Another form of hybrid trial designs with external information: extrapolation in Paediatrics

PSI Conference

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Disclaimer

- The views expressed in this presentation are mine and should not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or its committees or working parties.

EMA and ICH guidance on paediatric extrapolation

ICH harmonisation for better health

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27 August 2024
EMA/CHMP/ICH/205218/2022
Committee for Medicinal Products for Human Use

ICH E11A Guideline on pediatric extrapolation

Step 5

Transmission to CHMP	8 March 2022
Adoption by CHMP	24 March 2022
Release for public consultation	06 April 2022
Deadline for comments	06 August 2022
Final adoption by CHMP	25 July 2024
Date for coming into effect	25 January 2025

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7 October 2018
EMA/189724/2018

Reflection paper on the use of extrapolation in the development of medicines for paediatrics

Final

Draft agreed by Biostatistics Working Party, Modelling and Simulation Working Party, Pharmacokinetics Working Party and Scientific Advice Working Party	September 2017
Draft Adopted by PRAC	29 September 2017
Draft Adopted by PDCO	12 October 2017
Draft Adopted by CHMP	12 October 2017
Start of public consultation	13 October 2017
End of consultation (deadline for comments)	14 January 2018
Final version agreed by Biostatistics Working Party, Modelling and Simulation Working Party, Pharmacokinetics Working Party and Scientific Advice Working Party	July 2018
Final version Adopted by PRAC	7 August 2018
Final version Adopted by PDCO	17 October 2018
Final version Adopted by CHMP	17 October 2018

Extrapolation is defined as…

- *"extending information and conclusions available from studies in one or more subgroups of the patient population (source population(s)), or in related conditions or with related medicinal products, in order to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the amount of, or general need for, additional evidence generation (types of studies, design modifications, number of patients required) needed to reach conclusions"*

- General definition, potentially applicable to different settings
  - From adults to paediatrics (focus of this presentation)
  - …
- A different paradigm: There is relevant available information from adults that we can and should use it to reduce the size of paediatric clinical trials

A two-step process

1. Extrapolation concept

Rationale for extrapolation:

- What do we know?
    - Similarity of disease in adults and paediatrics
    - Similarity of drug (mode of action, clearance,…)
    - Efficacy and safety
- What are the gaps?

Outcome of extrapolation concept

- No/partial/full extrapolation possible

2. Extrapolation plan

Filling knowledge gaps

- If ‘No’ -> full development plan for paeds
- If ‘full’ -> M&S, no paeds studies needed
- If ‘partial’ -> studies needed to address gaps
    - PK/PD
    - Efficacy (focus of the following slides)

Methods

- How are data from adults going to be used to inform knowledge gaps paediatrics?

Partial extrapolation of efficacy

- EMA reflection paper, on study design considerations:

"***Once a reduced sample size supported by extrapolation of data from a source population has been justified, this should be translated to the prospective study design through appropriate statistical approaches.*** *Examples of approaches could be using a higher nominal significance level than the usual 5% two-sided, widening a non-inferiority margin or using Bayesian methods to explicitly borrow information (e.g. from adult trials, from control groups, from other paediatric clinical trials). The acceptability and appropriateness of each approach will depend on the knowledge generated in the context of the extrapolation exercise, both in terms of the adult data and any paediatric data.*"

- Approaches
- Data to borrow from
- Acceptability: even if an extrapolation approach looks good on paper, its acceptability will ultimately be a matter of regulatory assessment

Data sources to borrow from

- Results from trials in adults
  - PIP unlikely to be launched if development in adults unsuccessful
  - Good rationale already exists as per extrapolation concept
  - Borrowing treatment effects respects randomisation
  - Considerations to the estimand attributes beyond *population*
- Other paediatric trials
  - E.g. for another drug in the same class for the same indication **if** a good rationale exists
- External paediatric controls
  - More methodological challenges (see Florian's presentation)

