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Bayesian Applications for Extrapolation from Adult to Pediatric Data

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(Joint Work with May Mo, Amgen)

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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

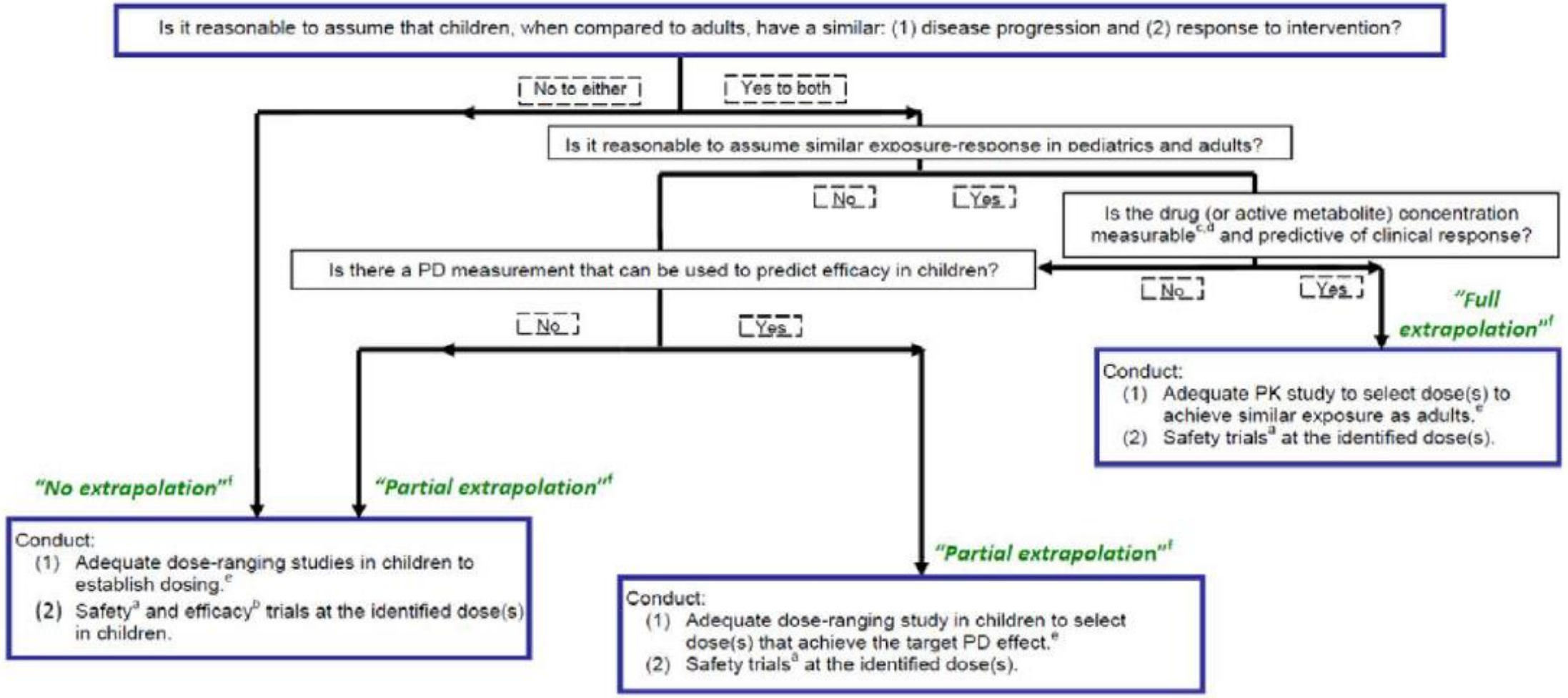
- **Rationale**
  - Goal to minimize exposure of children to clinical trials
  - Limited size of pediatric populations
  - Increased efficiency of pediatric drug development programs

- **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): Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans. March 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



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

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MAIN PAPER

WILEY

Statistical modeling for Bayesian extrapolation of adult clinical trial information in pediatric drug evaluation

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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.

