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

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Pediatric drug development is often associated with great challenges regarding the creation of robust efficacy data. For ethical and feasibility reasons, especially in rare diseases, pediatric trials are typically small. They also tend to focus on safety aspects and clinical pharmacology, and they are often not statistically powered to assess efficacy. This renders it difficult to reach conclusiveness, particularly on efficacy, based on the pediatric trial alone. However, since pediatric development usually starts after a positive benefit-risk has been established based on clinical trials in the adult population, partial extrapolation from these trials is an opportunity that is increasingly recommended and used to strengthen the evidence base (Gamalo et al, 2022). In such cases, it is desirable to pre-specify a sensible weight of the external evidence from trials in adults in a transparent and scientifically rigorous process, and to assess the sensitivity of inferences to the choice of this weight. We describe a Bayesian dynamic borrowing approach to the analysis of a continuous endpoint in this setting that is based on a robust meta-analytic predictive (MAP) prior, tipping point analysis and expert elicitation. The tipping point analysis, as recently proposed by Best at al. (2021) and slightly extended here, 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 consider hypothetical trial results and use the tipping point analysis as a tool to pre-specify the prior distribution. This is achieved by asking a panel of clinical experts in a formal expert elicitation exercise about conclusions they would draw from the total evidence in different 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, emphasizing workflow-related and graphical aspects. Further, we discuss compatibility with new draft guidance on pediatric extrapolation (ICH, 2022). A publicly available R package called “tipmap” is introduced to facilitate implementation of the described approach.

References:

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