Bayesian Applications for Extrapolation from Adult to Pediatric Data

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Outline

• Concept of (Pediatric) Extrapolation
• Recent Regulatory Guidelines
• Statistical Extrapolation – Bayesian Methods
• Case Study - Cinacalcet
• A Novel Approach to Use PK/PD Data to Inform Amount of Borrowing for Clinical Data
• Closing Remarks
Concept of Pediatric Extrapolation

• **What is extrapolation?**
  • Extending information and conclusions available from studies in one or more subgroups of the 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 reducing the need to generate additional information (types of studies, design modifications, number of patient required) to reach conclusions for the target population, or condition or medicinal product.

• **What is pediatric extrapolation?**
  • Extending information and conclusions from studies in adult populations (or other pediatric age groups) to pediatric populations.
Rationales for Pediatric Extrapolation and Types

• Rationale
  • Goal to minimize exposure of children to clinical trials
  • Limited size of pediatric populations
  • Increased efficiency of pediatric drug development programs

• Types
  • Full extrapolation
  • Partial extrapolation
  • No extrapolation
Recent Related Regulatory Guidelines

- **ICH. E11(R1):** Addendum: Guideline on Clinical Investigation of Medicinal Products in the Pediatric Population. April 2018
- **FDA.** Guidance for Industry: Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices. June 2016
- **FDA.** Guidance for Industry (Draft): General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products. December 2014
- **EMA.** Reflection Paper on Extrapolation of Efficacy and Safety in Pediatric Medicine Development, October 2018
Pediatric Study Planning and Extrapolation Algorithm

Is it reasonable to assume that children, when compared to adults, have a similar: (1) disease progression and (2) response to intervention?

- No to either
- Yes to both

Is it reasonable to assume similar exposure-response in pediatrics and adults?

- No
- Yes

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

- No
- Yes

Conduct:
- Partial extrapolation

"Full extrapolation" if

Is the drug (or active metabolite) concentration measurable\(^{10}\) and predictive of clinical response?

- No
- Yes

Conduct:
- (1) Adequate PK study to select dose(s) to achieve similar exposure as adults\(^{11}\)
- (2) Safety trials\(^{7}\) at the identified dose(s).

"No extrapolation" if

Conduct:
- (1) Adequate dose-ranging studies in children to establish dosing\(^{12}\)
- (2) Safety\(^{4}\) and efficacy\(^{5}\) trials at the identified dose(s) in children.
Bayesian Methods for Pediatric Extrapolation

• Bayesian methods are a natural choice for quantitatively extrapolating information from source to target population in a partial extrapolation setting (ICH, 2018; US FDA, 2016; EMA 2018)

• Some commonly used Bayesian methods
  • Bayesian hierarchical modeling (Carlin and Louis, 2008; FDA/CDRH/CBER, 2016)
    • Use the posterior from source as the prior for target population
  • Power prior (Ibrahim and Chen, 2000)
  • Commensurate prior (Hobbs et al, 2011)

• Bayesian mixture prior (Ye and Travis, 2007; review for belimumab, 2018)
Statistical modeling for Bayesian extrapolation of adult clinical trial information in pediatric drug evaluation

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H. Amy Xia10,  Karen Price1,  Ram Tiwari11,  Bradley P. Carlin12

Children represent a large underserved population of “therapeutic orphans,” as an estimated 80% of children are treated off-label. However, pediatric drug development often faces substantial challenges, including economic, logistical, technical, and ethical barriers, among others. Among many efforts trying to remove these barriers, increased recent attention has been paid to extrapolation; that is, the leveraging of available data from adults or older age groups to draw conclusions for the pediatric population. The Bayesian statistical paradigm is natural in this setting, as it permits the combining (or “borrowing”) of information across disparate sources, such as the adult and pediatric data. In this paper, authored by the pediatric subteam of the Drug Information Association Bayesian Scientific Working Group and Adaptive Design Working Group, we develop, illustrate, and provide suggestions on Bayesian statistical methods that could be used to design improved pediatric development programs that use all available information in the most efficient manner. A variety of relevant Bayesian approaches are described, several of which are illustrated through 2 case studies: extrapolating adult efficacy data to expand the labeling for Remicade to include pediatric ulcerative colitis and extrapolating adult exposure-response information for antiepileptic drugs to pediatrics.

