Partial extrapolation in pediatric drug development using robust meta-analytic predictive priors, tipping point analysis and expert elicitation

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Boehringer Ingelheim

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Task

Imagine a rare disease setting with an approved drug in adults...

Pre-specify an efficacy analysis in an underpowered pediatric trial (focussing on PK/PD and safety) with a fixed sample size that borrows information from existing trials in adults

Contents

- Introduction: extrapolation in pediatric drug development
- A case study using a Bayesian framework
  - Robust meta-analytic predictive (MAP) prior
  - Tipping point approach
  - Expert elicitation for determination of weights
- Discussion and take-home messages

FDA workshop ADEPT 7

Bayesian techniques in pediatric studies:

- Ethical imperative to minimize extent of trials
- Trials more consequential
- Assumption of clinical equipoise undermined
- Evidence for similarity of disease and treatment response
- Innovative statistical methodologies encouraged
- Acceptance of raised alpha-levels
- Transparency in data analysis and methodologies is critical
- More frequent interactions with regulators needed

ICH 11A guideline

- Bayesian borrowing techniques, including mixture priors
- Importance of
  - sensitivity analysis
  - visualization
  - transparency
- See also
  - Travis et al. (J Biopharm Stat, 2023)

ICH harmonisation for better health

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

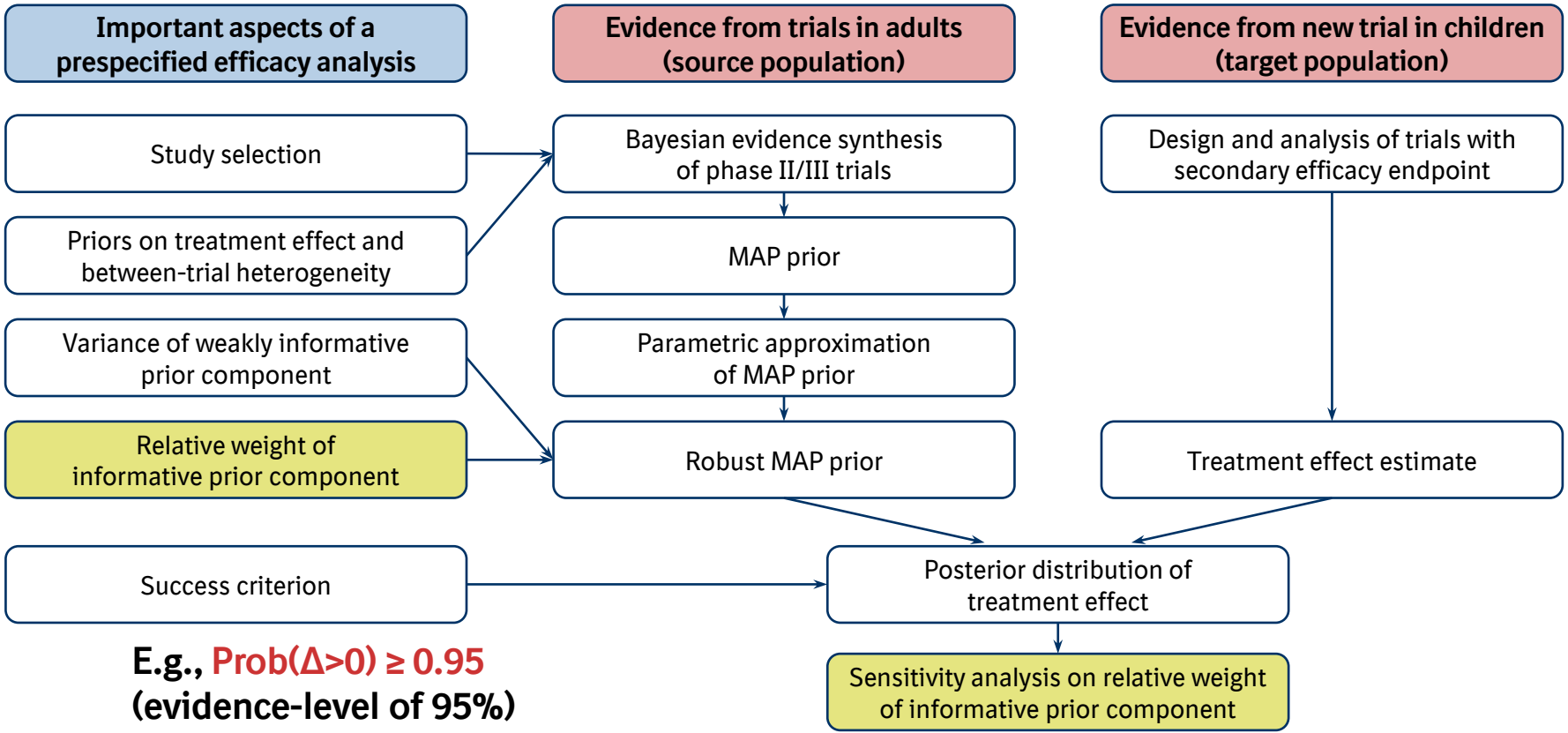
06 April 2022
EMA/CHMP/ICH/205218/2022
Committee for Medicinal Products for Human Use

