American Course on Drug Development and Regulatory Sciences

Pediatric Drug Development Workshop
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University of California, San Francisco
Schools of Pharmacy and Medicine
Department of Bioengineering and Therapeutic Sciences

Statistical Implications of Extrapolation on the Design and Analysis of Pediatric Clinical Trials
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Advanced Analytics, Eli Lilly & Co
Disclosures

• Employed at Eli Lilly & Co.
• Lilly Pediatric Steering Committee for some introductory slides and helpful comments
Key Take-aways

Extrapolation

- is triggered when the lead indication has a pediatric disease state that is similar in progression of disease and treatment response
- can minimize the requirements and accelerate timeline of the pediatric program
- requires designing adult program with some similarity in endpoints to pediatric program
Agenda

- Extrapolation
- Statistical implications of extrapolation
  - Bayesian Approach in partial extrapolation
  - Alternative designs for partial/no extrapolation
- Summary
Need to minimize number of subjects enrolled in pediatric clinical trials and the need to maximize the usefulness of the data obtained, while ensuring that the trials are **feasible**, **robust**, and **interpretable**. – Dunne et al. (2011)
Pediatric Drug Development current regulatory landscape

Obligation, Incentive, & Extrapolation
Extrapolation

Extending information and conclusions available from studies in one or more subgroups of patient population (source population) or in related conditions or with related medicinal products, to make inferences for another subgroup of the population (target population) or condition or product, thus minimizing the need to generate additional information (types of studies, number of patients required) to reach conclusions for the target population.

Source Population
Efficacy Conclusion

Target Population
Efficacy Conclusion

Similarity in Response to Therapy

Similarity in Disease Progression
Data Sources for Extrapolation

**Sufficient quality data on:**

- Adult indication for (similar) pediatric indication
- Other pediatric age groups
- Related pediatric indications
- External data
- Preclinical efficacy
- Formulations of same active ingredient
# FDA/CDER Decision Tree

<table>
<thead>
<tr>
<th></th>
<th>Full Extrapolation</th>
<th>Partial Extrapolation</th>
<th>No extrapolation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Similar progression of disease</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Similar response to treatment</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Similar exposure-response</td>
<td>Yes</td>
<td>Uncertain</td>
<td>No</td>
</tr>
<tr>
<td>Concentration predictive of response</td>
<td>Yes</td>
<td>Uncertain</td>
<td>No</td>
</tr>
<tr>
<td>Clinical Development</td>
<td>Supportive data</td>
<td>Optimized programme</td>
<td>Full programme</td>
</tr>
</tbody>
</table>
Agenda

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Current practice

- Uncontrolled; open-label
- Controlled; arbitrary sample size
- Non-inferiority trials
- Studies powered on surrogate endpoint
- Modeling
**Example 1: balsalazide**

**Mild to Moderate Ulcerative Colitis**

<table>
<thead>
<tr>
<th>Adults ≥18 y</th>
<th>Children 5-17 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>- R, DB, PG (2 doses: 2.25 g/day and 6.75 g/day; Azacol) in 154 patients (50, 53, 51)</td>
<td></td>
</tr>
<tr>
<td>- Improvement in stool blood, stool frequency, sigmoidoscopy at week 8</td>
<td></td>
</tr>
</tbody>
</table>

| R, DB, PG (2 doses: 2.25 g/day and 6.75 g/day) in 68 patients |
| Modified Sutherland UC Activity Index (MUCAI) at week 8 |

**Statistical reviewer notes:** Sample size based on feasibility rather than statistical power
Example 1: balsalazide

Clinical reviewer notes: “…the clinical response rate for the primary endpoint in children thus seems to correlate reasonably well with the response rate seen in adults (where the primary endpoint was reduction of rectal bleeding and improvement of at least one other assessed symptom) and would indicate that Colazal is similarly effective in improving symptoms in children and in adults.”

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>2.25 g/day</th>
<th>6.75 g/day</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult (improvement in)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stool blood</td>
<td>35%</td>
<td>55%</td>
<td>0.045</td>
</tr>
<tr>
<td>Stool frequency</td>
<td>25%</td>
<td>49%</td>
<td>0.013</td>
</tr>
<tr>
<td>Sigmoidoscopy</td>
<td>52%</td>
<td>74%</td>
<td>0.031</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUCAI decrease ≥ 3</td>
<td>37%</td>
<td>45%</td>
<td>0.623</td>
</tr>
</tbody>
</table>

