Paediatric medicine development will usually require efficacy and safety data in children

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Paediatric medicine development

Aim

Given existing knowlegde (adult data, etc), generation of **sufficient evidence** to support use in children:

- Age-appropriate formulation(s)
- Establish doses
- confirm/establish efficacy
- Safety (short/long-term)

→ Benefit/risk balance

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Feasibility constraints:

- Trial burden
- N of patients
- Time
- Ressources

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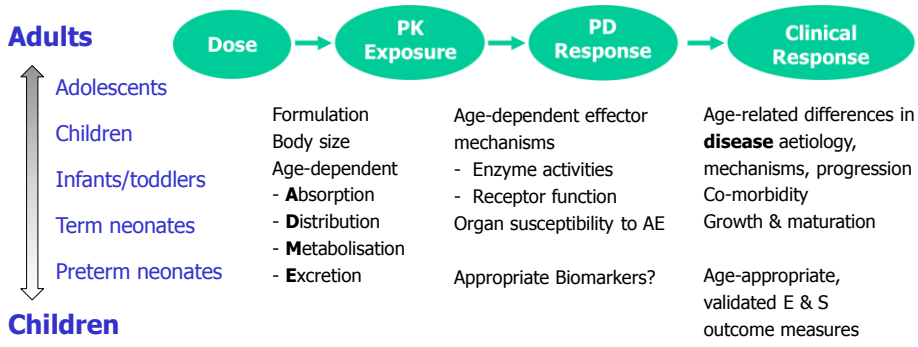
Extrapolation definition

Extending information and conclusions available from studies in one or more subgroups of the patient population (source population), …, to make inferences for another subgroup of the population (target population), …, thus minimizing the need to generate additional information to reach conclusions for the target population,...

EMA 2016, Reflection paper on extrapolation of efficacy and safety in paediatric medicine development

Linking between populations



Prediction from source to target population:

- Reasonable similarity, or
- Understanding of co-variables determining differences

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Extrapolation concept

Emphasis on quantifying the system for decision making

PK and PD: using existing data and physiology-based PK (and PD) modelling and simulation to investigate the relationship between PK/PD, body size, maturation, age and other important covariates (such as age, renal and hepatic function)

Disease progression: quantitative synthesis or modelling to characterise differences in disease progression between source and target population

Clinical response: of all relevant existing data to predict the degree of similarity in clinical response (efficacy, some safety aspects) between populations

Adapted from: E. Manolis

Proposed general strategy for paediatric dose finding and selection

Collect and systemize prior information

- **Collect and systemize drug and system data**
- *In vitro* drug data
- Non clinical drug data
- Adult drug data
- Paediatric drug data
- Adult and paediatric drug data on similar (model) substances, indications etc
- Adult and paediatric system data (such as relevant physiological, pathophysiological and PK and PD ontogeny data)

Define D-E-R in animals, adults, children

- **Define D-E-R and estimate relevant parameters and variability based on available data**
- PK parameters (F/ka, CL and V) and variability
- PD parameters and variability
- Efficacy and safety parameters and variability
- Establish covariate relationships
- Qualify the models for the existing data at the key interim and final stages

Potential methods
- Population PK/PD/response /safety models
- PBPK/PBPD
- system pharmacology models
- Bayesian methods

Predictions for the selected paediatric age subsets

- **Scale available predictions to the relevant paediatric population**
- Address major assumptions and potential impact of violating assumptions
- Uncertainty quantification such as sensitivity analysis of the important/main parameters (worst/best case scenarios)
- Evaluate if there are assumptions that mandate a conservative approach (titration from lower doses etc) or if there are opportunities for interpolation or partial extrapolation

Potential methods
- Allometric scaling
- Organ function
- Maturation function
- Co-variate structure

Study design optimization

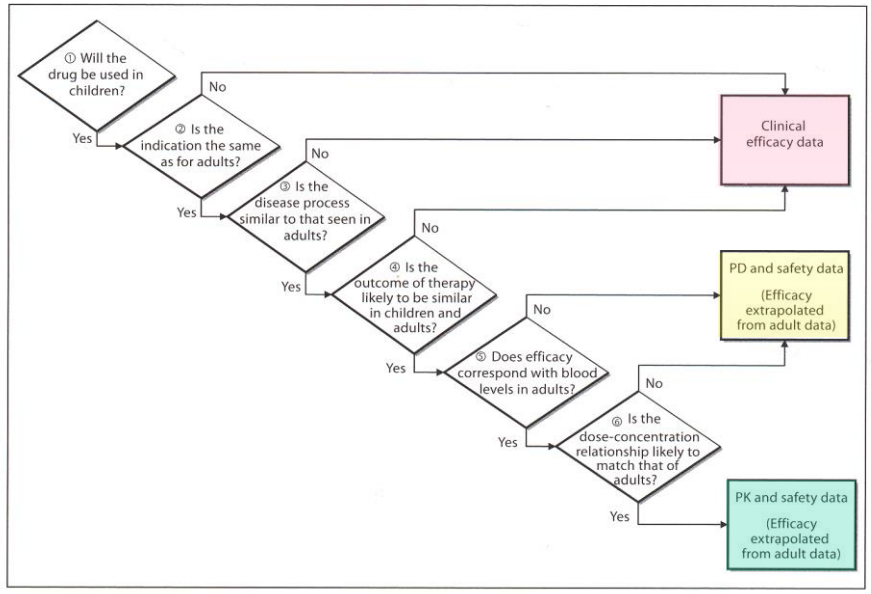
- **Determine type of study(ies) needed**
- separate PK study, separate PK/PD study, microdosing study, confirmation of PK/PD within a E&S study in an adaptive manner etc
- Determine the need for several doses in order to further inform on the D-E-R relationship also in paediatric patients
- Optimization of number of patients and sampling scheme for the PK and PD parameters

Potential methods
- Clinical trial simulations etc.