ICH guideline E11A on pediatric extrapolation
Step 2b

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

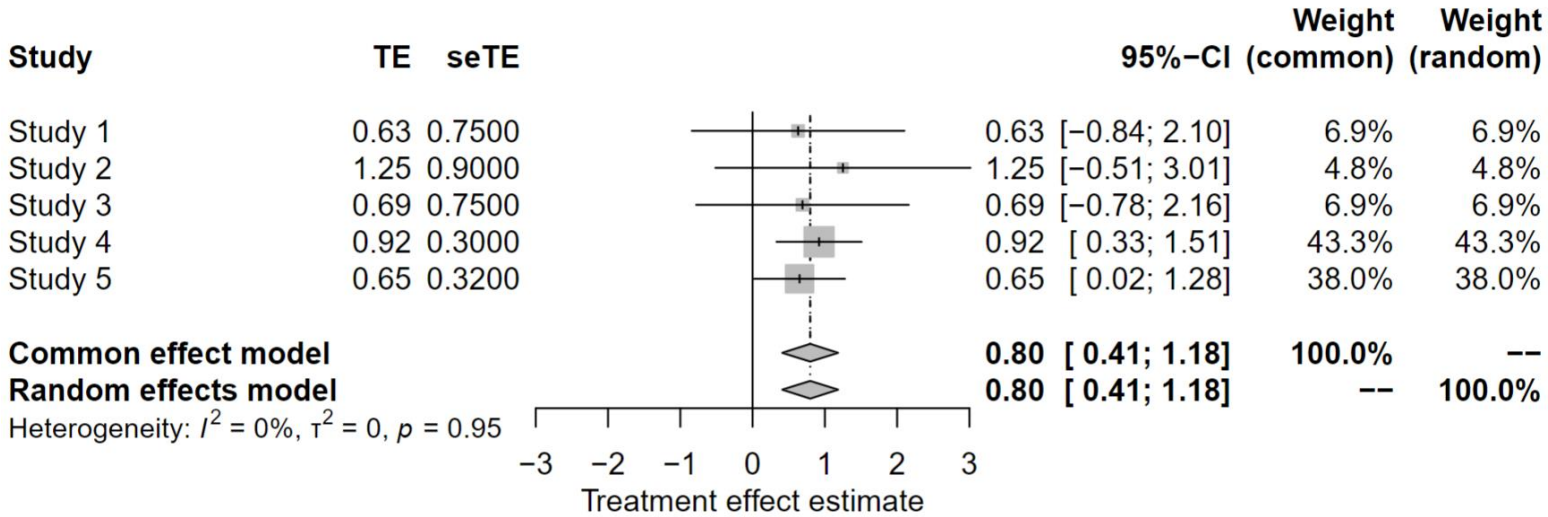
Comments should be provided using this template. The completed comments form should be sent to ich@ema.europa.eu

