184

Advances in pediatric extrapolation

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Sebastian Weber
Please provide a brief biography for the Presenting author(s)
Sebastian Weber is working as Director in the Department of Advanced Methodology and Data Science at Novartis. He holds a PhD in Physics from the TU Darmstadt and joined Novartis 10+ years ago. He has worked extensively on enabling the use of historical (control) information in clinical trials through consulting and working on tools to facilitate the application of historical control information from trial design to analysis. Furthermore, Sebastian has experience in designing Oncology phase I dose-escalation trails and is also involved in pediatric drug development programs, where he applies extrapolation concepts. His research interests include the application of pharmacometrics in statistics, model-based drug development and application of Bayesian methods for drug development.

Björn Bornkamp
Please provide a brief biography for the Presenting author(s)
Björn Bornkamp works as a Senior Director Statistical Consulting at Novartis in the Statistical Methodology group. In this role he consults and researches on topics related to dose-finding studies, subgroup analyses, Bayesian statistics as well as estimands and causal inference.

Christian Stock
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Christian Stock joined BI in 2018 as project statistician, methodology statistician since 2021. His focus areas are late phase clinical trial design and analysis, Bayesian methods and causal inference. Christian has an MSc in biostatistics (Heidelberg) and MSc in health sciences (York, UK), doctorate in epidemiology (Heidelberg), habilitation in epidemiology and biostatistics (Heidelberg); post-doc in biostatistics and clinical epidemiology (Heidelberg).

Rocío Lledó-García
Please provide a brief biography for the Presenting author(s)
Rocío Lledó-García, PhD is the Director of Quantitative Clinical Pharmacology (QCP) at UCB, a position she has held since 2011. Rocío has played a pivotal role in numerous drug development programs, primarily focusing on the Immunology therapeutic area, with additional contributions to Neurosciences. Her expertise spans from early to late-phase drug development, with a special interest in pediatric drug development. She has overseen pediatric submissions within the Immunology portfolio to various regulatory agencies. Recently, Rocío has expanded her expertise to the rare diseases area, particularly in Gene Therapy. Before joining UCB, Rocío worked at Esteve SA in Barcelona, Spain, where she established the company's Pharmacometrics expertise. She holds a PhD in Pharmacometrics and a BSc in Pharmacy from the University of Valencia, Spain. Rocío also completed a postdoctoral and Researcher fellowship in the Pharmacometrics group at the Biomedicinskt centrum at Uppsala University.

Single topic, multi-speaker session, Workshop or Single presentation submission

A single topic, mutli-speaker session/workshop

Single topic session or workshop abstracts

The American Statistical Association (ASA) Biopharmaceutical Section Statistics in Pediatric Drug Development Scientific Workgroup (SPDRx) Extrapolation Subteam is proposing a session on pediatrics extrapolation.

The proposed session aims to explore and discuss recent advancements in statistical methodologies for pediatric extrapolation, bringing together experts and practitioners to share insights, methodologies, and case studies.

Bellow are the abstracts for each of the three confirmed talks. Of note, the regulator's insights may be also included (if the PSI committee accepts to add this later) by Andrew Thompson (EMA) who indicated high personal interest in the session, however, his attendance cannot be confirmed before the deadline of the PSI abstract submissions.

Title 1: Developing Treatments for Rare Pediatric Diseases Using Bayesian Extrapolation (Author: Sebastian Weber, Björn Bornkamp)

Abstract 1: Developing treatments for rare diseases in adults is challenging, with pediatric development posing even greater difficulties. We present a case where a full extrapolation approach was agreed upon with authorities, using efficacy assessment within a Bayesian framework that incorporates key covariates and borrows from the adult data.

Key challenges included: (i) vastly different sample sizes between adult and pediatric data (adults had over 10 times more patients), (ii) the inability to discount adult study data based on between-trial heterogeneity due to confounding of study with key covariates, and (iii) complications to use covariates using Meta-Analytic-Predictive (MAP) priors.

To address these, we propose a MAP model as a prior, incorporating key covariates and age both as a continuous variable and in 12-year bins. This allows the model to account for response changes with age and apply a random walk prior to the categorical age variable, ensuring age-respecting discounting from the adult data by borrowing more from similarly aged patients.

The MAP model, informed by adult data, is summarized using a multivariate normal mixture distribution. Once pediatric baseline data becomes available, patient-specific predictions are derived, creating the final prior through marginalization.

This approach enables greater borrowing from younger adult patients and less from older ones and remains straightforward to apply.

Talk 2: Expert elicitation for pre-specification of priors in pediatric extrapolation studies: from one-parameter to multi-parameter scenarios (Author: Christian Stock)

Abstract 2: Pediatric drug trials following adult-driven drug development increasingly use explicit extrapolation from adult patient populations via Bayesian methods. The recently adopted ICH E11A guideline provides a framework for using extrapolation as a tool to support the development and authorization of pediatric medicines. It emphasizes the importance of pre-specification, transparency and sensitivity analysis. In practical applications, challenging questions commonly arise on the relevance, the synthesis and the weight of the existing evidence in adults. Medical experts can play an important role in answering these questions and in devising informative prior distributions for Bayesian models. This talk briefly reviews the role of expert elicitation in pediatric drug development, specifically in informing extrapolation analyses. It then explores opportunities and challenges of expanded model and elicitation complexity in comparison to (reduced) "one-parameter" scenarios. A case example of an efficacy endpoint analyzed by a Bayesian mixed model for repeated measures (MMRM) is used where multiple (correlated) parameters of a statistical model can be informed by trials in adults. 'Informative prior archetypes' for MMRMs are introduced and illustrated as a concept to facilitate the specification of meta-analytic predictive (MAP) priors for this type of model. Its underlying idea exploits that

marginal means linearly map to fixed effect parameters in MMRMs. Software implementation of the approach is facilitated through a publicly available R package. A general roadmap for pediatric extrapolation in this “multi-parameter” scenario is outlined. The talk concludes with remarks on the role of expert-informed Bayesian extrapolation models in the benefit/risk assessment in pediatric drug development.

Talk 3: The role of modeling and simulation in accelerating pediatric clinical development: A case study on pJIA pediatric extrapolation (Author: Rocio Lledo-Garcia)

Abstract 3: The ICH E11A guideline provides a comprehensive framework for using pediatric extrapolation to support drug development. This approach involves extending information on efficacy and safety from a reference population, such as adults, to a target population, like pediatric patients, when there are similarities in disease progression and anticipated treatment response between the populations. Pharmacometrics methodologies play a crucial role within this framework by supporting the extrapolation concept through various means.

Firstly, these methodologies help characterize disease progression across reference and pediatric populations, ensuring a robust foundation for extrapolation. Secondly, they explore the anticipated response to therapeutic interventions by leveraging information from other molecules with similar mechanisms of action or real-world evidence (RWE). Thirdly, modeling and simulation are employed to optimize pediatric trial design, including the dose regimen anticipated to be therapeutic in children, by scaling the pharmacokinetic-pharmacodynamic (PKPD) population model from adults to pediatrics. Lastly, during the conduct of the study, interim analyses confirm the appropriateness of the dose regimen in the pediatric population, and at the end of the study, population pharmacokinetics (popPK) and population pharmacokinetics-pharmacodynamics (popPKPD) are characterized across adult and pediatric populations. This process validates the extrapolation approach and confirms the dose regimen for the pediatric indication.

In this session, we will present a case study on the use of popPK methodology to support dose adjustment and final dose selection for an anti-TNF biologic, Cimzia, for the pediatric juvenile idiopathic arthritis (pJIA) indication, where extrapolation of efficacy substantiated the label indication.