Key words
comensurate prior, exchangeability, extrapolation, effective sample size, hierarchical model, model fit, power prior
Case Study: Cinacalcet Bayesian Extrapolation Analysis

- Cinacalcet is a calcimimetic agent which acts as an allosteric modulator of the calcium-sensing receptor (CaR) and regulates iPTH (intact parathyroid hormone) secretion by amplifying the sensitivity of the receptor to extracellular calcium, thereby reducing iPTH secretion.

- Cinacalcet is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease receiving dialysis.

http://www.sensiparhcp.com/secondary-hpt-therapies/#
Rationale for the Pediatric Extrapolation Strategy

• Pediatric and orphan indication
  • Point prevalence estimates using USRDS and DaVita databases for 2015 indicate that < 1000 patients 0 to < 18 years of age on dialysis will develop secondary HPT
    • Of these, approximately 300 patients are estimated to be 0 to 5 years of age, 220 aged 6 to 12 years and approximately 430 aged 13 to < 18 years.
  • The feasibility of conducting large studies in the target population was restricted

• The adult and pediatric populations are similar in the following aspects according to ICH E11 (ICH, 2000) and EMA reflection paper (2018)
  • Pediatric population in which cinacalcet has been studied is similar to the approved population in adults (i.e., patients with secondary HPT treated with dialysis)
  • The pathophysiology and course of the disease process (secondary HPT) is similar in adult and pediatric populations with CKD receiving dialysis
  • The outcome of therapy is likely to be comparable
  • The pharmacokinetic (PK) of cinacalcet in children and adults are similar; the exposure-response trend is consistent in children and adults
Rationale for Using Bayesian Methods in This Quantitative, Partial Extrapolation Analysis

• Partial extrapolation allows for an extension of information from the source population to the target population and reduces the sample size
  • For age 6 – 17
    • A RCT study, but the sample size was small to have adequate power
    • Adult data were borrowed to estimate treatment effect
  • For age younger than 6
    • Younger age study focused on safety rather than efficacy
    • A single arm study - No control arm in younger age study, and relative treatment effect in younger age cannot be directly estimated
    • Efficacy should be extrapolated from information gathered from adults and older age peds populations per agreement with regulatory agencies

• Bayesian methods are a natural choice in a partial extrapolation setting
  • As supportive analyses, Bayesian hierarchical modeling was used as the primary statistical method, while other Bayesian methods were used as sensitivity analyses (power priors, use the posterior from source as the prior for target population)
Primary endpoint
The proportion of subjects achieving ≥ 30% reduction from baseline in mean iPTH during Efficacy Evaluation Period

Exchangeability assumption at three levels: population, study and subject
Exchangeable means there is nothing known a priori that would imply one (subject, study, or population) would be better or worse in the outcome of interest than another (US FDA, 2016).

Random effects at each level to account for variabilities

Effective sample size (ESS) measures how much information was borrowed
Restrictions applied such that ESS ≤ target sample size
## Data Included in the Pediatric Extrapolation Analysis

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Cinacalcet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>Response rate (95% CI)$^a$ (%)</td>
</tr>
<tr>
<td>Pediatric studies</td>
<td>4/21</td>
<td>19.1 (5.5, 41.9)</td>
</tr>
<tr>
<td>Study 20070208</td>
<td>4/21</td>
<td>19.1 (5.5, 41.9)</td>
</tr>
<tr>
<td>Study 20110100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>cohort 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All adult studies</td>
<td>47/471</td>
<td>10.0 (7.4, 13.1)</td>
</tr>
<tr>
<td>Study 20000172</td>
<td>21/205</td>
<td>10.2 (6.5, 15.2)</td>
</tr>
<tr>
<td>Study 20000183</td>
<td>17/165</td>
<td>10.3 (6.1, 16.0)</td>
</tr>
<tr>
<td>Study 20000188</td>
<td>9/101</td>
<td>8.9 (4.2, 16.2)</td>
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</tbody>
</table>
3-level Bayesian Hierarchical Model

