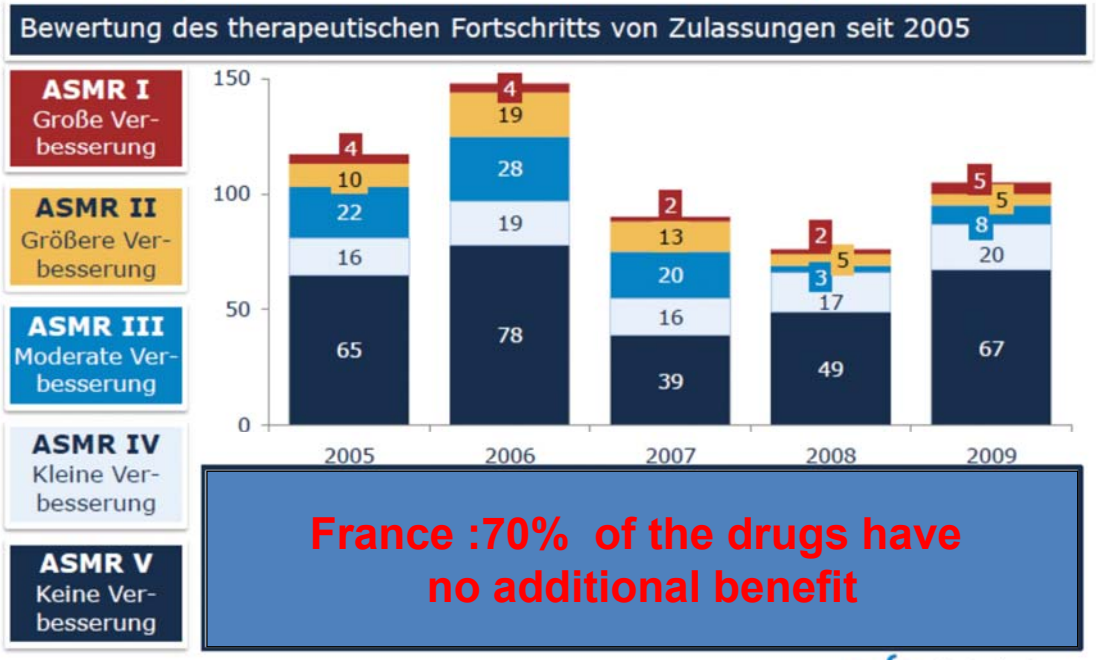
Bewertung des Zusatznutzens (ASMR) ist wichtig für die Preisverhandlungen



vfa. Die forschenden Pharma-Unternehmen

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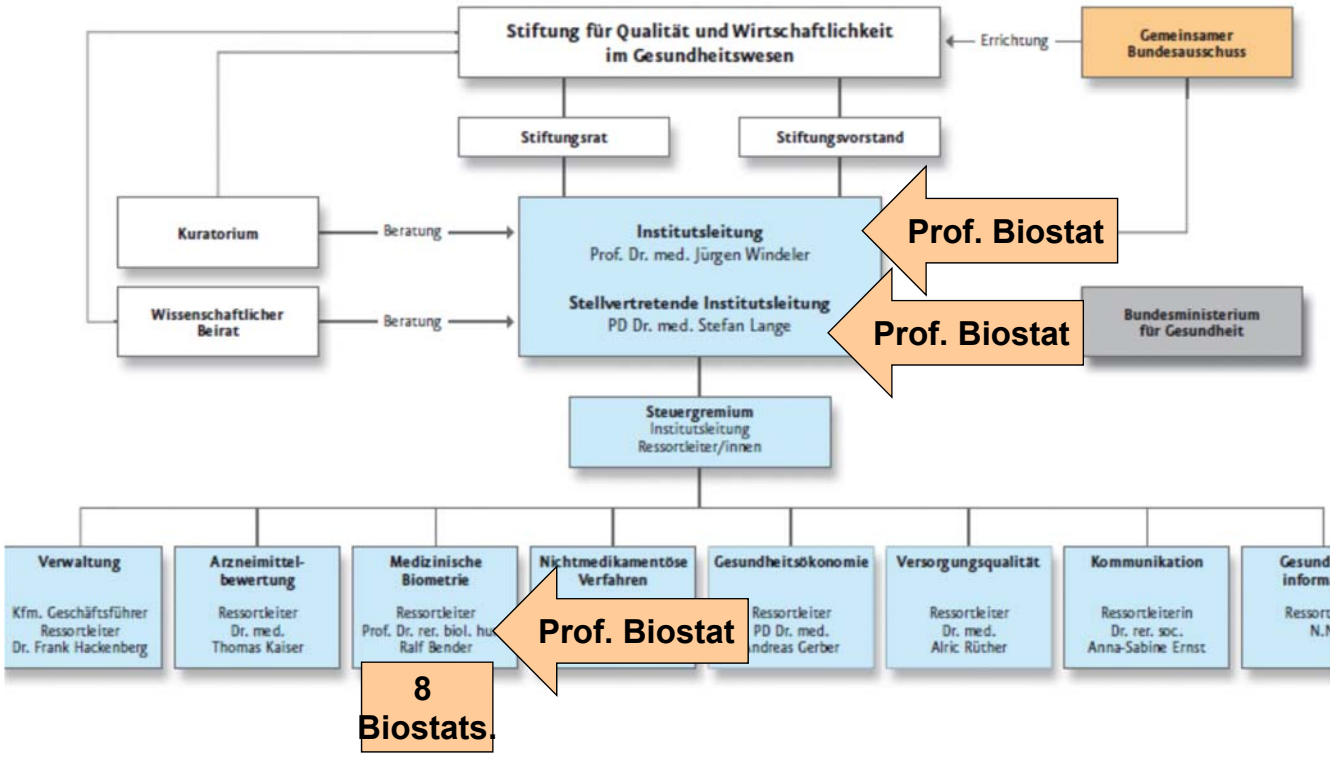
- IQWIG will Review the dossier
  - According standards of EBM and IQWiG Methodpaper
  - Validity and Completness
  - Quality of Design and Analysis
  - Is the additional benefit demonstrated ?
  - How strong is the Evidence ?
  - Certainty of the Results
  - Magnitude of the Effects ?
  - IQWiG Conclusion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



