Benefit-Risk Assessment in Drug Development

This thesis covers the development, testing and use of an eight-step structured method for data-driven benefit-risk assessment. The aim of this thesis was to create a tailored method for the assessment of clinical data. The focus has been on three major aspects: (i) A simple preliminary method was created and tested in a pilot study and was presented at an internal workshop in Novo Nordisk A/S, where the given project team was invited. Input from the project group was used to adjust and optimise the method, which was then tested in a new pilot study, and the results were presented at a new workshop. In total, four pilot studies and internal workshops were conducted. The method was therefore developed in an iterative fashion.

The method involves eight successive steps: 1) establishment of the decision context, 2) identification of benefit and risk criteria, 3) weighting, 4) scoring, 5) evaluation of uncertainty, 6) calculation of weighted scores, 7) visualisation, and 8) discussion and formulation of an overall conclusion. In order to reduce the impact of subjective judgments, scores are assigned to each criterion on the basis of objective information (data) wherever possible.

The method is comprehensive and supported by a qualitative framework with built-in quantitative measures. However, at the same time the method is transparent in the sense that all assumptions made in the various steps of the assessment are clearly expressed all the way to the final decision. This is important both to avoid that unreported biases and feedback distort the assessment, and to make it possible for the industrial partner and the regulatory agency to compare the results of their evaluation on a point-by-point basis. The qualitative framework ensures a structured approach to the assessment and a transparent communication of the results.

Clinical significance and relevance of data is defined in qualitative ways, but captured by quantitative measures, enabling a discussion of the clinical relevance of data. This has opened a new dimension in the discussions related to data. Different approaches to different types of data have been developed, tested and used.

Standardised diagrams for the visualisation of results from the assessment have been established, and different diagrams have been developed for different scenarios. For the visualisation of results from single and/or multiple similar trial assessments, tornado-like diagrams were designed. For dose-finding studies and multiple non-similar trial assessments, matrix diagrams have been developed and for events scoring tables have been set up. All of these different visualisation techniques enable a transparent communication of assumptions and decisions made in the assessment.

The method was successfully applied to three different cases: (i) colorectal cancer, (ii) schizophrenia, and (iii) telithromycin (Ketek®), and demonstrated its general applicability.