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
Overview

- **Part 1**
  - The AMNOG process
  - Some definitions
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  - Endpoints
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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 survival benefit observed anymore
    - Several cross-over corrections available, none is perfect
    - Any correction to be defined à 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 \( \geq 3 \), 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 modifier
- 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

- Sustained 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!
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<th>Date</th>
<th>Location</th>
<th>Presenter</th>
<th>Details</th>
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<td>Bayesian Methods for Dose Finding and Biomarkers</td>
<td>28\textsuperscript{th} February</td>
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<td>What's the big deal with big data and will it have a big impact on me?</td>
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