Partial extrapolation in pediatric drug development using robust meta-analytic predictive priors, tipping point analysis and expert elicitation

Christian Stock[1], Morten Dreher[1], Elvira Erhardt[1], Heiko Müller[1], Oliver Sailer[1], Florian Voss[1]

[1] Global Biostatistics and Data Sciences, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany.

Pediatric drug development is commonly associated with substantial challenges regarding the creation of robust efficacy data. We describe a pediatric extrapolation approach via Bayesian dynamic borrowing for a continuous endpoint that is based on a robust meta-analytic predictive (MAP) prior, tipping point analysis and expert elicitation. The tipping point analysis, as proposed by Best et al. (Pharm Stat, 2021), indicates, for given results of the pediatric trial and given one-sided evidence levels, how much weight on the informative component of the robust MAP prior is needed in order to conclude that the treatment is efficacious. At the planning stage, in addition to common criteria such as operating characteristics, we use the tipping point analysis as a tool to pre-specify the prior distribution. This is achieved through a formal expert elicitation exercise in which the experts are asked about inferences they would draw from the total evidence in different hypothetical scenarios and, consequently, the weights they would assign to the evidence from trials in adults. Once the data from the pediatric trial are available, the tipping point analysis serves as a sensitivity analysis to assess the impact of the chosen weight on the inferences based on the totality of the evidence. We illustrate the approach by an exemplary case study. Further, we discuss compatibility with new draft ICH guidance on pediatric extrapolation. The publicly available R package “tipmap” is introduced to facilitate implementation of the described approach.