Using historical data to inform extrapolation decisions in children

Ian Wadsworth\textsuperscript{1}, Lisa Hampson\textsuperscript{1}, Thomas Jaki\textsuperscript{1}, Graeme Sills\textsuperscript{2}, Tony Marson\textsuperscript{2}, Richard Appleton\textsuperscript{3}

\textsuperscript{1} Lancaster University, UK
\textsuperscript{2} University of Liverpool, UK,
\textsuperscript{3} Alder Hey Children’s Hospital, UK

PSI Extrapolation Meeting
22nd November 2017
We are grateful to acknowledge funding from the UK Medical Research Council (Grant number: MR/M013510/1).
European Medicines Agency defines extrapolation as

‘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) . . . ’

Strong assumptions are needed for extrapolations to be biologically plausible.
FDA paediatric decision tree

Source data can augment data from the target population or entirely substitute for it. Uncertainty determines whether extrapolations are ‘partial’ or ‘complete’.

Reasonable to assume that children and adults have
• similar disease progression?
• similar response to intervention?

No to either

Is there a PD measurement that can be used to predict efficacy in children?

No

Conduct PK studies to establish dosing, then safety and efficacy trials in children (A)

Yes

Conduct PK studies in children to achieve drug levels similar to adults
Conduct safety trials at proper dose (C)

Yes to both

Reasonable to assume similar exposure-response (ER) in children and adults?

No

Conduct PK/PD studies to establish ER in children for PD measurement
Conduct PK studies to achieve target concentrations based on ER
Conduct safety studies at proper dose (B)

Yes
FDA paediatric decision tree

Source data can augment data from the target population or entirely substitute for it. Uncertainty determines whether extrapolations are ‘partial’ or ‘complete’.

Reasonable to assume that children and adults have
• similar disease progression?
• similar response to intervention?

No to either

Is there a PD measurement that can be used to predict efficacy in children?

No

Conduct PK studies to establish dosing, then safety and efficacy trials in children

Yes

Conduct PK studies in children to achieve drug levels similar to adults
Conduct safety trials at proper dose (C)

Yes to both

Reasonable to assume similar exposure-response (ER) in children and adults?

No

Yes

Conduct PK/PD studies to establish ER in children for PD measurement
Conduct PK studies to achieve target concentrations based on ER
Conduct safety studies at proper dose (B)

Wadsworth, Hampson, Jaki, Sills, Marson, Appleton
Using historical data for extrapolation
**Aims**

**Existing data:** PK-PD data from \( \geq 1 \) study recruiting adults and adolescents.

**Assumption:** PK-PD relationships in adults and younger children are similar.

**Q:** How can we use the existing data to quantify our uncertainty about the extrapolation assumption and inform our choice of extrapolation strategy in younger children?
Aims

Existing data: PK-PD data from ≥ 1 study recruiting adults and adolescents.
Assumption: PK-PD relationships in adults and younger children are similar.

Q: How can we use the existing data to quantify our uncertainty about the extrapolation assumption and inform our choice of extrapolation strategy in younger children?

1. Perform a meta-analysis of existing data.
2. Elicit opinion on whether differences between PK-PD relationships in adults and adolescents are representative of differences between adults and children.
3. Correct meta-analysis results for elicited biases.
4. Derive probability extrapolation assumption holds.
Model existing data from J studies of adults and adolescents:

\[
\mathbb{E}[y_{ij}] = \gamma_0 + \gamma_{Ej} E_{ij} + \gamma_{Aj} A_{ij} + \gamma_{Ij} E_{ij} A_{ij}
\]

- \( y_{ij} \) is outcome for \( i \)th patient in \( j \)th study
- \( A \) is age (0 for adults; 1 for adolescents).
PK-PD models

Model existing data from J studies of adults and adolescents:

\[ \mathbb{E}[y_{ij}] = \gamma_0^j + \gamma_E^j E_{ij} + \gamma_A^j A_{ij} + \gamma_I^j E_{ij} A_{ij} \]

- \( y_{ij} \) is outcome for \( i \)th patient in \( j \)th study
- \( A \) is age (0 for adults; 1 for adolescents).