Learn & confirm paradigm - updating and refining the models with new information

Skottheim-Rusten, EMA EFPIA workshop on the importance of dose finding, December 2014

Decision tree for identification of study requirements in paediatric medicine development



Della Pasqua, in: Rose 2010, Guide to Paediatric Drug Development and Clinical Research

Difference in indication

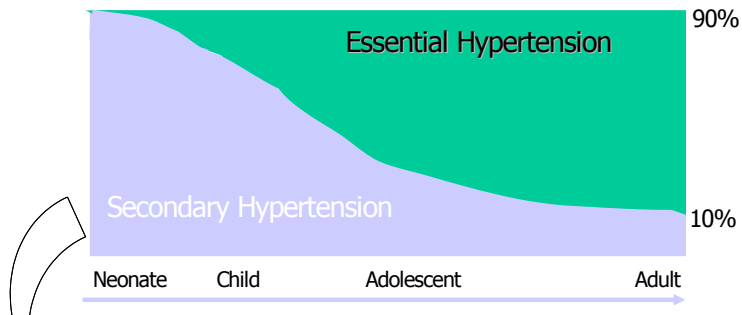
Example

Platelet aggregation inhibitors

Adults	Children
- Prevention of atherothrombotic events (MCI, stroke)	- Congenital heart disease (shunts, stents)
- Acute coronary syndrome	- Kawasaki Syndrom (with coronary aneuryms)
- Atrial fibrillation	- Arterial stroke

Age-specific disease aetiology

Example



Renoparenchymal	75 %
Renovascular	10 %
Aortic Coarctation	8 %
Endocrine and others	7 %

From: F. Schäffer

Age-appropriate outcome parameters

Challenges:

- Differences in measurement and interpretation of OC
- Difficulties to measure OC in children/some age-groups:
  - Tolerability (invasiveness)
  - Developmental capacity (PRO; exercise capacity, etc)
  - Infrequent OC, long latency
- Correlation with relevant clinical outcome and responsiveness to treatment need to be established (in children)

Measurement tools for pain

Infant toddler pre-school school-age adolescent

Physiological measures
- Heart rate
- Respiration
- Sweating
- Stress hormone levels

Behavioral Scales
- Facial expression
- Posture
- Movements
- Sleep
- Feeding

Self-reported Scales (gold standard)
- Faces scales
  - Word descriptor
    - Visual analog scales

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Extrapolation plan

Reduced set of supportive studies (*types of studies, design modifications, number of patients*) in the target population **in accordance with**

- Predicted degree of similarities
- Strength of existing evidence / lack of uncertainties

- Should confirm the extrapolation concept
- Should complement the information extrapolated from source population(s)

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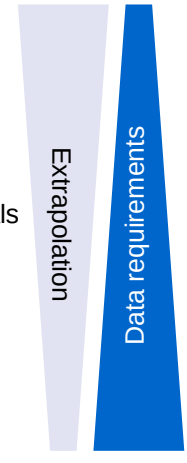
Inventory of extrapolation approaches used in PIPs

- PK or PK/PD studies only (including M&S)
- Dose-ranging or dose-titration studies
- Non-controlled ‚descriptive' efficacy / safety study
- Controlled study but ‚arbitrary' sample size
- Larger significance level, lower %age confidence intervals
- Studies powered on surrogate endpoint
- Interpolation (bridging)
- Modelling prior information from existing data sets (Bayesian, meta-analytic predictive)
- etc.



Spectrum of extrapolation in various therapeutic areas
some examples

Disease	Endpoints	Studies in children
HIV	PK (surrogacy accepted for children) Suppression of plasma viral load Safety	- PK study - Tolerability & safety
Haemophilia	FVIII/IX plasma levels prevention & treatment of bleeding Immunogenicity	- PK studies - Descriptive E & S - Dedicated immunogenicity study (partially post-MA)
Hypertension - Essential HT - Secondary HT	Reduction in blood pressure End organ damage (CV morbidity, mortality)	- PK studies; Dose ranging - Long-term E & S (partially non-controlled)
Thrombosis - Treatment - prevention	Recurrent thrombosis bleeding	- PK/PD studies - E & S (controlled but reduced sample size)
Heart failure - Cardiomyopathy - Cong. heart disease	No established surrogate endpoint Morbidity & mortality (composite)	- PK/PD studies - E & S study (sampe size?)

Conclusions

- Paediatric drug development should build upon all existing data (adults, other sources) and generate complementary data in children.
- Extrapolation from other sources depends on similarities in drug disposition, disease, and response to treatment; or our understanding of co-variables determining differences in children.
- For dose-finding, modelling tools are well established to integrate existing knowledge to predict dose-concentration-response relationships in children, thus optimizing studies and minimizing data requirements from children.
- Similar exposure or PD response as in adults, however, does not necessarily translate into comparable efficacy and safety in children.
- How much efficacy data and what types of study design are necessary to confirm the proof of concept from adults, will depend on our understanding of the disease process and on appropriate outcome parameters in children.
- Safety data will always be required from children because of the potential for unexpected age-specific adverse effects.