Adapted from FDA Clinical review
Example 2: infliximab

Moderate to Severe Ulcerative Colitis

<table>
<thead>
<tr>
<th>Adults $\geq 18$ y</th>
<th>Children 6-17 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ R, DB, PG (2 dose regimens; placebo)</td>
<td>▪ OL induction phase; R maintenance phase (2 dose regimens)</td>
</tr>
<tr>
<td>▪ Mayo score at week 8</td>
<td>▪ Mayo Score and PUCUI at week 8</td>
</tr>
</tbody>
</table>
Example 2: infliximab

<table>
<thead>
<tr>
<th></th>
<th>ACT 1</th>
<th>ACT 2</th>
<th>T72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endpoint</td>
<td>N = 121</td>
<td>N = 121</td>
<td>N = 60</td>
</tr>
<tr>
<td>Clinical response</td>
<td>84 (69.4%)</td>
<td>78 (64.5%)</td>
<td>44 (73.3%)</td>
</tr>
<tr>
<td>Clinical remission</td>
<td>47 (38.8%)</td>
<td>41 (33.9%)</td>
<td>24 (40.0%)</td>
</tr>
<tr>
<td>Mucosal healing</td>
<td>75 (62.0%)</td>
<td>73 (60.3%)</td>
<td>41 (68.3%)</td>
</tr>
</tbody>
</table>

Summary level data obtained from Rutgeerts et al, 2005\(^9\), and Hyams, et al., 2012\(^{10}\). Placebo response not shown.
Example 2: infliximab

Step 1: Assume combined placebo response in adults is the same as placebo response in pediatrics.
Step 2: Check pediatric clinical response within reasonable range of adult response.
Step 3: Compare confidence interval limits.
Statistical Considerations

Extrapolation requires...

- Quality data

- Some similarity in endpoint or design
  - Some common endpoint
  - Modeling to account for difference
  - Consistency of effect in source-target population

How is extrapolation of information and conclusion from adults to pediatrics structurally done?
“Bayesian” extrapolation

Design Trial

- Specify a prior using adult data: \( q_S(\theta_E) \propto L(\theta_E | Source\ Data)\pi(\theta_E) \)
- Conduct pediatric trial + compute likelihood: \( L(\theta_E | target\ Data) \)
- Apply Bayes theorem (likelihood + prior) to estimate of pediatric response 
  \( q_{T,S}(\theta_E) \propto L(\theta_E | Target\ Data)q(\theta_E) \)
Example 2: infliximab

**“Cursory”**

\[ q_S(\theta_P) \propto L(\theta_P | Source \ Data)\pi(\theta_P) \]

**Bayesian**

\[ \theta_P^* \sim q_S(\theta_P) \]

\[ r_P^* \sim Bin(\theta_P^*, n_T), U^* \text{ is 95\% CI of } \theta \]

based on the sample, \( \tau = E(U^*) \)

Bayesian extrapolation can be more conservative!
Bayesian approach formalizes what pediatricians do when they combine the results from large adult trials with the results of smaller pediatric trials to make treatment decisions.”

- Schoenfeld et al. 2009
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US Regulations: 21 CFR50, subpart D

Risk Pathways:

§ 50.51 “Clinical investigations not involving greater than minimal risk”

§ 50.52 “Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects”

§ 50.53 “Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition. The risk represents a minor increase over minimal risk”

Applied via component analysis
Hypothesis: $H_0: \theta \leq \theta_0$ vs $H_1: \theta > \theta_0$

- $\theta_0$ is the upper bound of adult placebo response; Historical Evidence of Sensitivity to Drug Effects (HESDE)

- Useful if large effects of treatment are seen in early clinical studies

- Where to get $\theta_0$?
  - Upper bound of placebo response confidence interval in adults
  - Upper bound of credible interval derived from the **predictive distribution of placebo response** from a sample of comparable size as the number of children given the treatment
  - Estimate of **placebo response via counterfactuals** from quality registry data
Single-Arm Trials

- Indirect comparison with adult placebo may be inadequate if there are changes over time in supportive care/quality of diagnostic staging techniques.

- Potential solutions:
  - Pediatric trial needs to be concurrent to the adult trial.
  - Use predictive distribution of placebo instead of confidence interval.

<table>
<thead>
<tr>
<th>Mean Resp*</th>
<th>Unconditional Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=60</td>
<td>N=80</td>
</tr>
<tr>
<td></td>
<td>Carry-over placebo</td>
</tr>
<tr>
<td></td>
<td>Carry-over placebo</td>
</tr>
<tr>
<td></td>
<td>Carry-over placebo</td>
</tr>
<tr>
<td>0.70</td>
<td>0.973</td>
</tr>
<tr>
<td>0.60</td>
<td>0.706</td>
</tr>
<tr>
<td>0.50</td>
<td>0.215</td>
</tr>
<tr>
<td>0.40</td>
<td>0.018</td>
</tr>
<tr>
<td>0.33</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Placebo response is 33%; adult sample size is 225 with 2:1 randomization; adult response = pbo response - 0.10.
Single-Arm Trials

$\theta_0$ determined through counterfactuals

“Threshold-crossing”: A Useful Way to Establish the Counterfactual in Clinical Trials?