Model data from future study enrolling adults and younger children:

\[ \mathbb{E}[y_{iT}] = \beta_0 + \beta_E^E E_{iT} + \beta_A^A A_{iT} + \beta_I^I E_{iT} A_{iT} \]

- \( A_{iT} \) is age (0 for adults; 1 for younger children)
- No difference between PK-PD relationships if \( \beta_A = \beta_I = 0 \)
- Use existing data to learn about \( \beta_A \) and \( \beta_I \).
Model existing data from jth completed study of adults and adolescents:

\[ y_{ij} = \gamma_0 + \gamma_{Ej}E_{ij} + \gamma_{Aj}A_{ij} + \gamma_{Ij}E_{ij}A_{ij} + \epsilon_{ij} \]

where \( \epsilon_{ij} \sim N(0, \sigma^2) \).
Model existing data from jth completed study of adults and adolescents:

\[ y_{ij} = \gamma_{0j} + \gamma_{Ej} E_{ij} + \gamma_{Aj} A_{ij} + \gamma_{Ij} E_{ij} A_{ij} + \epsilon_{ij} \]

where \( \epsilon_{ij} \sim N(0, \sigma^2) \).

At the second level of the meta-analytic model:

\[ \gamma_{Aj} \sim N(\gamma_A, \xi_1^2) \quad \text{and} \quad \gamma_{Ij} \mid \gamma_{Aj} \sim N(\lambda_0 + \lambda_1 (\gamma_A - \bar{\gamma}_{Aj}), \xi_2^2) \]

where \( \bar{\gamma}_{Aj} = (1/J) \sum \gamma_{Aj} \), implying a joint bivariate Normal distribution for \( \gamma_{Aj} \) and \( \gamma_{Ij} \).
Fitting the meta-analytic model using MCMC
Turner et al. (2009)

**Bias parameters:** Relate population means in source and target populations as:

\[ \beta_A = \gamma_A + \delta_A \quad \text{and} \quad \beta_I = \gamma_I + \delta_I. \]
Fitting the meta-analytic model using MCMC
Turner et al. (2009)

Bias parameters: Relate population means in source and target populations as:

$$\beta_A = \gamma_A + \delta_A$$  and  
$$\beta_I = \gamma_I + \delta_I.$$

Bias priors: We model expert opinion as $\delta \sim N_2(\mu_\delta, \Sigma_\delta)$.
Fitting the meta-analytic model using MCMC
Turner et al. (2009)

Bias parameters: Relate population means in source and target populations as:

\[ \beta_A = \gamma_A + \delta_A \quad \text{and} \quad \beta_I = \gamma_I + \delta_I. \]

Bias priors: We model expert opinion as \( \delta \sim N_2(\mu_{\delta}, \Sigma_{\delta}) \).

Fit model using MCMC and approximate joint posterior distribution for \((\gamma_0, \gamma_E, \gamma_A, \gamma_I)\).

Generate samples for \((\beta_A, \beta_I)\) by simulating values of \((\delta_A, \delta_I)\) and \((\gamma_A, \gamma_I)\).
Fitting the meta-analytic model using MCMC
Turner et al. (2009)

**Bias parameters:** Relate population means in source and target populations as:

\[
\begin{align*}
\beta_A &= \gamma_A + \delta_A \\
\beta_I &= \gamma_I + \delta_I.
\end{align*}
\]

**Bias priors:** We model expert opinion as \( \delta \sim N_2(\mu_\delta, \Sigma_\delta). \)

Fit model using MCMC and approximate joint posterior distribution for \((\gamma_0, \gamma_E, \gamma_A, \gamma_I)\).

Generate samples for \((\beta_A, \beta_I)\) by simulating values of \((\delta_A, \delta_I)\) and \((\gamma_A, \gamma_I)\).

