Utilizing historical information from adult and pediatric clinical trials: Results, limitations, and extensions of the meta-analytic predictive approach

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In pediatric clinical trials the number of available patients is often restricted. The necessary sample size for the usual requirements of confirmatory clinical trials can't be achieved. Thus, in a future pediatric study it is a valuable option to utilize historical information from previous adult and pediatric trials to increase the power or decrease the required sample size. Bayesian methods represent a flexible way to utilize external information in new clinical trials [1,2]. Neuenschwander [3] and Gerss [4] use a meta-analytic predictive approach to summarize historical information and to determine the amount of evidence. The aim is to assess the number of patients which can be saved for future recruitment ("prior effective sample size").
Hierarchical models and Markov chain Monte Carlo (MCMC) methods are applied to perform Bayesian meta-analyses and to estimate the study-specific effect in a future pediatric trial. The posterior predictive distribution of the study-specific effect will be used as informative prior distribution in the new trial. The information contained herein is translated into the "prior effectiv sample size".
The "prior effective sample size" is directly affected by the between-study variation of the historical trials. Non-informative prior distributions for hyperparameters are applied to emphasize the observed historical data [6,7]. Hence, model fitting problems could occur, especially in the case of few historical trials or very heterogeneous study outcomes. The prior distributions affect the posterior predictive distributions more than the observed data. Consequently, the Markov chains of the estimated parameters contain several extreme values. The corresponding means, variances and therefore the "prior effective sample size" are biased.

Various results of the meta-analytic predictive approach will be presented based on clinical study data. Further, the influence of different prior distributions on the "prior effective sample size" will be illustrated. In the case of normal-distributed endpoints, a trimming method for MCMC simulations is suggested. The Markov chains of all parameters are α-trimmed (α=0.001) with respect to the predictive study effect in a future pediatric trial. By this approach extreme values in the simulated Markov chains are removed.

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