Operating characteristics of clinical trials with borrowing from external data: one-arm and hybrid control arm trials

Annette Kopp-Schneider[(1)], Manuel Wiesenfarth[(1)], Vivienn Weru[(1)], Leonhard Held[(2)] and Silvia Calderazzo[(1)]

[(1)]Division of Biostatistics, German Cancer Research Center, Germany

[(2)] Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Switzerland

Borrowing of information from historical or external data to inform inference in a current trial is an expanding field in the era of precision medicine, where trials are often performed in small patient cohorts for practical or ethical reasons. Many approaches for borrowing from external data have been proposed. Even though these methods are mainly based on Bayesian approaches by incorporating external information into the prior for the current analysis, frequentist operating characteristics of the analysis strategy are of interest. In particular, type I error and power at a prespecified point alternative are in the focus. It is well-known that borrowing from external information may lead to the alteration of type I error rate.

We propose a procedure 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.

We show that no power gains are possible in one-sided one-arm and two-arm hybrid control trials with normal endpoint, a finding that had been proven in general before [1]. We illustrate that the Empirical Bayes power prior approach [2] that dynamically borrows information according to the similarity of current and external data avoids the exorbitant type I error inflation occurring when borrowing with fixed power prior. We have however observed that the power in the hybrid control two-arm trial doesn't reach the power of the test calibrated to borrowing, and power losses increase when considering unconditional power.

[1] A. Kopp-Schneider, S. Calderazzo, M. Wiesenfarth, *Biometrical Journal*, 62(2):361–374.

[2] Gravestock, I., Held, L.; COMBACTE-Net consortium (2017). Adaptive power priors with empirical Bayes for clinical trials. Pharm Stat. 16(5): 349-360.