**Prior confidence in extrapolation assumption is**

\[
P\{-\epsilon \leq S[f(Y_{0,A})] - S[f(Y_{0,C})] \leq \epsilon, \ -\epsilon \leq S[f(Y_{90,A})] - S[f(Y_{90,C})] \leq \epsilon\}
\]

where \( S \) is a chosen summary measure, and \( f(Y_{0,Age}) \) and \( f(Y_{90,Age}) \) are functions of the response for adults (Age = A) or younger children (Age = C) on placebo and \( EC_{90} \).
Extrapolation from adults to children with partial onset seizures (POS) is accepted:

- Quantitative not qualitative differences between effects in adults and children;
- Some disagreement where boundary of certainty lies (2 years vs 4 years).

Commonly used endpoints and models:

- **Pharmacokinetics (PK):** Average steady-state trough concentration \((C_{\text{min}})\).
- **Pharmacodynamics (PD):** Log of transformed percent change in seizure frequency from baseline, normally distributed.
- **PK-PD model:** Linear model
Eliciting opinion on biases

PK-PD relationship in younger children:

\[ y_{iT} = \beta_0 + \beta_E C_{\text{min, } iT} + (\gamma_A + \delta_A) + (\gamma_I + \delta_I) C_{\text{min, } iT} \]

Difficult to elicit opinion on biases directly. Instead condition on the observed historical data and for placebo, a moderate dose and a high dose, ask for:
Eliciting opinion on biases

PK-PD relationship in younger children:

\[ y_{iT} = \beta_0 + \beta_E C_{\text{min},iT} + (\gamma_A + \delta_A) + (\gamma_I + \delta_I) C_{\text{min},iT} \]

Difficult to elicit opinion on biases directly. Instead condition on the observed historical data and for placebo, a moderate dose and a high dose, ask for:

1. The most likely response \textit{on average} for younger children.
Eliciting opinion on biases

PK-PD relationship in younger children:

\[ y_{iT} = \beta_0 + \beta_E C_{\text{min},iT} + \left( \gamma_A + \delta_A \right) + \left( \gamma_I + \delta_I \right) C_{\text{min},iT} \]

Difficult to elicit opinion on biases directly. Instead condition on the observed historical data and for placebo, a moderate dose and a high dose, ask for:

1. The most likely response \textit{on average} for younger children.
2. A 90\% credibility interval around the average response line.
Eliciting opinion on biases

PK-PD relationship in younger children:

\[ y_{iT} = \beta_0 + \beta_E C_{\text{min},iT} + (\gamma_A + \delta_A) + (\gamma_I + \delta_I) C_{\text{min},iT} \]

Difficult to elicit opinion on biases directly. Instead condition on the observed historical data and for placebo, a moderate dose and a high dose, ask for:

1. The most likely response on average for younger children.
2. A 90% credibility interval around the average response line.
Eliciting opinion on biases

PK-PD relationship in younger children:

\[ y_{iT} = \beta_0 + \beta_E C_{\text{min},iT} + (\gamma_A + \delta_A) + (\gamma_I + \delta_I) C_{\text{min},iT} \]

Difficult to elicit opinion on biases directly. Instead condition on the observed historical data and for placebo, a moderate dose and a high dose, ask for:

1. The most likely response on average for younger children.
2. A 90% credibility interval around the average response line.
Eliciting opinion on biases

PK-PD relationship in younger children:

\[ y_{iT} = \beta_0 + \beta_E C_{\text{min},iT} + \left( \gamma_A + \delta_A \right) + \left( \gamma_I + \delta_I \right) C_{\text{min},iT} \]

Difficult to elicit opinion on biases directly. Instead condition on the observed historical data and for placebo, a moderate dose and a high dose, ask for:

1. The most likely response on average for younger children.
2. A 90% credibility interval around the average response line.
3. Distribution for the average response, using histogram.
Clinicians think in terms of dose-response relationship. Assume exposure is directly proportional to dose.

Search to find the prior for \((\delta_A, \delta_I)\) which best captures the expert’s answers.
Simulation study

Simulate data from $n_H$ PK-PD studies in epilepsy recruiting adults and adolescents:

- **Outcome:** $Y = \log \left\{ 100(S - B)/B + 110 \right\}$ (transformed % change from baseline);
- **Exposures:** $\log(C_{\min}) \sim \text{Normal}(\log(2.94), 0.921)$ truncated at $\log(17.27)$;
- **Number of patients per trial:** 30, 170;
- **Proportion of adolescents:** 15%.