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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

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Dossier Prozess is described

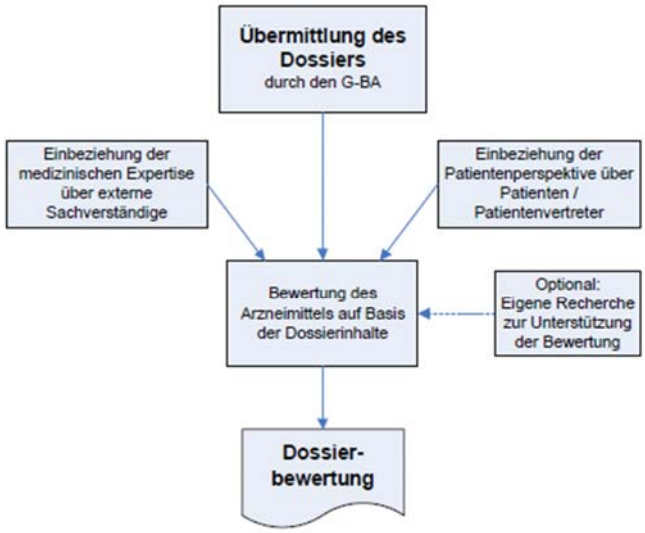

Abbildung 3: Ablauf der Erstellung einer Dossierbewertung

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- **Surrogate Endpoint**
  - (see also Rapid Report:Surrogate Endpoints in Oncology)
  - Not patient relevant
  - Validation through Meta Analyis 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

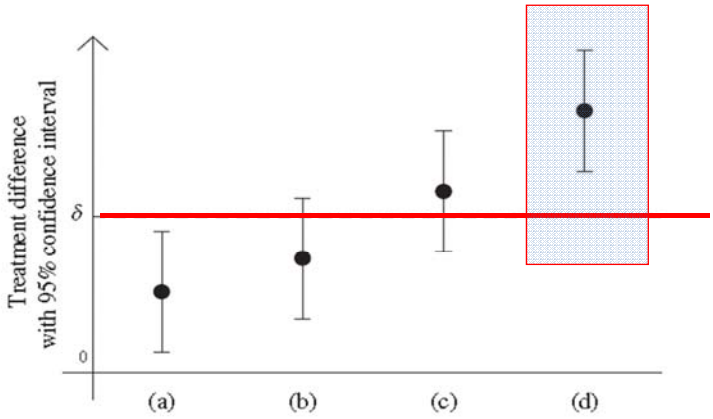

Figure 1. Criteria for a statistically significant result using the threshold δ (dashed line) that defines the minimum clinically relevant effect.

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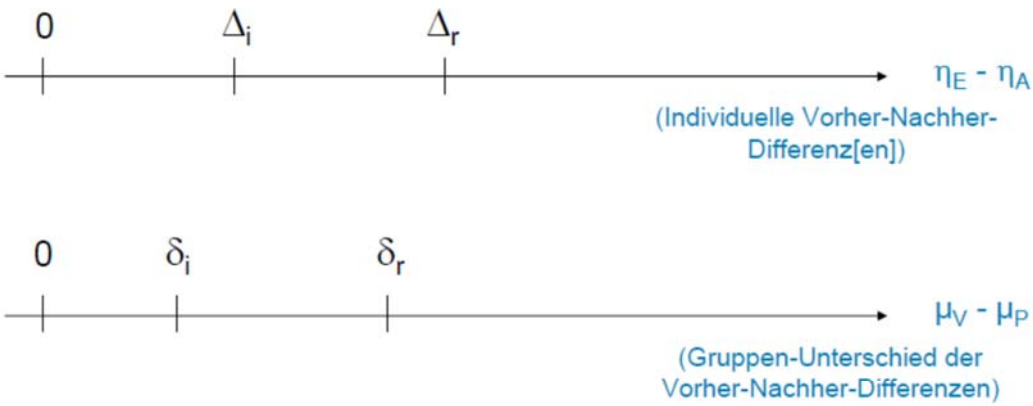

Δ_i / δ_i = sicher irrelevant

Δ_r / δ_r = sicher relevant

Victor

Step-procedure for Clinical Relevance

- 1) If a valid δ on for Group Level is available use this for shifted Nulhypothesis
- 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**
  - Abritary 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 Chareteristics, age sex
  - AMNOG:Identifiy Supgroups of patients with additional benefit
  - Difference between Studies and Meta Analysis
  - Data of Subgroups should only pooled , if there is no substantiell heterogenity
    - 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 tthan two subgroups– p>20% pool

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

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Module 4 Benefit and Additional benefit

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