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

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Outline

- Pediatric Regulations
- Incentives do not make trials feasible
- Extrapolation
  - Ethics of appropriately sized
  - Framework and variations in clinical program
  - Bayesian methodology
- Example on partial extrapolation
  - Modelling
  - Operating characteristics
- Additional validation requirements
- Considerations for streamlining development

Pediatric trials are required, monitored, and encouraged

PREA

Pediatric Research Equity Act (2003, 2007): mandatory; no exclusivity; orphan indications exempt. RACE Act (2017) requires every novel drug developed for adult cancer be developed in children molecular target is relevant in pediatric cancer

BPCA

Best Pharmaceuticals for Children Act (2002, 2007)
voluntary; exclusivity possible; written requests may be issued for orphan indications

Pediatric Regulation

EMA Pediatric Regulation (2007): mandatory; 6-mo Supplementary Protection Certificate

- Japan, Canada, Switzerland have laws encouraging pediatric drug development.
- USA, EU Japan, Canada and Australia meet regularly through the pediatric cluster.

Despite Incentives, Pediatric Drug Development Remains Challenging

- Completion of many paediatric studies required under the Paediatric Regulation are generally delayed [8]
- Up to half of pediatric clinical trials are abandoned or never published based on a retrospective, cross-sectional study of 559 pediatric randomized clinical trials (RCTs) registered in ClinicalTrials.gov from 2008 to 2010 that were completed by 2012 (Hwang, T. J., Tomasi, P. A., & Bourgeois, F. T. , 2018).
- Nearly one out of five trials (N=104) ended early primarily due to recruitment challenges with a proportion of trials withdrawn before recruitment began (Pica, N., & Bourgeois, F. , 2016).
- On top of recruitment issues, there are ethical, technical, and logistical challenges that may diminish the feasibility of conducting clinical trials of the size necessary to demonstrate statistical significance by traditional means and contribute to the nearly 9 years lapse between initial adult label and pediatric label updates (Wharton et al., 2014).

Moral obligation for the use of pediatric extrapolation

Pediatric Extrapolation ``as an approach to providing evidence in support of the safe and effective use of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric (target) and reference (source) population'' (ICH E11[R1]).

- Children and adolescents are unable to consent for themselves to research participation, and thus are considered a vulnerable population requiring additional safeguards.
- **Scientific necessity**: a child should only be enrolled in a clinical trial if it is necessary to answer an important question about the health and welfare of children (Belmont Report). In effect, if the answer to the scientific question can be obtained by enrolling adult subjects in a clinical trial, children and adolescents should not be exposed to those research risks.
- The use of extrapolation reduces ``the amount of, or general need for, additional information (types of studies, design modifications, number of patients required) needed to reach conclusions.'' Thus, there is an obligation to build the foundation for the use of pediatric extrapolation and related innovative analytical strategies with appropriately designed adult clinical trials.

Extrapolation requires information sources to determine gaps in knowledge

- Other pediatric age groups
- Other formulations of same active ingredient
- Related pediatric indications
- Adult indication for (similar) pediatric indication
- Real World Evidence or historical controls
- Preclinical efficacy extrapolation

Dunne et al Pediatrics. 2011; 128(5):e1242-e1249

NB:

- Regulators are more inclined to support extrapolation in disease areas where a successful trial in pediatric patients has been observed, e.g. JIA but not for type 2 diabetes.
- First-in-class investigational compounds often need to do more studies and extrapolation is generally uncertain.
- High benefit-risk and unmet medical needs still play a role in the extent of data required for extrapolation.

Variations in clinical development depending on knowledge gaps

	No extrapolation
Similar progression of disease	No
Similar response to treatment	No
Similar exposure-response	No
Concentration predictive of response	No
Clinical Development	Full programme

No Extrapolation:
Two adequate well controlled efficacy trials

Full Extrapolation:
PK + Safety Trial

Partial Extrapolation

- Single adequate well controlled efficacy and safety trial + PK
- Single controlled/uncontrolled efficacy and safety trial + PK
- Single E/R trial + PK + safety
- PK/PD study + uncontrolled efficacy + safety
- PK/PD study + safety

NB: (1) In EU, no such types exist because PIP is required by completion of phase 1 PK study where at this stage little is known about the experimental drug. (2) Despite the concept of an iterative approach, rarely is there an iteration in a PIP/PSP. In fact, plans have to be approved and modified only later if infeasible.