**Decision criterion for extrapolation:**

$$P\{ -10 \leq \mathcal{M}[\exp(Y_{0,A}) - 110] - \mathcal{M}[\exp(Y_{0,C}) - 110] \leq 10, $$

$$-10 \leq \mathcal{M}[\exp(Y_{90,A}) - 110] - \mathcal{M}[\exp(Y_{90,C}) - 110] \leq 10 \}$$

where $\mathcal{M}$ is the median.
Existing data: PK-PD relationships in adults and adolescents

**Adult PK-PD:** \( y_{ij} = 4.45 - 0.06 C_{\text{min},ij} + \epsilon_{ij} \)

- **Scenario 1:** E-R relationships in adolescents identical to adults
- **Scenario 2:** Lower response rate on placebo in adolescents; worse effect of exposure on response (just satisfies extrapolation criterion)
- **Scenario 3:** Lower response rate on placebo in adolescents; much worse effect of exposure on response (clearly do not satisfy extrapolation criterion)
For each scenario and variation considered we have simulated 1000 sets of existing studies, fitted the meta-analytic model and approximated the joint posterior distribution for \((\gamma_0, \gamma_E, \gamma_A, \gamma_I)\).

Next relate population means in existing studies and to future study using additive biases:

\[
\beta_A = \gamma_A + \delta_A \quad \text{and} \\
\beta_I = \gamma_I + \delta_I.
\]
Relating existing data to target question

Bias prior:

\[
\begin{pmatrix}
\delta_A \\
\delta_I
\end{pmatrix} \sim N \left( \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 0.1^2 & 0.00004 \\ 0.00004 & 0.016^2 \end{pmatrix} \right)
\]

Figures show the PK-PD relationship for younger children:
Relating existing data to target question

Bias prior:

\[
\begin{pmatrix}
\delta_A \\
\delta_I
\end{pmatrix} \sim N\left( \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 0.1^2 & 0.00004 \\ 0.00004 & 0.016^2 \end{pmatrix} \right)
\]

Figures show the PK-PD relationship for younger children:
Relating existing data to target question

Bias prior:

\[
\begin{pmatrix}
\delta_A \\
\delta_I
\end{pmatrix} \sim N \left( \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 0.1^2 & 0.00004 \\ 0.00004 & 0.016^2 \end{pmatrix} \right)
\]

Figures show the PK-PD relationship for younger children:
Results: Probability of the extrapolation assumption holding

(e) Scenario 1: Adult and adolescent PK-PD curves identical
Results: Effective sample size of the joint posterior of $(\beta_A, \beta_I)$

(f) Scenario 1: Adult and adolescent PK-PD curves identical
Results: Probability of the extrapolation assumption holding

(g) Scenario 2: Adult and adolescent PK-PD curves different
Results: Probability of the extrapolation assumption holding

<table>
<thead>
<tr>
<th>Number of historical studies</th>
<th>Probability similar PK−PD curves for adults &amp; younger children</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.00</td>
</tr>
<tr>
<td>3</td>
<td>0.05</td>
</tr>
<tr>
<td>4</td>
<td>0.10</td>
</tr>
<tr>
<td>5</td>
<td>0.15</td>
</tr>
<tr>
<td>10</td>
<td>0.20</td>
</tr>
<tr>
<td>20</td>
<td>0.25</td>
</tr>
</tbody>
</table>

- **Very high heterogeneity**
- **Low heterogeneity**

(h) Scenario 3: Adult and adolescent PK-PD curves very different
Conclusions

- Developed quantitative approach to using existing data to support extrapolation decisions.
- Prior elicitation Shiny app trialled at epilepsy conference with expert clinicians.
- Even in scenario where adults, adolescents and younger children identical on average, largest probability of extrapolation only 0.57 - Strong influence of expert uncertainty.
- Prior probability of an extrapolation assumption can be feed into Bayesian decision theoretic approach to determine whether additional data needed to verify assumption.


Morita S, Thal PF, Müller P. Determining the effective sample size of a parametric prior. *Biometrics* 2008: 64:595.