• **Notations**
  - treatment group $c$
    - $c = 0$ for placebo
    - $c = 1$ for cinacalcet
  - patient population $p$
    - $p = 0$ for pediatric
    - $p = 1$ for adult
  - study $k$
    - when $p = 0$: $k = 1$ for Study 20070208; $k = 2$ for Study 20110100 cohort 1
    - when $p = 1$: $k = 1$ for adult Study 20000172; $k = 2$ for adult Study 20000183; $k = 3$ for adult Study 20000188
  - $n_{pkc}$ be the number of subjects for population $p$, study $k$ and treatment group $c$
  - $Y_{pkc}$ be the number of responders
  - $p_{pkc}$ be the proportion of responders (response rate)
3-level Bayesian Hierarchical Model

- **Level 1 – subject level**
  \[ Y_{p_{kc}} | p_{p_{kc}} \sim \text{Binomial}(n_{p_{kc}}, p_{p_{kc}}) \]

- **Level 2 – study level**
  - Study level random effects are introduced to account for the between-study variabilities:
    \[ \text{logit}(p_{p_{kc}}) = \beta_{pc} + \gamma_{p_{kc}} \]
    where
    \[ \beta_{pc} \text{ is the population effect,} \]
    \[ \gamma_{p_{kc}} \text{ is the study level random effect,} \]
    \[ \gamma_{p_{kc}} \sim N(0, \sigma_{pc}^2), \text{ where } \sigma_{pc}^2 \text{ accounts for the between-study variation} \]
Level 3 – population level

Pediatric and adult population parameters are assumed to be random samples from an overall patient population, that is:

$$\beta_{pc} = \beta_c + \mu_{pc}$$

where

- $\beta_c$ is the treatment effect such that $\text{expit}(\beta_c)$ is the overall response rate for treatment group $c$ across all age groups
- $\mu_{pc} \sim N(0, \sigma_c^2)$ captures the between-population variability
### 3-level Bayesian Hierarchical Model

<table>
<thead>
<tr>
<th></th>
<th>Placebo Median (95% CrI)</th>
<th>Cinacalcet Median (95% CrI)</th>
<th>Difference (Δ) Median (95% CrI)</th>
<th>Δ &gt; 0%</th>
<th>Δ &gt; 10%</th>
<th>Δ &gt; 20%</th>
<th>Δ &gt; 30%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No extrapolation, fit 208 and 100 data only</strong></td>
<td></td>
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</tr>
<tr>
<td>Overall Pediatric (28 days to &lt; 18 years) response rates (%)</td>
<td>21.5 (2.1, 86.6)</td>
<td>80.8 (27.4, 98.2)</td>
<td>53.2 (-19.9, 90)</td>
<td>92.4</td>
<td>87.9</td>
<td>81.9</td>
<td>74.2</td>
</tr>
<tr>
<td><strong>With extrapolation, fit adult and pediatric data together</strong></td>
<td></td>
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</tr>
<tr>
<td>Pediatric patients 28 days to &lt; 18 years response rates (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17.5 (2.6, 62)</td>
<td>69.3 (36.1, 90.2)</td>
<td>48.6 (-2.3, 79.7)</td>
<td>97.0</td>
<td>93.9</td>
<td>88.4</td>
<td>79.2</td>
</tr>
<tr>
<td>ESS/n_ped</td>
<td>21.0 / 21&lt;sup&gt;b&lt;/sup&gt;</td>
<td>25.1 / 29&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pediatric patients 28 days to &lt; 6 years response rates (%)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>18.0 (1.2, 78.7)</td>
<td>93.1 (66.4, 99.5)</td>
<td>71.8 (10.7, 95.1)</td>
<td>99.0</td>
<td>97.6</td>
<td>95.5</td>
<td>92.5</td>
</tr>
<tr>
<td>ESS/n_100</td>
<td>-&lt;sup&gt;e&lt;/sup&gt;</td>
<td>-0.6 / 7&lt;sup&gt;f&lt;/sup&gt;</td>
<td>-</td>
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</table>
Use of PK/PD Data to Inform Amount of Borrowing for Clinical Data