Use of Bayesian methodology as a quantitative approach to achieve “desired’’ level of uncertainty

- Allow the possibility of borrowing information from previous studies to specify the proper extent of this borrowing, perhaps determined by study quality or the similarity of the various data sources and expert opinion
  - Sponsor’s previous studies, legally available data on the same or similar products (e.g., ClinicalStudyRequest.com), data registries, information from other cohorts, data on control groups (e.g., Transcelerate)
  - Requirement of `*exchangeability*’ in the development of realistic models for combining trial data with prior information (CDRH FDA, 2006).
- The structure of borrowing of information in a Bayesian methodology is essentially a quantitative application of extrapolation (henceforth, Bayesian extrapolation). Given prior information about a treatment response, pediatric data is collected for which the likelihood function of the parameter representing the treatment response is computed given the collected data.

<u>Proper use</u> of these priors illustrates the power of Bayesian methods: appropriate precision of clinical trials ↔appropriately size trial ↔ arrive at decision faster

Summarizing information into the prior

Working Model: Suppose $\boldsymbol{D}_0 = \{Y_1, \dots, Y_K\}$ with $Y_k|\vartheta_k \sim F(\vartheta_k; n_k)$ and $\theta_k = g(\vartheta_k)|\zeta \sim G(\zeta) = N(\theta_0, \tau^2), \zeta \sim H$

$$p(\boldsymbol{\theta}, \theta_0, \tau^2|D_0) \propto L_0(\boldsymbol{\theta}, \theta_0|\boldsymbol{D}_0)\pi_0^*(\theta_0|\tau^2)\pi_0^*(\tau^2)$$

for prior $\boldsymbol{\theta} = (\theta_1, \dots, \theta_K)$. Interest is in $\hat{p}(\theta_0|\boldsymbol{D}_0)$ which will serve as prior for θ_{K+1} in the proposed pediatric trial.

- Robust MAP (Schmidli et al., 2014) approach

$$\hat{p}(\theta_0|\boldsymbol{D}_0) = \sum_{i=1}^{m} p_i \phi\left(\theta_0 \middle| \theta_i, \tau_i^2\right), p_i > 0, \sum_{i=1}^{m} p_i = 0$$

$$\pi(\theta_{K+1}) = (1-w)\hat{p}(\theta_0|\boldsymbol{D}_0) + wp(\theta)$$

- Model average of all possible subsets of K MEM models $q(\theta_0|\Omega_k, D_0)$ which spans the power set of some number of historical data $\boldsymbol{D}_0$ (Kaizer et al, 2017)

$$\pi(\theta_{K+1}) = \sum_{k=1}^{K} w_k q(\theta_0|\Omega_k, \boldsymbol{D}_0)$$

- Can also be done via commensurate (Hobbs, 2011, 2012) and power prior (Ibrahim & Chen, 2000).
- What can we do when there is some similarity in endpoint measurement?

Partial Extrapolation Example: infliximab for moderate to severe ulcerative colitis in children (2011)

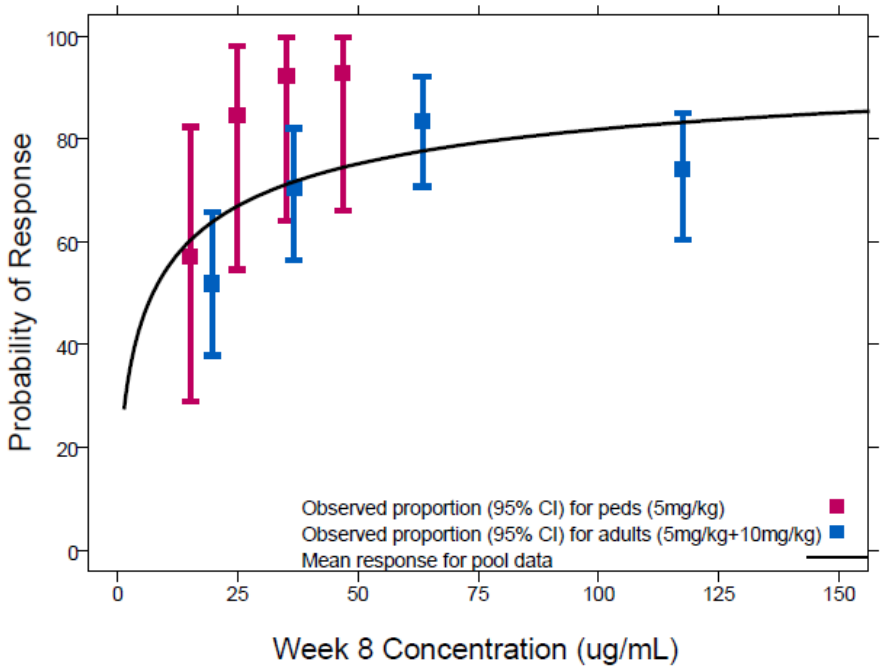
- The course of the disease and response to treatment are expected to be sufficiently similar between adults and children with UC
- Product has been approved in plaque PS, rheumatoid PS, PsA, AxSpa, UC, CD
- It was not clear whether a similar exposure-response relationship in children and adults could be assumed.
- Data package to support partial extrapolation of efficacy through PK & exposure-response analyses, and an open label trial (induction phase)

