IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

Institute for Quality and Efficiency in Health Care

IQWiG in dialogue 2015

"How confirmatory is HTA?"

Abstracts of presentations

Claudia Nicolay (Eli Lilly) & Friedhelm Leverkus (Pfizer)

HTA meets EMA – Methodological areas of debate from an industry point of view

Clinical registration trials serve to prove efficacy by means of prospectively planned confirmatory statistical tests. One or a few primary endpoints are analysed using Neyman-Pearson hypothesis tests. On the basis of these results, a dichotomous conclusion is drawn. In this context, Type I and II errors are controlled; secondary endpoints are only supportive and are not part of the testing.

According to the Act on the Reform of the Market for Medicinal Products (AMNOG), the early benefit assessment is based on the methods of evidence-based medicine. This assessment aims to draw quantified conclusions on the added benefit of a new drug on the basis of data from clinical registration trials. The methods used for this purpose comprise retrospective analyses, as also described in the Cochrane Handbook. An abundance of patient-relevant endpoints and subgroups is analysed. In this context, no distinction is made between primary and secondary endpoints; all endpoints are of equal relevance. The main focus is on the estimation of effects; Type I and II errors are not controlled. The p-value is interpreted in terms of Fisher's significance test.

These two different approaches in the evaluation of the same data lead to debates about methodological issues and data interpretation, which are highlighted from an industry point of view.

Jan Müller-Berghaus (Paul Ehrlich Institut, PEI)

The regulatory process between confirmatory studies and benefit-risk assessment

Confirmatory registration studies prove the efficacy of a medicine in the study population. However, it can be assumed that patients of the study population differ from those of the general population, that is, an extrapolation of efficacy data must be performed in any case. The marketing authorisation of a medicine, which is primarily reflected in the text on the therapeutic indication provided in the summary of product characteristics (SmPC), takes place after further evaluation of the overall data on the medicine and contains elements of value judgement. Besides the assessment of efficacy, the most important additional areas are the assessment of safety and tolerability. Different approaches are used, for example, the assessment of study quality on the basis of inspection and study findings, statistical procedures such as subgroup analyses by means of certain population characteristics, and an assessment involving preclinical toxicological results. Further factors may include issues related to therapeutic area, for example, experience with medicines of the same class, the type of medical care provided in the treatment of patients, and the availability of therapeutic alternatives. Ultimately, the consideration of benefits and risks in the population described in the SmPC determines the decision on marketing authorisation.

Armin Koch & Yvonne Ziert (Hannover Medical School)

Decision strategies in approval and benefit assessment from a biometric point of view

The commencement of the Act on the Reform of the Market for Medicinal Products (AMNOG) on 1 January 2011 provoked a number of discussions between the different stakeholders in the healthcare system. The methodological part of the debate primarily focuses on the comparison of the statistical-methodological decision strategies used by the responsible institutions to assess clinical study results.

In this context, criticism is primarily aimed at the methods developed by the Institute for Quality and Efficiency in Health Care (IQWiG), which are judged on the basis of the established methods of drug approval. The comments on deviations between the statistical assessment procedures refer, for example, to the different interpretation of subgroup results or to the acceptance and weighting of endpoints.

The presentation aims to show that the assessments by the institutions responsible for drug approval and for the assessment of the added benefit follow different aims, but that their statistical-methodological decision strategies are similar. It should also be considered that the requirements within the framework of formal proof of efficacy are often equated with the procedure for the assessment of an essentially positive benefit-risk ratio or the assessment of added benefit. Depending on the perspective, the procedure applied in drug approval or that applied by IQWiG then seems more liberal or conservative.

Concepts are developed to illustrate under which conditions consistent decisions would be expected or confirmatory conclusions would be necessary or possible.

Gerald Gartlehner (Danube University Krems, Austria)

How reliable are HTA decisions based on single RCTs?

In health technology assessments (HTA), rarely is a sufficient amount of high-quality evidence available to enable decisions without uncertainties. At times, HTA researchers only have a single randomized controlled trial (RCT) to answer a specific question. Although RCTs are regarded as the best study design to minimize bias and confounding, assessments of the quality of the evidence (e.g. according to GRADE [Grading of Recommendations Assessment, Development and Evaluation]), based on a single RCT, are less than ideal because the consistency of results cannot be compared to other RCTs.

The presentation will address the reliability of single RCTs in evidence-based decision-making. Results of a US Agency for Healthcare Research and Quality methods project are used to compare the treatment effects depicted in meta-analyses with high-quality evidence (according to GRADE) with those first published from RCTs. The presentation will look at the factors influencing the reliability of the results of single RCTs and use real world examples from publications to delve more deeply into the issue.

*** Please note: the presentations are in German. The programme and abstracts are also provided in English as a service to English-language readers.**