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

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Paediatric medicine development

Aim

Given existing knowledge (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

Feasibility constraints:
- Trial burden
- N of patients
- Time
- Resources

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

Adults
- Adolescents
- Children
- Infants/toddlers
- Term neonates
- Preterm neonates

Children

Prediction from source to target population:
- Reasonable similarity, or
- Understanding of co-variables determining differences

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

1. Collect and systemize drug and system data
   - in vitro drug data
   - Main clinical drug data
   - Animal drug data
   - Paediatric drug data
   - Adult and paediatric data on similar (model) species, indications (etc)
   - Adult and paediatric system data (such as relevant physiological, pathophysiological and PK and PD category data)

2. Define D-E-R and estimate relevant parameters and variability based on available data
   - PK parameters (fU, CL, V) and variability
   - PD parameters and variability
   - Efficacy and safety parameters and variability
   - Estimation covariance relationships
   - Qualify the models for the existing data at the key interim and final stages

3. Score available predictions to the relevant paediatric population
   - Address near assumptions and potential impact of various assumptions
   - Inconsistency quantified
   - Such as sensitivity analysis of the importatant parameters (validated case scenarios)

4. Evaluate if there are assumptions that mandate a conservative approach (limitation from lower doses etc)
   - Or if there are opportunities for extrapolation or partial extrapolation

5. Determine type of study(ies) needed
   - Separate PK study, separate PD study, microdosing study
   - Confirmation of PK/DS within a clinical study
   - Inception of PK/PD study in an adaptive manner etc

6. Determine the need for several doses as in order to further explore the D-E-R relationship in paediatric patients

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

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Decision tree for identification of study requirements in paediatric medicine development

1. Will the drug be used in children? (Yes/No)
2. Is the indication the same as for adults? (Yes/No)
3. Is the disease process similar to that seen in adults? (Yes/No)
4. Is the outcome of therapy likely to be similar in children and adults? (Yes/No)
5. Does efficacy correspond with blood levels in adults? (Yes/No)
6. g. Is the dose-concentration relationship likely to match that of adults? (Yes/No)
7. PD and safety data (Efficacy extrapolated from adult data)
8. PK and safety data (Efficacy extrapolated from adult data)

Clinical efficacy data

**Difference in indication**

*Example*

**Platelet aggregation inhibitors**

**Adults**
- Prevention of atherothrombotic events (MCI, stroke)
- Acute coronary syndrome
- Atrial fibrillation

**Children**
- Congenital heart disease (shunts, stents)
- Kawasaki Syndrome (with coronary aneurysms)
- Arterial stroke

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**Age-specific disease aetiology**

*Example*

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

<table>
<thead>
<tr>
<th>Infant</th>
<th>toddler</th>
<th>pre-school</th>
<th>school-age</th>
<th>adolescent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiological measures</strong></td>
<td><strong>Self-reported Scales</strong> (gold standard)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Heart rate</td>
<td>- Faces scales</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- Respiration</td>
<td>- Word descriptor</td>
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<tr>
<td>- Sweating</td>
<td>- Visual analog scales</td>
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<td></td>
<td></td>
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<tr>
<td>- Stress hormone levels</td>
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</tbody>
</table>

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

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

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

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.