KEYWORDS

commensurate prior, exchangeability, extrapolation, effective sample size, hierarchical model, model fit, power prior

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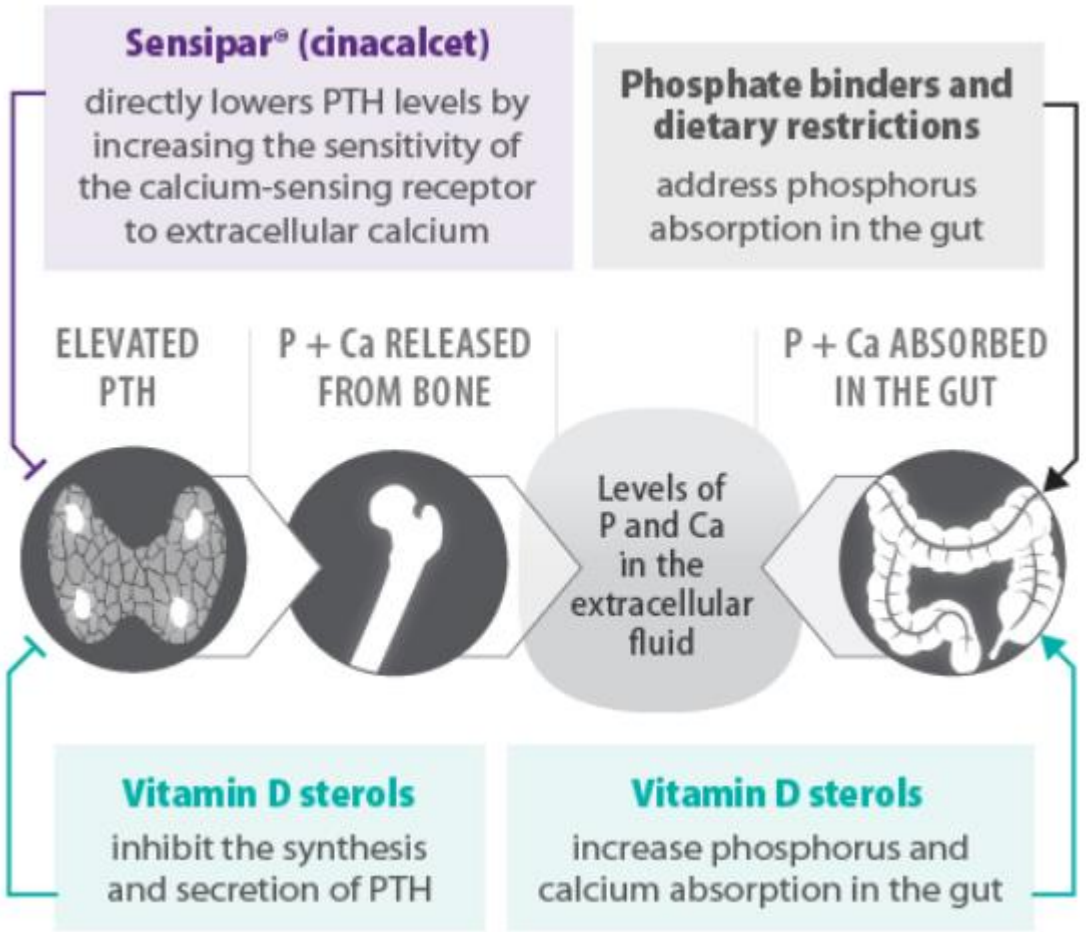
Case Study: Cinacalcet Bayesian Extrapolation Analysis



http://www.sensiparhcp.com/secondary-hpt-therapies/#

- 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.