H-G Eichler$^1$, B Bloechl-Daum$^2$, P Bauer$^3$, F Bretz$^4$, J Brown$^5$, LV Hampson$^6$, P Honig$^7$, M Krams$^8$, H Leufkens$^9$, R Lim$^{10}$, MM Lumpkin$^{11}$, MJ Murphy$^{12}$, F Pignatti$^1$, M Posch$^3$, S Schneeweiss$^{13}$, M Trusheim$^{14}$ and F Koenig$^3$

A central question in the assessment of benefit/harm of new treatments is: how does the average outcome on the new treatment (the factual) compare to the average outcome had patients received no treatment or a different treatment known to be effective (the counterfactual)? Randomized controlled trials (RCTs) are the standard for comparing the factual with the counterfactual. Recent developments necessitate and enable a new way of determining the counterfactual for some new medicines. For select situations, we propose a new framework for evidence generation, which we call “threshold-crossing.” This framework leverages the wealth of information that is becoming available from completed RCTs and from real world data sources. Relying on formalized procedures, information gleaned from these data is used to estimate the counterfactual, enabling efficacy assessment of new drugs. We propose future (research) activities to enable “threshold-crossing” for carefully selected products and indications in which RCTs are not feasible.
Registries may be established to evaluate the natural history of a disease, meaning its characteristics, management, and outcomes with and/or without treatment.

**Possible testing strategy:**
1. Estimate $\theta_0$ from matched pbo patients, then compare whether $\theta > \theta_0$
2. Determine whether average treatment effect (ATE) > 0.
Single-Arm Trials

- Matching observations are not selected on the basis of their response but on the basis of a preselected set of baseline covariates.
- May require restricting search to contemporaneous registry data.
- Requires that the registry and the treated children have similar collected measurements (endpoint and baseline).
Indication: improved survival and invasive ventilator-free survival with infantile-onset Pompe disease

Study 1602:
- 18 ptx [1.2mo – 7.3mo] randomized to 2 doses of Myozyme
- Comparator: 62 untreated ptx serving as historical control;

Historical control group has clinical status similar to entry criteria of the Study; included all subjects who died within the first few months of life

Statistician noted: “The use of matched control...would have permitted a more appropriate statistical analysis.”
- Applicants analyses compared proportion of survivors/survival rates by age
Explore ways to exploit extrapolation in pediatric drug development.

Plan ahead and strategically –
- If extrapolation is used, ensure adult clinical trial efficacy outcomes can be supportive of pediatric efficacy outcomes;
- Should I need a registry data; what measurements should my pediatric trial have

Push the boundaries of innovative/alternative design


Assess level of risk presented by each intervention or procedure in the proposed research

- **Minimal Risk 46.404/50.51**
- **More than Minimal Risk**

**Approve, Disapprove, or Consider 46.407/50.54**

- Prospect of direct benefit with greater than minimal risk 46.405/50.52

(1) Risk justified by anticipated benefit to subjects? 46.405(a)/50.52(a); (2) Relation of anticipated benefit to risk at least as favorable to subjects as that presented by available alternative approaches. 46.405(b)/50.52(b)

**Approve, Disapprove, or Consider 46.407/50.54**

- Minor increase over minimal risk 46.406(a)/50.53(a)
- **Evaluate the possibility of direct benefit to the child from each procedure or intervention**

**Approve, Disapprove, or Consider 46.407/50.54**

- No prospect of direct benefit 46.406/50.53
- **Elevated level of risk**

- **Greater than minor increase over minimal risk 46.407(a)/50.54(a)**

- Knowledge to ameliorate disorder or condition 46.406(c)/50.53(a)
- No knowledge to ameliorate disorder or condition 46.406(c)/50.53(c)

**Approve, Disapprove, or Consider 46.407/50.54**

- Experiences reasonably commensurate 46.406(b)/50.53(b)
- Experiences not reasonably commensurate 46.406(b)/50.53(b)

**Approve, Disapprove, or Consider 46.407/50.54**

- Yield vitally important generalizable knowledge 46.406(c)/50.53(c)
- Does not yield vitally important, generalizable knowledge 46.406(c)/50.53(c)

**Approve**

**Disapprove, or Consider 46.407/50.54**

- Reasonable opportunity for generalizable knowledge, and in accord with sound ethical principles 46.407(a)/50.54(a)
- Not a reasonable opportunity for generalizable knowledge, or violates sound ethical principles 46.407(a)/50.54(a)

**Disapprove**