Extrapolation and bridging of adult information in early-phase dose-finding pediatric studies
How adult information is used in practice?

<table>
<thead>
<tr>
<th>Number of publications with a dose justification</th>
<th>Dose-finding (n = 48)</th>
<th>Randomisation (n = 8)</th>
<th>Total (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How are dose chosen?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arbitrary choice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From Safety: - of Adult</td>
<td>37 (77)</td>
<td>4 (50)</td>
<td>41 (73)</td>
</tr>
<tr>
<td>- of Children</td>
<td>11 (23)</td>
<td>2 (25)</td>
<td>13 (23)</td>
</tr>
<tr>
<td>- of Preclinic studies</td>
<td>1 (2)</td>
<td>2 (25)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>From PK: - of Adult</td>
<td>2 (4)</td>
<td>1 (12.5)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>- of Children</td>
<td>2 (4)</td>
<td>-</td>
<td>2 (3.5)</td>
</tr>
<tr>
<td>Modelling and simulation from Preclinic studies</td>
<td>1 (&lt;1)</td>
<td>-</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>
ICH E11(R1) guideline on clinical investigation of medicinal products in the pediatric population

5. Approaches to optimize pediatric drug development
   5.1. Use of existing knowledge in pediatric drug development
   5.1.1. The use of extrapolation in pediatric drug development
   5.1.2. The use of modelling and simulation in pediatric drug development

Additional approaches to optimize pediatric drug development may include, but are not limited to, statistical and pharmacometric methods, including M&S that integrate and leverage existing knowledge, as well as extrapolation of information from other populations (adults or pediatric subgroups).
Use of existing knowledge

Before the **beginning** of the trial

- Pre-clinical, off-label data
- EHR
- Medical literature
- Expert’s opinion
- Data from other populations, indication, disease

During the trial

- PK/PD
- Efficacy data
- Toxicity data
- Sub groups (biomarkers, age, etc.)
- New findings
- Results from other clinical trials
Planning a pediatric dose-finding using adults information

Questions

• How to take into account adults prior knowledge? How to down-weight this information?
  • How to determine the dose range for the pediatrics setting?
  • How to determine the initial guessed dose-toxicity and dose-efficacy relationship?
    • Algorithm-based or model-based designs?
    • Frequentist or Bayesian inference?
• What is the optimal dose? What are the targets according to age subgroups
• Can the sampling number and time be optimized?
Use of adult knowledge:
  • Starting dose was 80% of the MTD found in adults

Can we do better?
How to determine the dose range?

• Available data: PK model in adults
  • Assumption: similar AUC target

• Extrapolation\(^1,2\)

\[
d_{ch} = d_{ad} \times \left( \frac{BW_{ch}}{BW_{ad}} \right)^{0.75} \times K_{mat,ch}(AGE)
\]

K\(_{mat,ch}\) is a combination of several physiological process

• Illustration

<table>
<thead>
<tr>
<th>Adults doses (mg)</th>
<th>100</th>
<th>150</th>
<th>200</th>
<th>250</th>
<th>300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric dose with maturation adjustment. Ex: 2-5 years old</td>
<td>30</td>
<td>45</td>
<td>55</td>
<td>70</td>
<td>85</td>
</tr>
</tbody>
</table>

How to determine the initial guessed dose-toxicity and dose-efficacy relationship?

- Available data (i): AUC-toxicity relationship in adults\(^1\)

<table>
<thead>
<tr>
<th>Adult doses (mg)</th>
<th>100 mg</th>
<th>150 mg</th>
<th>200 mg</th>
<th>250 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>(AUC = d/Cl_{ad})</td>
<td>25.3</td>
<td>37.9</td>
<td>50.6</td>
<td>63.3</td>
</tr>
<tr>
<td>Probability of toxicity (\gamma^{(1)})</td>
<td>0.13</td>
<td>0.24</td>
<td>0.40</td>
<td>0.60</td>
</tr>
</tbody>
</table>

- Available data (ii): Early phase trials toxicity observations in adults\(^2\)

<table>
<thead>
<tr>
<th>Publication</th>
<th>100 mg</th>
<th>150 mg</th>
<th>200 mg</th>
<th>250 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prados et al.</td>
<td>0 (3)</td>
<td>1 (3)</td>
<td>0 (3)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Raizer et al.</td>
<td>-</td>
<td>11 (99)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thepot et al.</td>
<td>0 (5)</td>
<td>3 (25)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Calvo et al.</td>
<td>-</td>
<td>1 (25)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Van den Bent et al.</td>
<td>-</td>
<td>-</td>
<td>6 (54)</td>
<td>-</td>
</tr>
<tr>
<td>Sheikh et al</td>
<td>-</td>
<td>167 (307)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Essai ROCHE</td>
<td>-</td>
<td>11 (59)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Adult doses (mg)  

<table>
<thead>
<tr>
<th>Adult doses (mg)</th>
<th>100 mg</th>
<th>150 mg</th>
<th>200 mg</th>
<th>250 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of toxicity (\gamma^{(2)})</td>
<td>0.07</td>
<td>0.19</td>
<td>0.34</td>
<td>0.49</td>
</tr>
</tbody>
</table>

1 Thomas, F. et al., Eur J Cancer 45 (2009), 2316–23
Under Bayesian inference: How to incorporate information into the dose-finding model parameters prior?

Available data: Early phase trials toxicity observations in adults

Toxicity: Efficacy:

\[
R(d_k) = P(Y = 1|d_k) \quad Q(d_k) = P(Z = 1|Y = 0, d_k)
\]

\[
R(d_k) = \psi(d_k, a) \quad Q(d_k) = \phi(d_k, b)
\]

Construction of the prior distribution:

- In terms of the effective sample size\(^1\). More informative a prior is, more patients are needed to compensate for it.

- If the chosen prior is too informative or misspecified → introducing the concept of ‘adaptive-prior’\(^2\) (switch during the trial to a less informative prior)

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\(^2\) Morita, S., Thall, P., and Müller, P., Biometrics 64 (June 2008), 595–602.
How to optimize the sampling time?

- Available data: PK measures in adults
- Pediatrics PK sampling can be associated with some constraints

Using model and simulation approach for optimization according to each pediatric sub group of age.
Conclusions and discussion

• Several tools and methods have been proposed for extrapolation in early phase dose-finding trials.
• From our simulation study the methods seems robust.
• More extrapolation should be used when planning clinical trials in pediatrics.
References


- R package « dfped » should be released end of April 2017
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