Schwenke Consulting:
Strategies and Solutions in Statistics

Statistical Issues in the Benefit Assessment acc. to the German AMNOG

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Overview

- **Part 1**
  - **The AMNOG process**
  - **Some definitions**
  - **Studies acceptable for the dossier**
- **Part 2**
  - **Endpoints**
  - **Subgroup analyses**
  - **Surrogates**
- **Part 3**
  - **Metaanalyses**
  - **Indirect comparisons**
    - **Adjusted ITCs**
    - **Historical comparisons**

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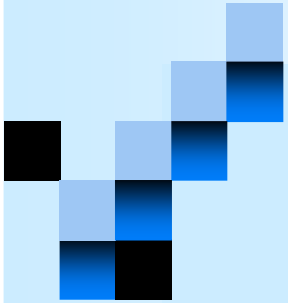


PART 1

The players for the benefit assessment…

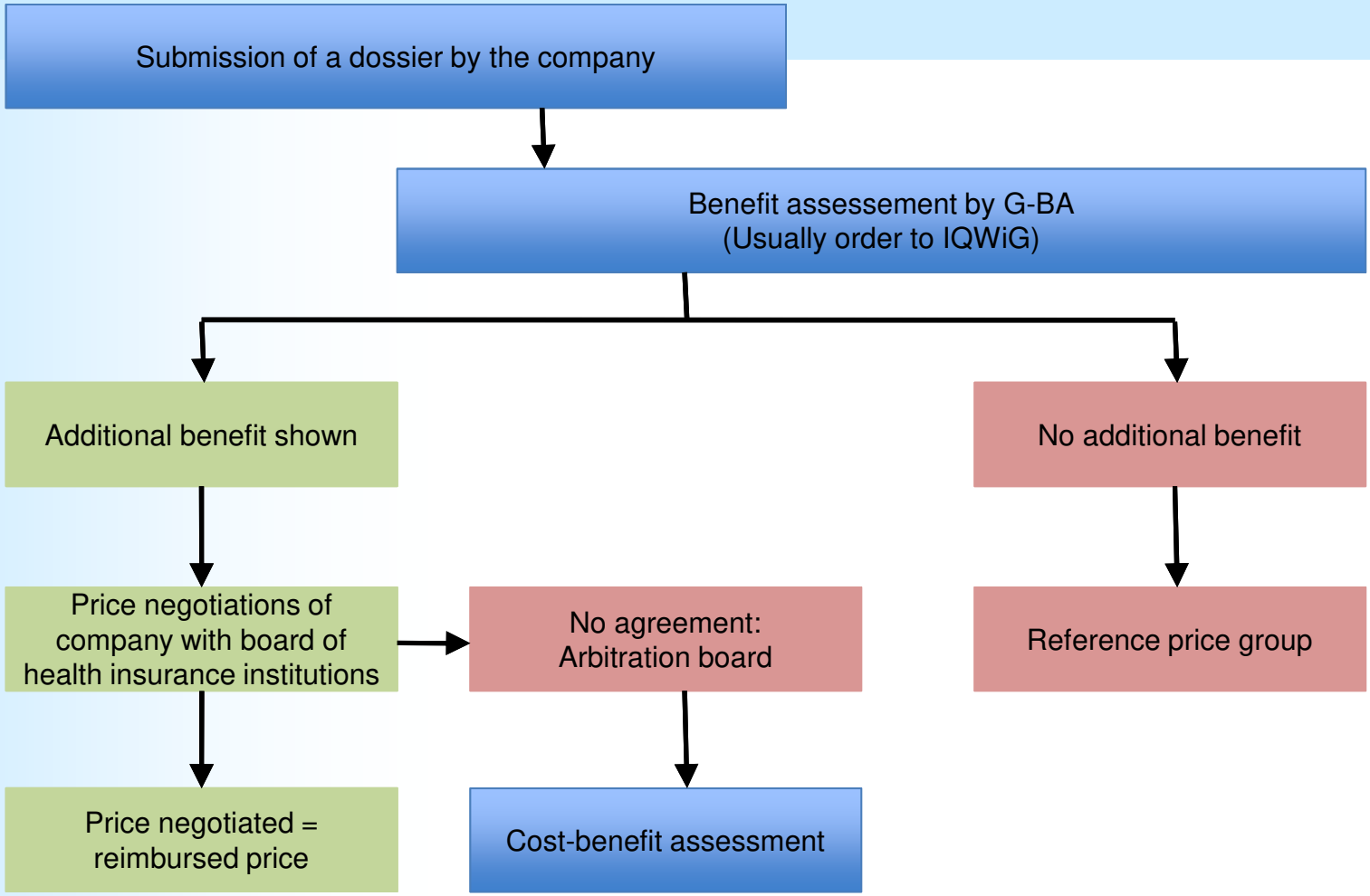
- G-BA = Joint Federal Committee (Gemeinsamer Bundesausschuss