Adults ≥18 y	Children 6-17 y
▪ Randomized, Double-blind, parallel group (2 dose regimens; placebo) ▪ Mayo score at week 8	▪ Open label induction phase; R maintenance phase (2 dose regimens) ▪ Mayo Score and PUCAI at week 8

Validation of extrapolation assumptions: Exposure-Response & Clinical Response

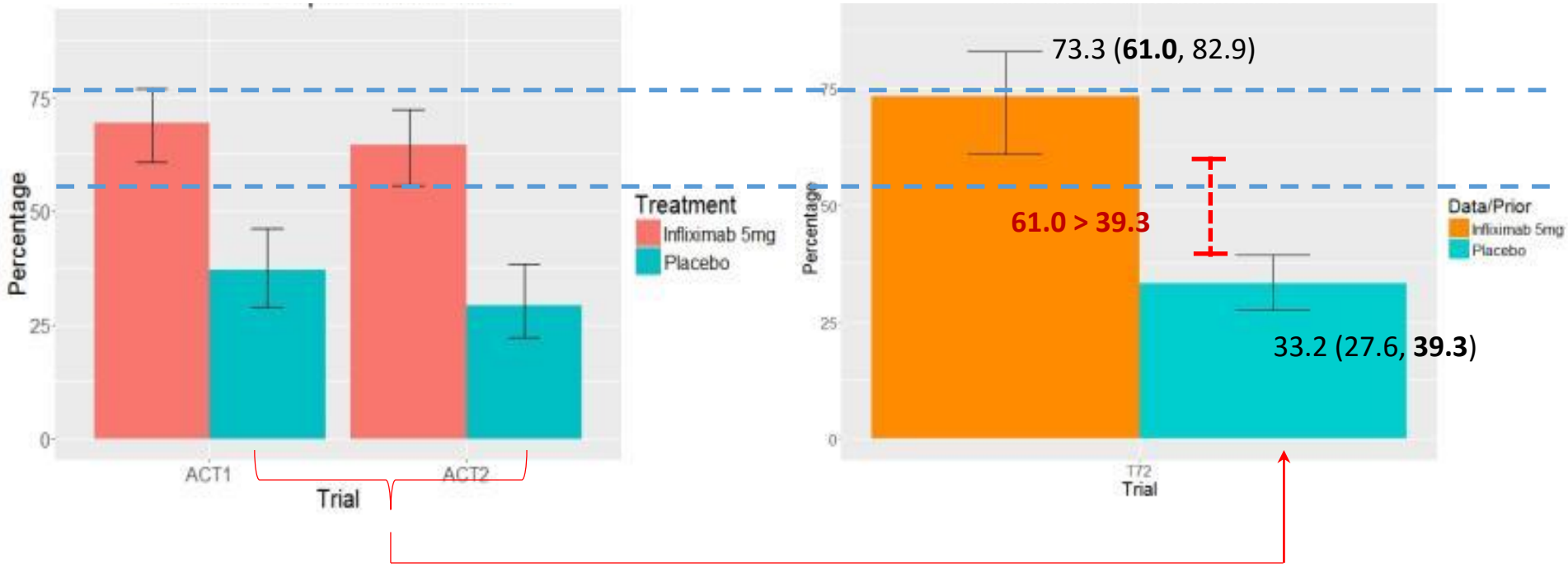
- Pediatric exposure-response does not appear different from adults
- Clinical responses in both adults and children appear similar

