Schwenke Consulting:
Strategies and Solutions in Statistics

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

Dr. Carsten Schwenke

Karmeliterweg 42
D-13465 Berlin
+49-30-60409712

consult@scossis.de
www.scossis.de
www.scossis.com

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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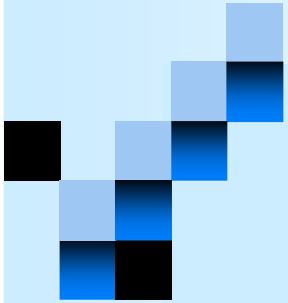


PART 3

Meta-Analyses

Reference: IQWiG Methods Paper Version 5.0

Definition

- Meta-analysis are systematic reviews
  - Based on systematic literature search
  - Search performed within 3 months of dossier submission
  - Search terms should include
    - The population
    - The indication
    - The study design
    - The endpoints (mortality, morbidity, QoL, safety)

Literature search

- Search in publication databases
  - Medline
  - Embase
  - Cochrane Central Register of Controlled Trials
- Search in trial registries
  - Clinicaltrials.gov
  - EU Clinical Trials Register
  - International Clinical Trials Registry Platform Search Portal
  - PharmNet.Bund

Literature search

- Restrictions are to be documented and rationale given (e.g. restriction on year of publication)
- Selection of studies to be done by two independent reviewers

Meta-analyses

- Statistical summary of published results
- Can be based on
  - Aggregated data
  - Patient individual data (if available)
- Presentation of results by forest plots
- Test on heterogeneity needed
  - If the p-value is below 0.05, considerable heterogeneity is assumed
    - Reasons for heterogeneity should be assessed
    - Meta-analysis should be performed for the whole set of studies if heterogeneity can be explained clearly

Meta-analyses

- Binary endpoints
  - Relative effect measures are recommended
    - i.e. risk ratio and odds ratio
  - In case of empty cells, use 0.5 addition for each cell

(Deeks JJ, Higgins JPT, Altman DG. Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (Ed). Cochrane handbook for systematic reviews of interventions. Chichester: Wiley; 2008. S. 243-296.)

  - In case of rare events, the Peto-odds-ratio approach may be used

Meta-analyses

- Meta-regression on different effect sizes by different patient characteristics need patient individual data for all studies
  - Aggregated data may lead to bias when averages of patient characteristics is used

Requirements for studies to enter a meta-analysis

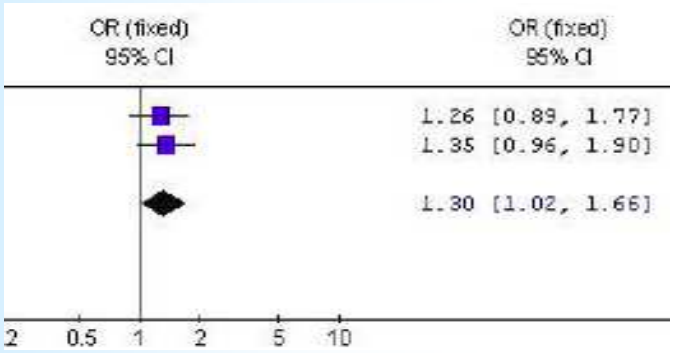
- Studies need to be sufficiently similar in terms of
  - Study design
  - Endpoint definitions
  - In- / exclusion criteria
  - Study population
  - Follow-up time
  - Etc.

