Session 3: Extrapolation plan and PK/PD studies

Panel Discussion

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Different Objectives

E.g.,

- Safety, dose finding for subsequent efficacy studies in the target population.
- Validation of extrapolation assumptions to justify extrapolation of Efficacy/Safety from adults.
  - to learn to which extend PK/PD can reduce the uncertainty if Efficacy/Safety data from adults can be extrapolated to children.
  - To determine the size and design of efficacy studies in children.

Optimizing the Design of PK/PD Studies

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- Using information from adults to derive optimal designs (with independent estimation of outcome parameters)
- Adaptive studies that collect additional data only if results are inconclusive
- Evidence synthesis with data from adults assuming similarity of models and parameter estimates.
  - Extrapolating model assumptions and parameter values
  - *Challenge to assess model misspecifications based on limited data*

Required Levels of Evidence

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- Specification of acceptable widths of confidence intervals and coverage probabilities
- Power to detect significant deviations from model assumptions
- When do we need **confirmatory trial standards** in PK/PD studies?
  - Control for multiplicity for several parameters (Simultaneous CI?)
  - Pre-specification of design and analysis of PK/PD Studies.
    (Many approaches include model selection and other adaptive elements that may lead to biased estimates and confidence intervals that do not control the coverage probabilities.)
  - Sufficient confidence in model assumptions.