Methods for extrapolation of efficacy

- Formal methods to increase type I error rarely used
- Hlavin et al (2015) developed a framework to increase type I error
- Involves Bayesian thinking
- Framework based on
  - Power $\Pr(\text{reject } H_0 \mid H_1)$
  - Positive predictive value $\Pr(H_1 \mid H_0 \text{ rejected})$
- Framework relies on eliciting 'probability of extrapolation', i.e. the belief that adults data do not differ systematically from adults

Research Article

Statistics in Medicine

Received 19 December 2014, Accepted 13 December 2015 Published online 11 January 2016 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.6865

Evidence, eminence and extrapolation

Gerald Hlavin,[a*†] Franz Koenig,[a] Christoph Male,[b] Martin Posch[a] and Peter Bauer[a]

EMA

Methods for extrapolation of efficacy

- Bayesian approaches to construct a prior from the adult data
  - Fixed borrowing
    - Conditional power prior
  - Dynamic borrowing
    - Power-prior family of approaches: normalised PP, commensurate PP, empirical PP, p-value based PP,…
    - Robust mixture prior
    - Elastic priors
    - …
- The resulting priors are robust (de Finetti, 1960's), which is desirable
  - Heavy tails
  - Ability to react to 'prior-data conflict' or 'drift' (results in adults and paediatrics differ) by discarding prior knowledge

Risk of a wrong conclusion

- It is in no one's interest to approve marketing authorisation for medicines that do not help patients
- The job of regulators is to ensure the risk of such a wrong conclusion is minimal
  - There will always be some uncertainty on the efficacy of a drug
  - The goal of a medicine development program is to reduce that uncertainty to low limits
- Regulatory principle implemented in frequentist setting with strict control of type 1 error in hypothesis testing
- With Bayesian methods using informative priors, 'frequentist type I error' cannot be controlled
  - In the context of extrapolation, there's belief in relevance of adults data to inform paediatrics
  - So we expect the risk of a wrong conclusion to be low, but no zero!

Considerations – pre-specification is key

Design

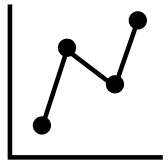
Characterise your prior:

- Prior mean of treatment effect and 95%CrI?
- Prior probability of 'success'?

OC's under different drift scenarios:

- Frequentist type 1 error (drift = $-y_A$) and power (e.g. drift = 0)
- Bias, precision,...
- How much info brings the prior?

Primary analysis



- Interpretability of parameters
- Transparency. How does the prior update with the paediatric data?
- Analytical calculation of the posterior?
- MCMC needed to obtain a sample of the posterior? Convergence?
- Posterior summaries, including posterior probability statements
- Info coming from the prior (ESS)

Sensitivity analysis

- Those that could also be expected for a frequentist primary analysis
- 'Credibility analyses', to contextualise the results with respect to choices made to construct the prior

