Daniel Saure
Dr. sc. hum.

Sequential meta-analysis of safety data

Promotionsfach: Medizinische Biometrie und Informatik
Doktorvater: Prof. Dr. sc. hum. Meinhard Kieser

In this thesis, the application of Fisher's combination test within sequential meta-analyses covering situations typical for drug development was investigated with regard to the type I error rate control. Therefore, sequential meta-analyses approaches were examined in the setting of binary outcomes, including trials based on both small rates and small sample sizes. The main focus lay on fixed effect meta-analyses assessing both superiority and noninferiority.

Fulfilment of the so-called *p* clud condition (Brannath, 2002) assures type I error rate control applying Fisher's combination test. However, for discrete data and especially in case of sparse data, the validity of this condition was questionable when applying the usually applied *p*-values that are based on the asymptotic distribution of the underlying test statistic.

As a first step, meta-analytic methods for superiority were extended to noninferiority assessment. A particular emphasis on estimating the variance of the combined effect measure when performing meta-analysis based on the inverse-variance method was done for the risk difference. Since the respective asymptotic test could be based either on restricted or unrestricted ML estimators, comparisons with respect to the type I error and the power were conducted. Based on these results, the test statistic that is based on the RML estimator was generally recommended for practical situations.

An investigation of the extent of the type I error rate inflation within cumulative meta-analysis providing an interim analysis after each included trial, emphasized the application of designs that provide accurate type I error rate control.

Thus, the application of Fisher's combination test was investigated by examining the *p* clud condition. Furthermore, a weaker condition assuring the type I error rate control of Fisher's combination test was presented and investigated in those cases, where the *p* clud condition was not fulfilled. An important feature of the proposed methodology is the fact that an upper boundary of the actual type I error rate of Fisher's combination test can be calculated without specifying the, generally unknown, true event rates.

The *p* clud condition was investigated within several scenarios for usually applied *p*-values that are based on the asymptotic distribution of the underlying test statistic. It was examined in the situation of independent *p*-values covering the situation of Fisher's combination test with fixed sample size per stage within a full-sequential meta-analysis approach. Furthermore, an approach based on two trials per stage was considered.

In summary, most of the *p*-values did not meet the *p* clud condition as they were not valid. Even the above mentioned weaker condition was not fulfilled for most cases based on the full-sequential approach. Improved results were observed in a sequential approach including two trials per stage. Nevertheless, application of exact *p*-values, which are always valid, was recommended for most situations, especially those characterized by small sample sizes.