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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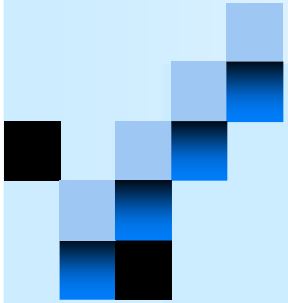


PART 2

Required endpoint dimensions

- Mortality
- Morbidity
- Health-related quality of life
- Safety (treatment-emergent adverse events)

Mortality

- Analysis as defined in the clinical study
  - E.g. time to death of any cause assessed by Cox regression in oncologic trials
  - E.g. Proportion of patients with fatal adverse events
    - Effect measures: Relative risk, Odds Ratio and Risk difference with respective 95% CIs
  - Additionally subgroup analyses for each endpoint with all predefined subgroups as defined in CSRs
  - Publications and EPAR to be checked for additional subgroup definitions that may be shown in addition

PFS and other response endpoints

- PFS, ORR and other response endpoints in oncology are only accepted if they are based on symptoms
- Assessments by radiographic imaging is not sufficient
  - PFS etc. regarded as surrogates
  - Surrogates are to be validated against the clinical outcome

Cross-over in oncological trials

- OS not unbiased if cross-over is allowed
- In many studies, PFS is regarded primary, so that cross-over is of lesser impact for marketing authorization
- Major issue in benefit assessments
  - PFS = surrogate
  - OS biased, often no surival benefit observed anymore
    - Several cross-over corrections available, non is perfect
    - Any correction to be defined á priori, more than one to be defined in the SAP

Morbidity

- Analysis as defined in the clinical study
  - E.g. SVR (HCV and HIV)
  - E.g. Time to first skeletal event (oncology)
  - E.g. Symptoms measured by PROs (EORTC-QLQ-C30 symptoms)
  - E.g. EQ-5D-VAS
- In Dossier
  - Preferably responder analyses based on a predefined, validated and established minimal clinically important difference (MCID)
    - Validation studies are required as reference for a MCID
    - To be checked whether an endpoint was already assessed by G-BA to find accepted MCIDs
      - E.g. MCIDs of 7mm and 10mm for EQ-5D-VAS in oncology
      - E.g. MCID of 10 points for the change from baseline for each of the symptoms of EORTC-QLQ-C30 in oncology
  - Additionally subgroup analyses for each endpoint

hr-QoL

- Endpoints
  - E.g. SF-36 (generic QoL)
  - E.g. EORTC-QLQ-C30 function classes
- Data available?
  - If yes, ...
    - Questionnaires validated?
    - Commonly accepted for the indication?
  - If no, ...
- In Dossier
    - Ideally, responder analyses similar to PROs for morbidity based on accepted MCIDs
    - Subgroup analyses like for morbidity

Adverse events

- To be reported as
  - Number of patients with any TEAE (descriptive only)
  - Number of patients with any serious TEAE
  - Number of patients with any severe TEAE (TEAEs with CTCAE Grade ≥ 3, especially in oncologic indications)
  - Number of patients with adverse events leading to treatment discontinuation
  - Number of patients with TEAE of special interest
    - Frequency tables of all PTs and all SOCs

Adverse events

- In Dossier
  - Equal follow-up times in treatment groups
    - Relative Risk, Odds Ratio and Risk Difference with 95% CIs
  - Unequal follow-up times in treatment groups (e.g. oncology)
    - Hazard Ratio with 95% CI
  - Subgroup analyses for main categories
- Treatment-related adverse events are not regarded
- Special care needed to define AEs of special interest to be reported in the benefit dossier

Subgroups

Aim of the G-BA: Search for subgroups with add. benefit

- Analyses requested for all endpoints for following subgroups
  - Prospectively planned subgroups from RCTs
- Requested subgroups for all dossiers (if applicable): Gender, age, severity of disease and region
- Subgroups need to be based on baseline factors to qualify for an effect modificator
- Subgroup analyses have to be done for all endpoints used in the benefit assessment

Subgroups

Test for interaction of subgroup by treatment (IQWIG MP 5.0)

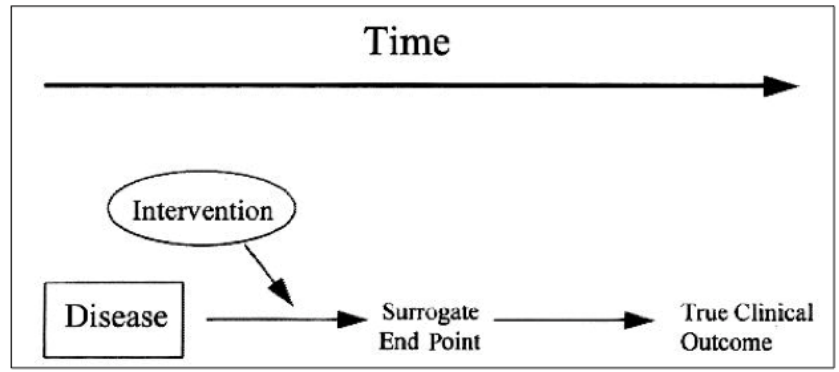
- $p<0.05$
  - Interaction significant, i.e. proof of an interaction
  - subgroups may be assessed separately
    - Any patterns across endpoints?
    - Any biological rationale?
  - If subgroups are assessed separately, total population not considered for this endpoint

Subgroups

- CAPRIE study (CAPRIE steering committee, Lancet 348, 1996)
  - A randomized, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE)
  - Primary endpoint
    - Combined endpoint (stroke, myocardial infarction, PAOD)
  - Results
    - Stroke RRR (95% KI) = 7.3% (-5.7; 18.7)
    - MI RRR (95% KI) = -3.7% (-22.1; 12.0)
    - PAOD RRR (95% KI) = 23.8% (8.9; 36.2)
    - Total RRR (95% KI) = 8.7% (0.3; 16.5)
  - Test on heterogeneity of groups: p=0.042
  - ⇒ Components of endpoints heterogeneous, different populations, need to be assessed separately.
  - ⇒ Additional benefit only in PAOD patients

Surrogates

- Surrogates have to be validated in the indication for the drug class
- Validation of surrogates have to be done according to IQWiG methodology
  - Nearly impossible to validate a surrogate

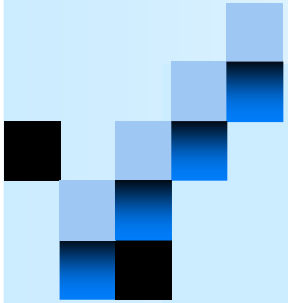


(Fleming & DeMets, Annals of Internal Medicine 1996, 125: 605-613)

Surrogates - SVR

- Sustainted virological response (Boceprevir and Telaprevir assessments)
  - IQWiG defined the SVR not as a patient relevant stand-alone endpoint.
  - SVR regarded as **valid** surrogate for HCC, but **not a validated** surrogate for HCC
  - No formal validation was performed to adequately show the validity of the surrogate.
  - HCC is regarded as patient relevant serious complication of the HCV infection.
  - To establish SVR as validated surrogate, high-quality RCTs need to be performed that show a high correlation of the surrogate with the endpoint. This is not feasible in HCV due to ethical reasons.

- Consequence: downgrading of additional benefit to „not quantifyable“



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