	ACT 1	ACT 2	T72
	Infliximab 5mg/kg	Infliximab 5mg/kg	Infliximab 5mg/kg
Endpoint	N = 121	N = 121	N = 60
Clinical response	**84 (69.4%)**	**78 (64.5%)**	**44 (73.3%)**
Clinical remission	47 (38.8%)	41 (33.9%)	24 (40.0%)
Mucosal healing	75 (62.0%)	73 (60.3%)	41 (68.3%)



Summary level data obtained from Rutgeerts et al, 2005[9], and Hyams, et al., 2012[10]. Placebo response not shown.
Other information found Gastrointestinal AC meeting on this link: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/UCM266697.pdf

Additional analysis for validation of extrapolation assumptions: Clinical Response



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.

Application of Bayesian method in partial extrapolation

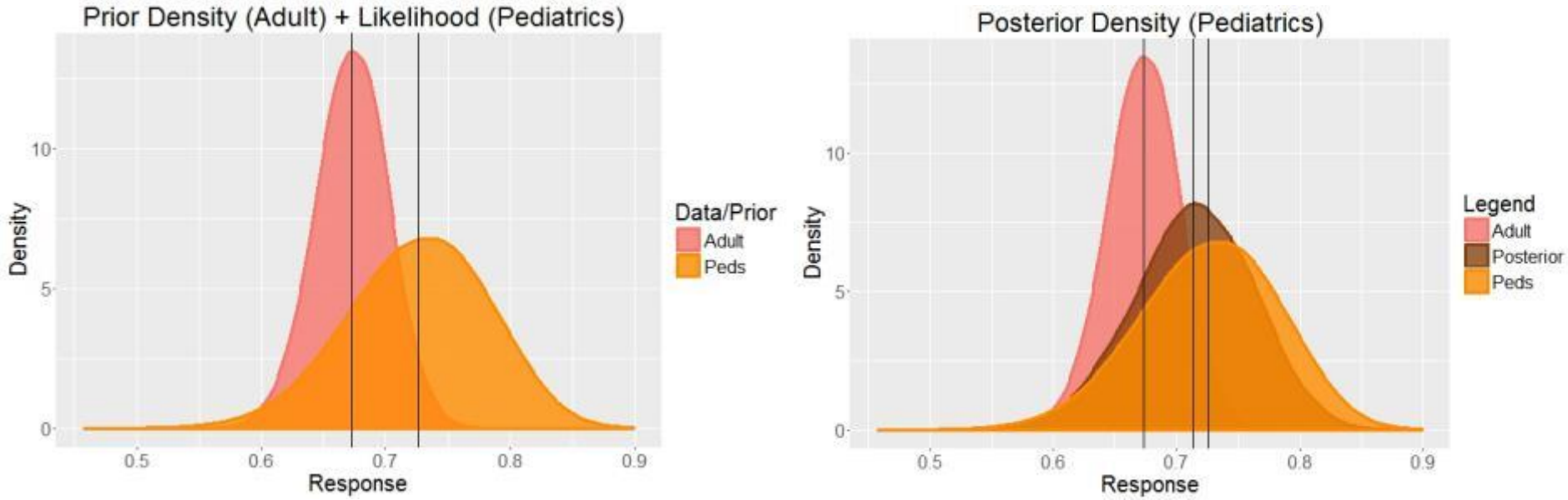
- Specify a prior using source population data (Results from 2 Adult trials, $\boldsymbol{D}_0 = (Y_1, Y_2)$)
- Conduct pediatric trial (T72, $D = Y_3$)+ compute likelihood $L(\theta_1, \theta_2 | D_0) = \prod_{k=1}^{2} Bin(n_k, \theta_k)$
- Apply Bayes theorem (likelihood + prior) to estimate of pediatric response: **prior**

$$\pi_0(\theta_k) = Beta\big(\kappa_\alpha \mu_\alpha, \kappa_\alpha(1-\mu_\alpha)\big)$$
$$\kappa_\alpha \sim Uniform\,(2, 122)$$
$$\mu_\alpha \sim Beta(1,1)$$

$$q(\kappa_\alpha, \mu_\alpha) = Beta\left(\kappa_\alpha \mu_\alpha + \sum_{k=1}^{2} Y_k\,, \kappa_\alpha(1-\mu_\alpha) + \sum_{k=1}^{2} (n_k - Y_k)\right)$$

$$\pi(\theta_3) = Beta\left(\kappa_\alpha \mu_\alpha, r\kappa_\alpha(1-\mu_\alpha)\right), r \in (0,1) \rightarrow r \sim Beta(1,1)$$