Example: scientific advice in respiratory paediatric study

Scientific Advice request

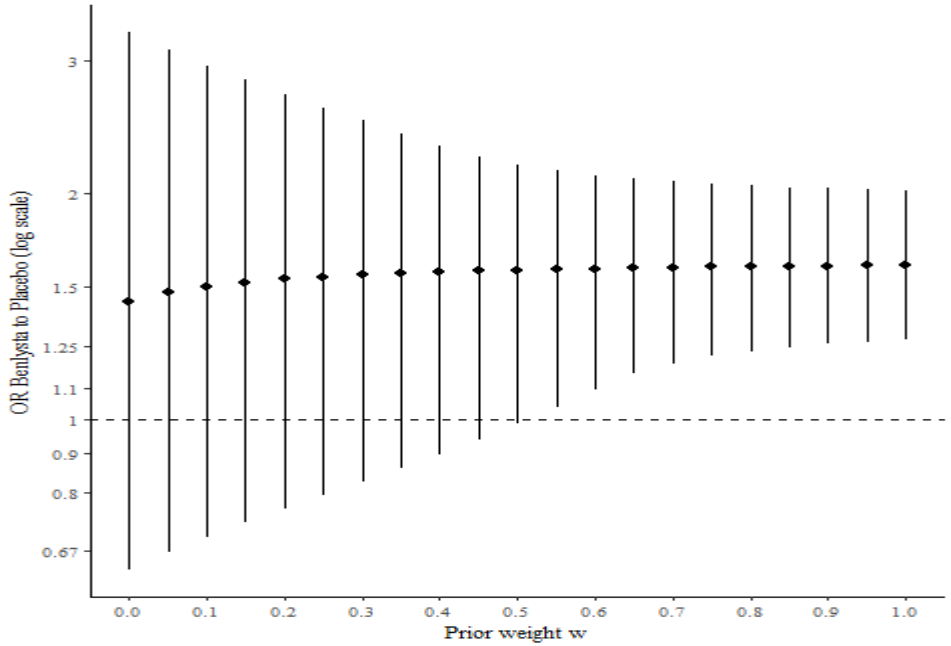
- *Would the Agency consider acceptable, the potential use of Bayesian techniques (in addition to within study comparisons) to incorporate historical <endpoint> data into the analysis in order to increase the precision of the estimated treatment difference in <endpoint> between treatment A+B vs treatment A*
- *The historical data will be summarized in the form of a Bayesian prior distribution… and a method which incorporates dynamic borrowing from the prior will be used so that inference from the study is not dominated by historical data if there is a discrepancy between current and past trials.*

CHMP response

- *CHMP is willing to explore the use of Bayesian methodology in the clinical extrapolation from adults to adolescents and there is a particular rationale in clinical settings where previously adolescents and adults have been studied together.*
- *The proposed metric is agreeable: historical adult information should not be allowed to dominate the outcome of the paediatric trial and limits need to be fixed in advance and justified from where onwards one would be willing to extrapolate to the adolescent population. The chosen strategy to use 'dynamic borrowing' could be acceptable*

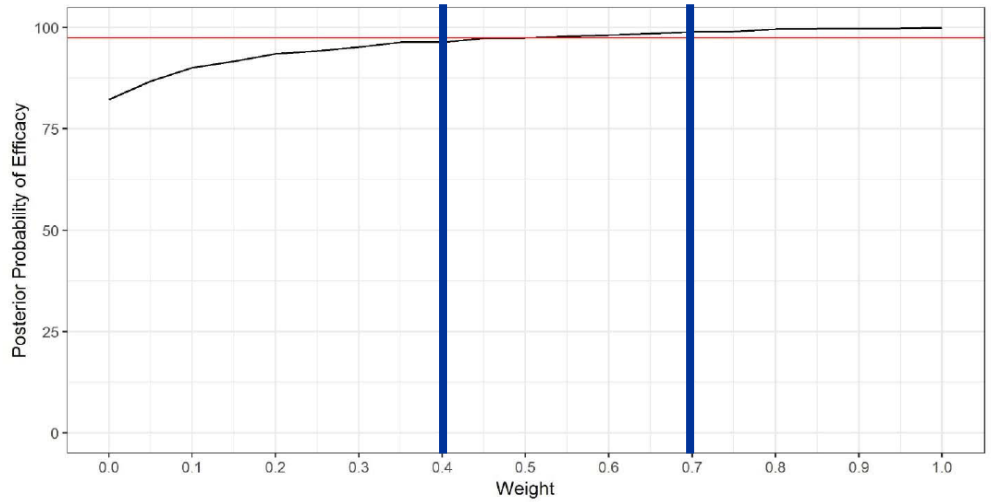
Example: FDA approval of belimumab for SLE in paediatric patients

- Label extension application based on paeds study including over 90 subjects
- FDA reviewer requested post-hoc analysis of PE borrowing from the 2 studies in adults
- Company provided analysis using RMP, including 'tipping point' type of sensitivity analyses



- Interestingly, the FDA reviewer plotted the results differently

Figure 22. Posterior probability of efficacy across different weight values



Source: FDA Statistical Reviewer

- Smooth/drastic changes in posterior probability of efficacy as prior weight varies?

https://www.fda.gov/media/127912/download

Borrowing information or buying trouble?

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Thank you

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