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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

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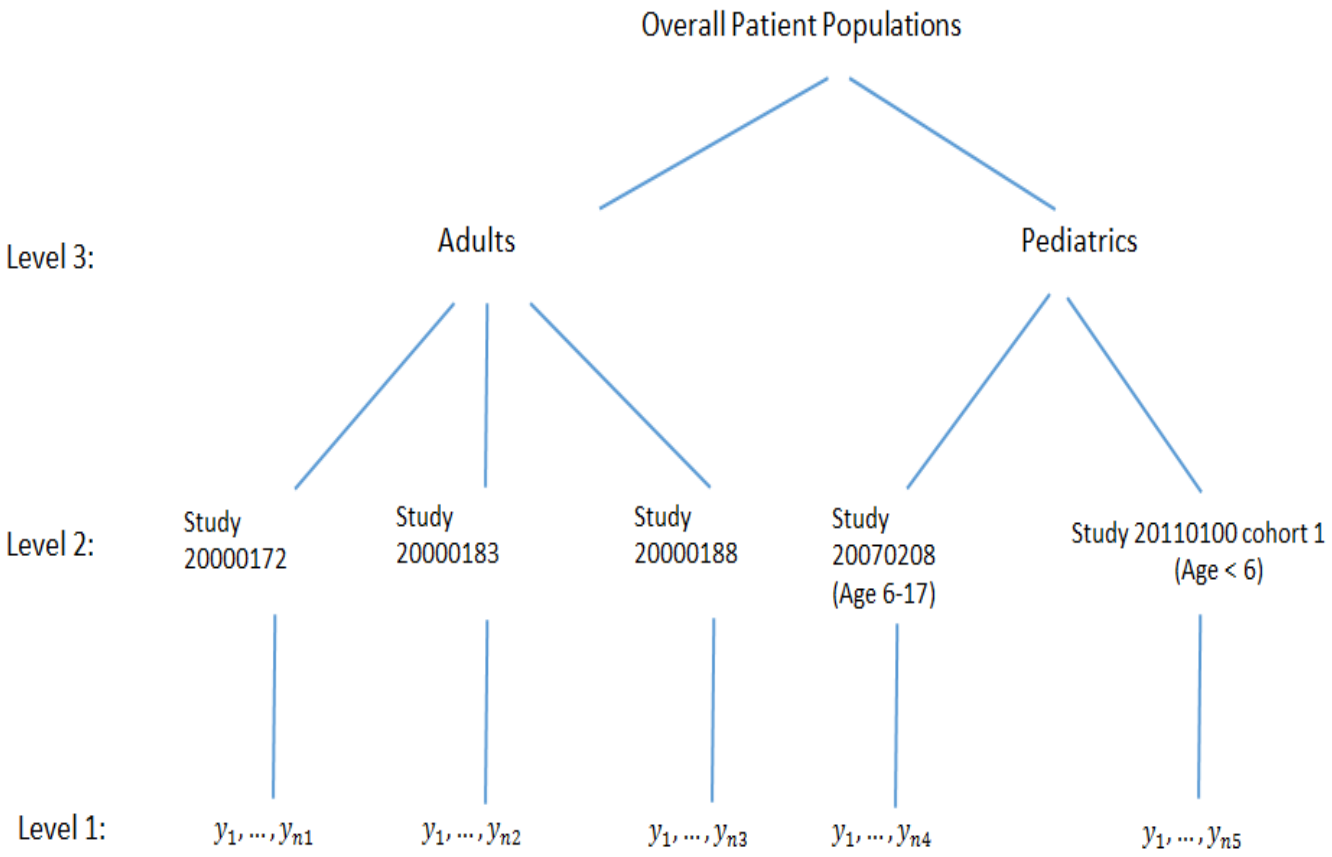
Rationale for Using Bayesian Methods in This Quantitative, Partial Extrapolation Analysis

- 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)

3-level Bayesian Hierarchical Model – Primary Method for Regulatory Submission



- **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

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Data Included in the Pediatric Extrapolation Analysis

	Placebo		Cinacalcet	
	n/N	Response rate (95% CI)[a] (%)	n/N	Response rate (95% CI)[a] (%)
Pediatric studies	4/21	19.1 (5.5, 41.9)	19/29	65.5 (45.7, 82.1)
Study 20070208	4/21	19.1 (5.5, 41.9)	12/22	54.6 (32.2, 75.6)
Study 20110100 cohort 1	-	-	7/7	100 (59.0, 100.0)
All adult studies	47/471	10.0 (7.4, 13.1)	411/665	61.8 (58.0, 65.5)
Study 20000172	21/205	10.2 (6.5, 15.2)	126/205	61.5 (54.4, 68.2)
Study 20000183	17/165	10.3 (6.1, 16.0)	112/166	67.5 (59.8, 74.5)
Study 20000188	9/101	8.9 (4.2, 16.2)	173/294	58.8 (53.0, 64.5)