  => Decision making body

- IQWiG = Institute for quality and efficiency in health care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

  => assesses the dossier from a methodological view (suggests a benefit)

AMNOG Process



G-BA

- Consists of 13 voting members
  - 5 members from the board of the statutory health insurances
  - 5 members of care givers (hospital association (DKG), association of physicians (KBV), association of dentists (KZBV))
  - 3 independent members including Prof. Hecken (chairperson)
- Makes decisions on every aspect of reimbursement in the German health care system
  - e.g. new pharmaceuticals, reimbursement of medical devices

IQWiG

- Institute to assess the benefit dossiers by order of the G-BA
- Participate in the oral hearings to defend their dossier assessment
- Assessments are based on the methods paper (actual version 5.0)

  (www.iqwig.de/en/methods/methods-paper.3020.html)

Timelines

- Advice meeting: ca. 10 weeks after submission of request
- Dossier preparation: ca. 6-12 months
- Dossier submission: at day of report in Lauer Taxe (ca. 4 weeks after approval)
- IQWiG (or G-BA) Dossier Assessment: 3 months after submission
- Written response: 21 days after publication of assessment
- Oral hearing: ca. 2-3 weeks after submission date for written response

- No clock-stop
- No delays allowed

Definitions

- **Effect size**
  - Size of an treatment effect (should be provided as relative effect, e.g. odds ratio, relative risk, hazard ratio).
- **Confidence in benefit**
  - Provides the confidence, that the results of the study (-ies) or metaanalyses is close to the truth.
  - Will be assessed based on the potential for bias and the size of the statistical uncertainty.

Definitions

- **§ 3 Benefit**
  - (1) The benefit of a new drug is the patient relevant therapeutic effect with regard to an increased health status, reduction of duration of disease, prolongation of survival, reduction of adverse events or increased QoL.

  => Shown by marketing authorization by EMA

  - Approval
    - Authority decides on the benefit-risk-ratio
    - Dichotomized decision

Definitions

- **§ 3 Additional benefit**
  - (2) The additional benefit of a new drug is a benefit acc. to (1) and the benefit is higher with regard to quality or quantity compared to a G-BA-defined comparator.

  => Early benefit assessment

  - Benefit assessment
    - G-BA assesses additional benefit of approved drugs
    - Determination of effect size and confidence in benefit
    - Assessment of size of evidence

Definitions

- **§ 5 (7) Size of additional benefit**
  - Major
    - Healing, major prolongation of survival, long-lasting absence of serious symptoms, mostly avoiding serious adverse events
  - Considerable
    - Moderate prolongation of survival, attenuation of serious symptoms, remarkable relief of disease, relevant prevention from serious adverse events, major prevention from other adverse events
  - Minor
    - Reduction of non-serious symptoms, relevant prevention from adverse events
  - Not quantifiable
  - No additional benefit
  - Benefit lower than benefit of FJC-defined comparator

IQWiG assessment

Assessment is based on relative effect measures below 1

	Mortality	Serious symptoms or AEs and QoL	Non-serious symptoms or AEs
Major	0.85	0.75 and Risk ≥ 5%	-
Considerable	0.95	0.90	0.80
Minor	1.00	1.00	0.90

95% CI must be below the limits shown in the table

Source: IQWiG methods paper, Version 5.0

Evidence level

- I a systematic Reviews of studies of level Ib
- I b randomised, controlled, clinical study (RCT)
- II a systematic Reviews of studies of level IIb
- II b prospective cohort studies
- III retrospective studies to compare treatments
- IV Case series and other non-comparing studies (e.g. single-arm clinical studies)
- V Case reports, consensus papers, etc.

