The impact of German benefit assessment on endpoint selection in clinical research and drug development in Germany
Lessons to be learned from AMNOG

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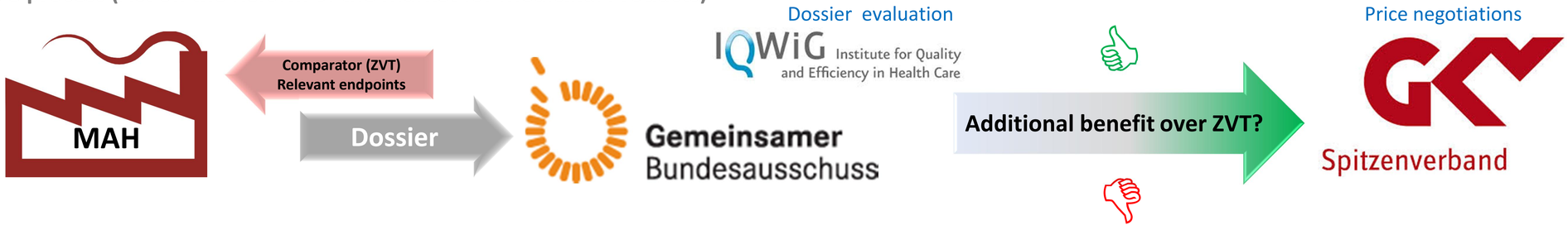
Background

Since 2011, for newly licensed medicinal products in Germany, marketing authorization holders (**MAH**) are required to submit a dossier to the Federal Joint Committee (**G-BA**), the highest decision making body in the German health care system. In this dossier, additional benefit is to be demonstrated *vs*. an appropriate comparator (ZVT) based on clinical studies. Additional benefit is granted on the basis of significant data for **patient-relevant** endpoints reflecting ***mortality***, ***morbidity***, ***quality of life (QoL)*** and ***adverse events***. Based on the outcome of evaluation of the dossier, negotiations about the amount of reimbursement may follow with the **GKV** (Central Federal Association of Health Insurance Funds) according to §130b SGB V.

Overview of the AMNOG process (Act on the Reform of the Market for Medicinal Products)



The dilemma

Regulatory approval and product benefit assessment are regulated by different laws and have different goals. Consequently, some efficacy endpoints accepted by regulatory authorities are sometimes not accepted in a benefit assessment according to §35a SGB V, as they do not fulfil the criteria of patient relevance within this context. Especially, surrogate endpoints for efficacy are frequently not accepted in a benefit assessment due to lack of (appropriate) validation.

Bound to fail

Mortality: *Progression-free survival (PFS) as a surrogate for overall survival*

- Composite endpoint
  → death for any reason + usually several progression parameters
- Relevance of parameters for the patient
  → clinical parameters utilized to detect progression are often based on radiological findings and/or laboratory parameters, whose relevance for the patient is often doubted (i.e. needs to be shown)
- Surrogate validity
  → validity needs to be shown for the specific indication , population and the specific intervention

Morbidity: *Laboratory parameters*

- Relevance for the patient questionable
- Surrogate validity needs to be demonstrated

Chance of success

Mortality: *Overall survival*

- Relevance for patients undoubted

Morbidity: *Disease symptoms*

- Relevance for patients undoubted
- Information obtained by direct assessment or via adverse event reporting
- Assessment also possible via questionnaires (e.g. QoL)
  → CAVE validation, bias in open-label studies
- Ensure bi-directionality of assessments

Health related quality of life (QoL)

- Relevance for patients undoubted
- CAVE validation (language!), bias in open label studies
- CAVE response rate (min. 70%)

Considerations for endpoint selection

Consider the requirements for benefit assessments already in the planning of a clinical trial. More specifically:

- Plan analysis for benefit strategy in advance, as non-randomized comparisons are less likely to be accepted.
- Involve clinicians and patients in assessing relevance for novel endpoints. Survey findings might shed light on new relevant aspects.
- Consider patient relevance of endpoints according to § 35a SGB V.
- Additional benefit can only be granted for statistically significant differences. Therefore, power calculation for key endpoints/strata for benefit assessments should be performed during study planning.
- Put strong emphasis on correct operationalization of endpoints. A valid endpoint can still be jeopardized by invalid data capture.
- Assess disease symptoms, utilizing appropriate assessments.
- For composite endpoints, ensure valid data capture of each component.
- Put more emphasis on (blinded) QoL assessment! Motivate patients to participate (e.g. by explaining the importance of these assessments).
- Utilize only validated surrogate endpoints for benefit assessment.
- Create synergies within developmental (but also academic) programs in order to obtain data for endpoint validation.
- Carefully consider the effects of protocol amendments and deviations on endpoint validity and evaluability as well as on statistical power.

Conclusions

More than 3 years and 100 value dossiers since its initiation, all key stakeholders agree on two things: the AMNOG-process is still to be considered a “learning process” and it is here to stay!
In the long term, achieving additional benefit is not only in the interest of the pharmaceutical industry, but mainly in the interest of patients, and ultimately, of the entire German health care system. Thus the repercussions of this process are also relevant for academia and all stake holders in clinical research and development.
It is essential to follow the developments in this field and to consider AMNOG-related issues early during planning of individual clinical studies and entire clinical research programs, in order to fulfill the quality requirements for demonstrating additional benefit.
Striking the right balance between fulfilling regulatory requirements in different countries, while keeping AMNOG in mind appears challenging. Especially the selection of endpoints is critical for achieving additional benefit, however the relevance of given endpoints for the patients is often debated. Thus, critical assessment of patient relevance of endpoints, their validity and operationalization as well as possibilities of complementation with additional assessments are essential.

Disclaimer

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