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**

$$Y_{pkc}|p_{pkc} \sim \text{Binomial}(n_{pkc}, p_{pkc})$$

- **Level 2 – study level**
  - Study level random effects are introduced to account for the between-study variabilities:

$$\text{logit}(p_{pkc}) = \beta_{pc} + \gamma_{pkc}$$

where

β_{pc} is the population effect,

γ_{pkc} is the study level random effect,

$\gamma_{pkc} \sim N(0, \sigma_{pc}^2)$, where σ_{pc}^2 accounts for the between-study variation

3-level Bayesian Hierarchical Model

- **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

β_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

	Placebo	Cinacalcet	Difference (Δ)	Posterior Exceedance Probability			
	Median (95% CrI)	Median (95% CrI)	Median (95% CrI)	Δ > 0%	Δ > 10%	Δ > 20%	Δ > 30%
No extrapolation, fit 208 and 100 data only							
Overall Pediatric (28 days to < 18 years) response rates (%)	21.5 (2.1, 86.6)	80.8 (27.4, 98.2)	53.2 (-19.9, 90)	92.4	87.9	81.9	74.2
With extrapolation, fit adult and pediatric data together							
Pediatric patients 28 days to < 18 years response rates (%)[a]	17.5 (2.6, 62)	69.3 (36.1, 90.2)	48.6 (-2.3, 79.7)	97.0	93.9	88.4	79.2
ESS /n_ped	21.0 / 21[b]	25.1 / 29[c]	-	-	-	-	-
Pediatric patients 28 days to < 6 years response rates (%)[d]	18.0 (1.2, 78.7)	93.1 (66.4, 99.5)	71.8 (10.7, 95.1)	99.0	97.6	95.5	92.5
ESS/n_100	-*	-0.6/7[e]	-	-	-	-	-

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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 (HPT) 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.

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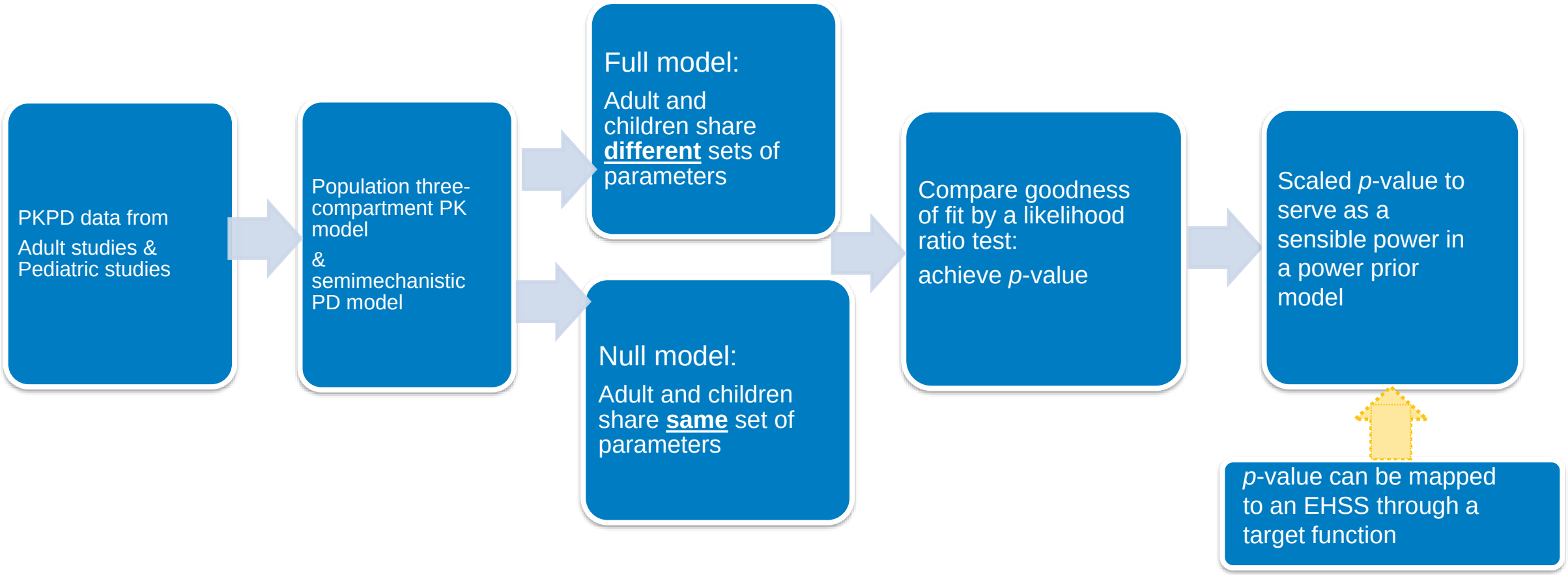
PK/PD Informed Borrowing

