

MEDICAL SCHOOL

Methodology for extrapolation in the EU FP7 ASTERIX, IDeAI and InSPiRe projects

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Integrated DEsign and AnaLysis of small population group trials



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(Some) Statistical issues in extrapolation

Comparison of adult and paediatric populations To construct models for extrapolation To determine feasibility of extrapolation

'Borrowing' information from adult to paediatric populations For evaluation of efficacy and/or safety For determination of appropriate dose

Assessment of decision-making in paediatric trials For regulation on basis of extrapolation

Comparison of adult and paediatric populations

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Dette et al. (IDEAL)
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Comparison of dose-response curves to enable pooling if paediatric and adult data are similar Current work on optimal design for curve comparison will extend via Bayesian model uncertainty analysis

Karlsson et al. (IDEAL)

Randomization tests and model-based resampling methods using non-linear mixed effects models and mechanistic pharmacometric models Investigate model misspecification and uncertainty

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'Borrowing' information from adult to paediatric populations

Zohar *et al.* (InSPiRe)

Using patient-level PK/PD data in dose-finding studies Enables incorporation of population-level PK/PD information via Bayesian hierarchical model

Friede et al. (InSPiRe)

Generalized evidence synthesis methods e.g. using observational data in design & interpretation of RCT

Both relevant to extrapolation if combining adult population/observational data with paediatric RCT data

Assessment of decision-making in paediatric trials

Posch (ASTERIX, InSPiRe), Koenig (IDEAL) *et al.*Quantitative concept for extrapolation
Evaluate information required in PIP for pivotal paediatric trial in light of adult efficacy data
'Skepticism factor': probability results can be extrapolated Leads to relaxed significance level for pivotal trial without compromising overall evidence level

(Some) Key statistical themes

Modelling of outcomes in related populations joint models, shared functional form, shared parameters
Bayesian methods for accumulation and combination of evidence
Optimal design for efficient evidence collection
Modelling of decision-making

Collaboration with clinicians, industry and regulators