Meta-analyses

- High evidence for similar studies
  - Use a fixed effects model (e.g. using inverse variance approach)
- In all other cases
  - Use a random effects model (preferably according to the Knapp-Hartung method)
  - With <5 studies, the CIs may be wide
    - May use fixed effects model or
    - Use qualitative summary

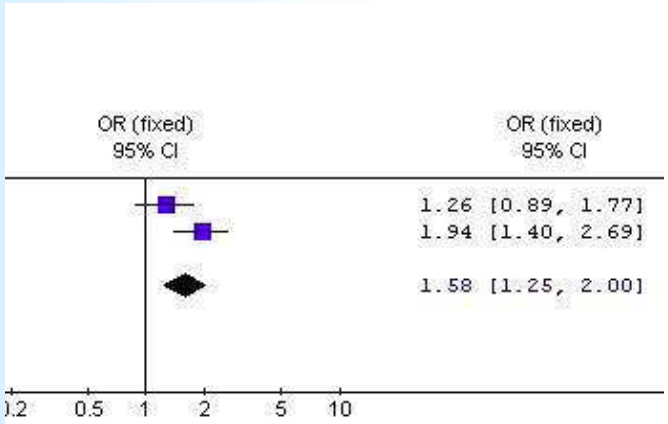
Meta-Analyses – Examples

- **Metaanalysis, no heterogenity (I^2 = 0%, p>0.05)**



no significant studies
Accepted acc. to IQWiG methods
Metaanalysis with significant OR
Add. Benefit shown, quantifyable

- **Metaanalysis, heterogenity (I^2 = 70%, p<0.05)**



One significant study
No pooling acc. to IQWiG methods
Add. benefit shown by one study,
but not quantifyable

Indirect Comparisons

Indirect comparisons

- Needed if no H2H RCT vs. the G-BA chosen comparator is available
- ITCs need a common bridge comparator
  - To be used in a similar way in all studies under consideration
  - Not necessarily according to the German label
  - Historical controls are accepted in special situations only (e.g. HCV and HIV)

Literature search

- Similar as for meta-analyses
- Search to be done for each possible comparator to identify all possible ITCs

What to be reported in the dossier

- Bridge comparator and rationale for its choice
- Precise specification of the statistical model including model assumptions
  - Bayesian model: a-priori-distributions with rationale
- Approach to assess homogeneity of direct comparisons
- Approach to assess consistence of direct and indirect evidence (if applicable)
- Code of computer software in readable format along with type of software used (modules, packages, procedures, etc.
- Type and extend of sensitivity analyses

MAICs

- Matching adjusted indirect comparisons
  - Usually not accepted as matching is done for a small number of baseline parameters, not for all / all relevant
  - IQWiG: if adjustment is done for some parameters, this may introduce even higher bias compared to unadjusted ITCs
  - May be used as sensitivity analyses

Bucher Method

- Simple approach
- Accepted method by IQWiG and G-BA
- No adjustment possible
  - Studies need to be very similar
  - No network analysis possible

Network meta-analysis

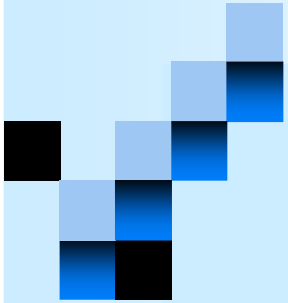
- Covers different bridges in a network
- Make use of direct and indirect comparisons
- Approach is based on various assumptions
  - Dependent on a-priori distribution used
  - Dependent on several other assumptions that influence the outcome
  - All assumptions need precise descriptions of all assumptions and the reasons for each assumption

Benefit assessment

- ITCs are of lower evidence level than H2H comparisons
- Requirements
  - Comparator adequate?
  - Literature search complete?
  - Studies in general appropriate for the objective?
  - Statistical method appropriate?
  - Other requirements (e.g. homogeneity, consistence) fulfilled?
  - Data on all endpoint dimensions available (mortality, morbidity, QoL and safety)?

Reasons why ITCs failed

- Ca. 10% of all ITCs were accepted by IQWiG
  - Ca 10% with inadequate comparator
  - Ca. 45% with incomplete literature search
  - Ca. 30% with inadequate similarity of studies
  - Ca. 15% with inadequate statistical approach (mostly historical comparisons with no dramatic effect)
- Ca. 30% of all ITCs were accepted by G-BA
  - Most of them were historical comparisons in the indications HCV and HIV due to special situation



Thank you for your attention!

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