- 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.

Diagram of PK/PD Informed Borrowing



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

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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)
- Carlin, B. P., Louis, T. A. (2008). *Bayseian Methods for Data Analysis*. 3rd ed. Boca Raton, FL: Chapman & Hall/CRC Press.
- European Medicines Agency. Reflection paper on the use of extrapolation in the development of medicines for paediatrics, October 2018. https://www.ema.europa.eu/documents/scientific-guideline/adopted-reflection-paper-use-extrapolation-development-medicinespaediatrics-revision-1_en.pdf. Accessed March 16 2020.
- Gamalo-Siebers M, Savic J, Basu C, Zhao X, Gopalakrishnan M, Gao A, Song G, Baygani S, Thompson L, Xia HA, Price K, Tiwari R, Carlin BP. Statistical modeling for Bayesian extrapolation of adult clinical trial information in pediatric drug evaluation.Pharm Stat. 2017 Jul;16(4):232-249. doi: 10.1002/pst.1807. Epub 2017 Apr 27.
- Hobbs, B.P., Carlin, B.P., Mandrekar, S.J., and Sargent, D.J. Hierarchical Commensurate and Power Prior Models for Adaptive Incorporation of Historical Information in Clinical Trials. Biometrics. 2011; 67(3), 1047-1056. DOI: 10.1111/j.1541-0420.2011.01564.x.
- Ibrahim JG, Chen MH. Power prior distributions for regression models. Statistical Science. 2000; 46-60.
- ICH. Final Concept Paper: E11(R1): Clinical Investigation of Medicinal Products in the Pediatric Population. July 2014.
- ICH. E11(R1): Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population. April 2018. https://www.fda.gov/media/101398/download. Accessed March 16 2020.
- ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Clinical Investigation of Medicinal Products in the Pediatric Population, E11. 20 July 2000.
- United States Food and Drug Administration. BLA 125370/s-064 and BLA 761043/s-007 Multi-disciplinary Review and Evalaution Benlysta® (belimumab) for Intravenous Infusion in Children 5 to 17 Years of Age with SLE, 2018. https://www.fda.gov/media/127912/download. Accessed 25 April 2020.
- United States Food and Drug Administration. Guidance for Industry: Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices. June 2016. http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm444591.pdf. Accessed 15 September 2016.
- United States Food and Drug Administration. Guidance for Industry: Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans. March 2016. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm360507.pdf. Accessed 15 September 2016.
- United States Food and Drug Administration. Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products. December 2014. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425885.pdf. Accessed 15 September 2016.
- United States Food and Drug Administration. Guidance for Industry: Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials. February 2010. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071121.pdf. Accessed 15 September 2016.
- Ye, J. and Travis, J. A Bayesian Approach to Incorporating Adult Clinical Data into Pediatric Clinical Trials; 2017 FDA Public Workshop on “Pediatric Trial Design and Modeling: Moving into the Next Decade”. https://www.fda.gov/drugs/news-events-human-drugs/pediatric-trial-design-and-modeling-moving-next-decade. Accessed 25 April 2020.

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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)