Application of Bayesian method in partial extrapolation



Two-step		Commensurate Prior		Power Prior	
r (ESS)	$E(\theta_3 \mid D, \boldsymbol{D}_0)$	κ_α (ESS)	$E(\theta_3 \mid D, \boldsymbol{D}_0)$	α_0 (ESS)	$E(\theta_3 \mid D, \boldsymbol{D}_0)$
0.01 (62.4)	0.729 (0.616, 0.832)	1 (62.4)	0,730 (0.622, 0.837)	0 (62)	0.725 (0.615, 0.835)
0.25 (121)	0.687 (0.607, 0.761)	10 (84)	0.724 (0.620, 0.828)	0.25 (123)	0.710 (0.631, 0.790)
0.5(181)	0.667 (0.602, 0.728)	50 (181)	0.705 (0.617, 0.793)	0.5 (183)	0.705 (0.638, 0.770)
1(302)	0.659 (0.606, 0.711)	100 (302)	0.700 (0.622, 0.778)	1 (302	0.700 (0.648, 0.752)

Partial extrapolation of efficacy in ulcerative colitis (2016)

- Ulcerative colitis is similar in adult and paediatric patients in terms of overall disease pathology and progression and possible treatment targets (**Development of new medicinal products for the treatment of ulcerative colitis, EMA 2016**)
- FDA has concluded that **partial extrapolation of efficacy is acceptable** from adequate and well-controlled studies in adults for a systemically active drug. (FDA Guidance, Ulcerative Colitis)

Plug: FDA, in collaboration with the University of Maryland CERSI, is planning a one day workshop this coming fall (16 November 18) on Pediatric IBD trials.

Understanding Operating Characteristics and Prior Effective Sample Size

- FDA Guidance for the Use of Bayesian Statistics for Medical Device Clinical Trials: demonstration of operating characteristics of Bayesian Decision from a frequentist perspective (expected Type-I error rates)
  - When used to determine whether the drug is efficacious over infinitely many samples, must arrive at a conclusion less often on average than some pre-specified desired rate.

- Prior Effective sample size: how much information is gained with the use of the prior
  - Generally related to Type-I error and bias
  - Morita: interpolated sample size that minimized the prior to posterior distance
  - Malec: ratio of posterior variance without borrowing to posterior variance with borrowing

Should there be additional validation of similarity of treatment response in RCT?

- Comparison of adult and children's clinical response to treatment:
  - Compare whether treatment clinical response is greater than the lower limit of the 95% Credible Interval of the estimate of the posterior mean of treatment in the adult studies.
  - In controlled trials, this is an important step (though not necessary because of internal validity) to effective extrapolation, i.e., provide rules toward proper extrapolation aside from the calibration of extrapolation which can be implemented empirically through the Bayesian methodology.
  - For externally controlled trials, this is the most logical hypothesis that needs to be tested.
- Comparison of adult and children's clinical response to placebo or relative comparator:
  - For controlled trials, this may not be relevant.
  - For externally controlled trials, this comparison needs to be established.

Recommendations in Streamlining Pediatric Drug Development

- Early planning during adult development is necessary to generate the required data to extrapolate to the overall pediatric population or to pediatric subgroups so that adult trials can be designed with awareness of how this can support pediatric labeling in the future
- The identification of the correct pediatric dose(s) in pediatric trials is important, especially when a product is studied for a pediatric disease that has different underlying etiology and pathophysiology compared to the adult disease.
  - Testing more than one dose provides valuable information regarding dose response relationships, which are critical to selecting the optimal dose.
  - Exploring a broad range of tolerated doses may also be useful to determine if drug exposure beyond that which is efficacious in adults is necessary.
- Emphasis on sufficient quality of data from adult population in terms of study design, data collection, and measurement.

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