A confirmatory adaptive Phase II/III design with Bayesian decision rules for dose selection and sample size re-estimation – a case study

Adaptive trial designs are increasingly used in the pharmaceutical industry for various ethical and economic reasons. The possibility of adaptations during the trial can decrease the time-to-market for effective treatments and reduce the burden on patients and companies involved in continued investigation of non-effective treatments. However, interim adaptations can increase the overall frequentist type-I error and are therefore a concern in particular for regulatory agencies in the confirmatory setting.

In this talk, we will present a case study of an adaptive seamless phase II/III design in radicular leg pain with two primary endpoints. The design uses Bayesian decision rules at two interim analyses and a frequentist approach at final analysis that controls the overall type-I error. At the first interim analysis, futility assessment and dose selection is conducted based on posterior probabilities from a Bayesian mixed model for repeated measures (Bayesian MMRM). At the second interim analysis, Bayesian predictive probabilities of success (PPoS) at the final analysis are used for a second futility assessment as well as sample size re-estimation. The final analysis is a frequentist MMRM testing two primary hypotheses. The frequentist type-I error control is guaranteed by the use of closed testing together with the combination test principle.

Our aim is to cover general statistical aspects of the study design and provide practical details on trial simulations, for example the use of INLA (Integrated Nested Laplace Approximation) for posterior approximations. Additionally, we will discuss simulation-guided calibrations and how these have supported clinical and economic decision-making.

SHORT BIO

Jan Priel is currently a Research Consultant at Cytel Inc. in the Strategic Consulting Team. He has over 6 years of experience as a statistician in the pharmaceutical industry. At Cytel, he is involved in complex innovative designs of clinical trials with a focus on adaptive Bayesian designs. He has supported various trial design projects with trial simulations and exploratory analyses. Jan has a Doctoral degree in Mathematics from University of Hamburg (Germany).