Bayesian methods for early clinical trials

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After a short introduction to the principles of Bayesian statistical methods, their use for early clinical trials is discussed, especially in the context of pediatric trials with very small sample sizes. In the situation of dose-finding in Phase I trials, relevant adult Phase I trial information can at first be used for the selection of dose levels to be tested. Furthermore, when using Continual Reassessment Methods for the design of the trial, the prior distribution of parameters in the pediatric dose-toxicity model can be informed by the respective adult model.

Also in Phase II trials, borrowing from external data, e.g. from adult trials, is achieved by informing the prior distribution for the current analysis. Several methods have been proposed that dynamically discount the amount of information borrowed from external data based on the conformity with current data. The frequentist operating characteristics of such an analysis strategy are often of interest. In particular, type I error rate and power at a prespecified point alternative are the focus. A procedure is proposed to investigate and report the frequentist operating characteristics in this context. The approach evaluates type I error rate of the test with borrowing from external data and calibrates the test without borrowing to this type I error rate. On this basis, a fair comparison of power between the test with and without borrowing is achieved. It is illustrated that no power gains are possible in one-sided one-arm and two-arm hybrid control trials with normal endpoint, a finding proven in general before. The concept of prior effective sample size facilitates quantification and communication of prior information by equating it to a sample size. When prior information arises from historical observations, the traditional approach identifies the ESS with a historical sample size. However, this measure is independent of newly observed data, and thus would not capture an actual "loss of information" induced by the prior in case of prior-data conflict. The effective current sample size of a prior is introduced which relates prior impact to the number of (virtual) samples from the current data model. In a further development, a Bayesian decision-theoretic approach is presented. An integrated risk approach is proposed that incorporates losses arising from testing, estimation, and sampling. A weighted combination of the integrated risk arising from testing and estimation allows moving smoothly between these two targets.

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