PK/PD Data Extrapolation Models for Improved Pediatric Efficacy and Toxicity Estimation, with Application to Secondary Hyperparathyroidism

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Summary

In most drug development settings, the regulatory approval process is accompanied by extensive studies performed to understand the drug’s pharmacokinetic (PK) and pharmacodynamic (PD) properties. In this paper, we attempt to utilize the rich PK/PD data to inform the borrowing of information from adults during pediatric drug development. In pediatric settings, it is especially crucial that we are parsimonious with the patients recruited for experimentation. We illustrate our approaches in the context of clinical trials of cinacalcet for treating secondary hyperparathyroidism (SHPT) in pediatric and adult patients with chronic kidney disease (CKD), where we model both parathyroid hormone (efficacy endpoint) and corrected calcium levels (safety endpoint). We use population PK/PD modeling of the cinacalcet data to quantitatively assess the similarity between adults and children, and use this information in various hierarchical Bayesian adult borrowing rules whose statistical properties can then be evaluated. In particular, we simulate the bias and mean square error performance of our approaches in settings where borrowing is and is not warranted to inform guidelines for the future use of our methods.
PK/PD Informed Borrowing

- PK and PD similarity between adults and pediatrics is a fundamental principle for extrapolation of data.
- Extensive studies were performed to understand the drug’s PK and PD properties.
- The rich PK/PD data can be utilized to quantify the degree of similarity between adult and children, which can further inform the borrowing of information from adults to pediatric population.
PKPD data from Adult studies & Pediatric studies

Population three-compartment PK model & semimechanistic PD model

Full model: Adult and children share different sets of parameters

Null model: Adult and children share same set of parameters

Compare goodness of fit by a likelihood ratio test: achieve p-value

Scaled p-value to serve as a sensible power in a power prior model

p-value can be mapped to an EHSS through a target function
Closing Remarks

• Approaches for pediatric drug development need to be efficient and flexible while maintaining valid and persuasive evidentiary standards

• Pediatric extrapolation requires a substantive combination of qualitative and quantitative evidence to support regulatory approval for new pediatric labeling

• Justifications for extrapolation need to be carefully examined
  • Collaborative work with PK/PD and Clinical teams

• The use of statistical extrapolation to support pediatric trials is an emerging tool

• Bayesian extrapolation helps with sample size limitations and missing control arms in pediatric setting

• Sensitivity analyses using different statistical methods are useful

• Further work on leveraging data from other sources (e.g. PK/PD) to inform borrowing will be helpful

• More experiences and case studies are needed in the future
References

- Basu C, Ma X, Mo M, Xia HA, Brundage R, Al-Kofahi M, Carlin BP. PK/PD and Clinical Adult Data Extrapolation Models for Improved Efficacy and Safety Estimation in Pediatric Hyperparathyroidism (submitted for peer review)
Thank you!
Back-up Slides
Effective Sample Size

- The information borrowed from the source population can be quantified using effective sample size (ESS) calculated based on variance reduction.
- ESS was selected using a grid search method following the FDA Guidance (US FDA, 2010) that the ESS could not exceed the observed sample size in the target population.
- The restriction was implemented to prevent the adult data from being too informative and dominate the limited pediatric data.
Example target function mapping p-value to EHSS

- $p$ is close to 1 → Willing to borrow nearly all of the adult data’s strength
- $p$ is close to 0 → Minimum borrowing from adult
- In our analysis, a power that results in an EHSS of roughly 50 adult patients were used.

$f(p) = \Psi \times p^\alpha$, $\Psi$ can be EHSS or ratio (EHSS/n)