Definition confidence in benefit

- IQWiG uses three categories for the grading based on the study and the endpoints:
  - **High confidence**: RCT with low potential for bias.
  - **Moderate confidence**: RCT with high potential for bias.
  - **Low confidence**: Results of non-randomized studies.

In early benefit assessments only one phase III trial available.

- i.e. at most hint for benefit possible (except for Mega-trials with more than 1,000 patients (e.g. assessment of Ticagrelor))
- Downgrading, if high potential for bias for the single endpoint (e.g. QoL)
  - Unidirectional results for subgroups, but not all with significance
  - Oncology: unidirectional hazard ratio for OS for different time-cuts, but not all significant (e.g. assessment of Eribulin)

Definitions

- **Confidence in benefit (IQWiG Methods paper 5.0 chapter 3.1.4)**
  - Proof
    - Statistical significance in ≥ 2 RCTs with high confidence in benefit
  - Hint
    - Statistical significance in one RCT with high confidence in benefit or in ≥ 2 RCTs with moderate confidence in benefit
  - Clue
    - Statistical significance in one RCT with moderate confidence in benefit or in ≥ 2 RCTs with low confidence in benefit
  - No confidence

Assessment Ipilimumab 2nd line

- Dossier BMS
  - OS — Proof for major add. benefit
  - AEs — AEs can be treated, no add. harm
  - Overall — Proof for major add. benefit
- IQWiG
  - OS — Hint for major add. benefit
  - AEs — Hint for major add. harm
  - Overall — Hint for considerable add. benefit
- FJC
  - OS — Hint for considerable add. benefit
  - AEs — AEs can be treated, no add. harm
  - Overall — Hint for considerable add. benefit

Acceptable study types

- Studies with the highest evidence to be reported
  - If RCTs available, then these are to be reported
  - If no RCT is available, the studies with next highest evidence to be reported
    - E.g. single-arm studies
    - E.g. non-randomized studies

Most wanted…

Randomized controlled Trials (RCTs)

- Blinded allocation of patients preferred
- Control group mandatory (ideally the FJC-defined comparator)
- Blinding preferred (at least single-blind, better double-blind if possible)
- Randomization mandatory (if applicable)
- Adequate statistical methods mandatory
- Subgroup analyses mandatory at least for (if applicable)
  - Gender
  - Agegroups
  - Severity of disease
  - Country / Region
- Appropriate description of loss-to-follow-up patients / drop-outs

Intent-to-Treat Analysis

- All randomized patients
  - Analyzed as randomized,
  - Not taking into account any protocol deviations
    - In- and exclusion criteria
    - Actual treatment

Fisher LD et al. (1990): Intention to treat in clinical trials. In: Peace KE (ed.): Statistical Issues in Drug Research and Development.

- Primary population for results in benefit dossier

Other populations in clin. studies

- 'Full Analysis Set' (FAS) = modified ITT (ICH E9)
  - Close to intent-to-treat principle
  - Modifications like
    - Patients with at least one dose
    - Safety analysis: analyzed as treated (not as randomized)
  - Acceptable for dossier, if deviance from ITT < 5%
- 'Per Protocol Set' (PP)
  - Patients without major protocol deviations
  - Not acceptable for dossier.

Upcoming events

Promoting Statistical Insight

One day meeting
Bayesian Methods for Dose Finding and Biomarkers

28th February

RSS, 12 Errol Street, London

Training Course
Missing data

6th-7th March

Heathrow, UK

Presented by Michael O'Kelly

Webinar
Big Data

22nd March, 3pm

What's the big deal with big data and will it have a big impact on me?

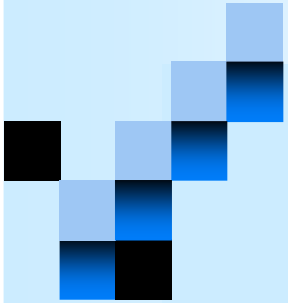
Please visit www.psiweb.org/events for more information

3-6th June 2018 : PSI Conference

Promoting Statistical Insight

All the details can be found at: **http://psiweb.org/psi-2018/psi-conference-2018**

Poster Abstract deadline : 28th February 2018
Early Bird Discount : 21st March 2018



Thank you for your attention!