Bayesian framework for extrapolation



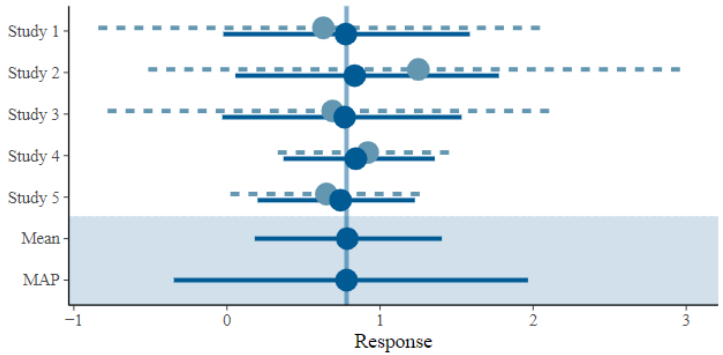
Classical (frequentist) meta-analysis of phase II/III trials

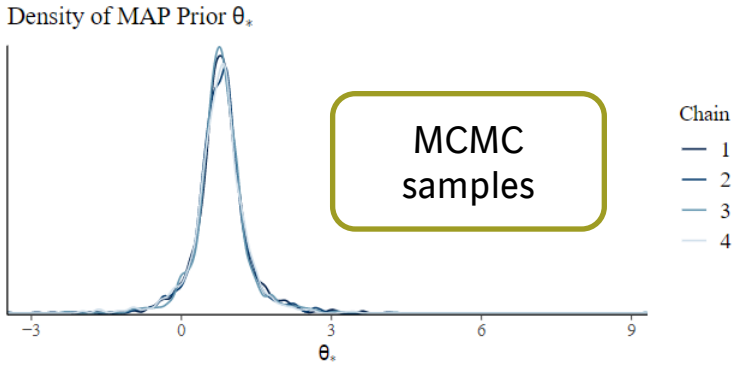
Case study using hypothetical data:



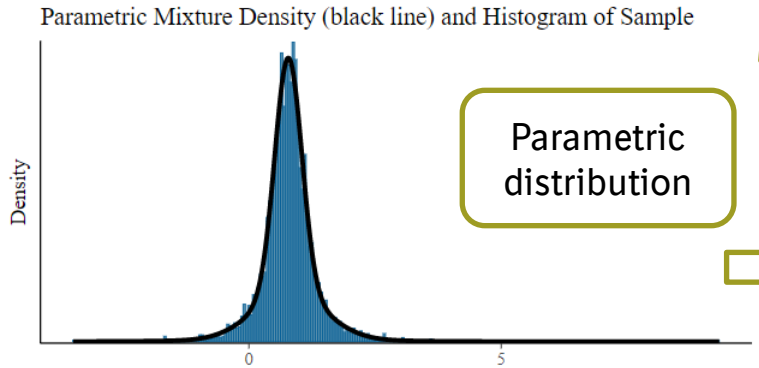
⇨ Down-weighting will be required

Bayesian meta-analysis and MAP prior derivation





MCMC samples

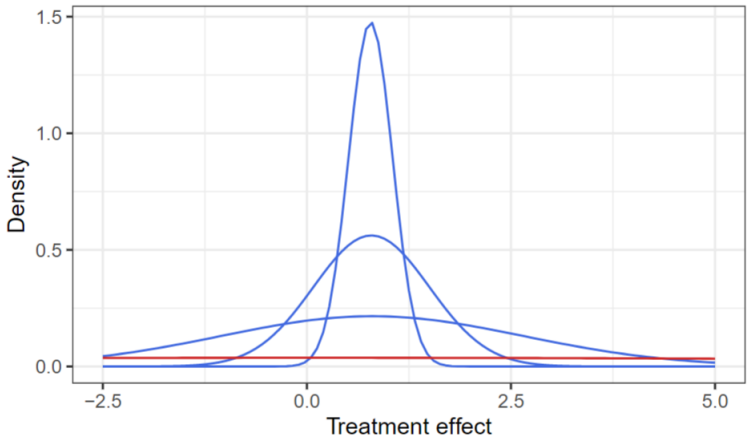


Parametric distribution

3-component mixture of normals:

	Comp 1	Comp 2	Comp 3
Weight	0.63	0.33	0.03
Mean	0.78	0.79	0.80
SD	0.27	0.71	1.85

Robustification of the MAP prior



4-component mixture of normals:

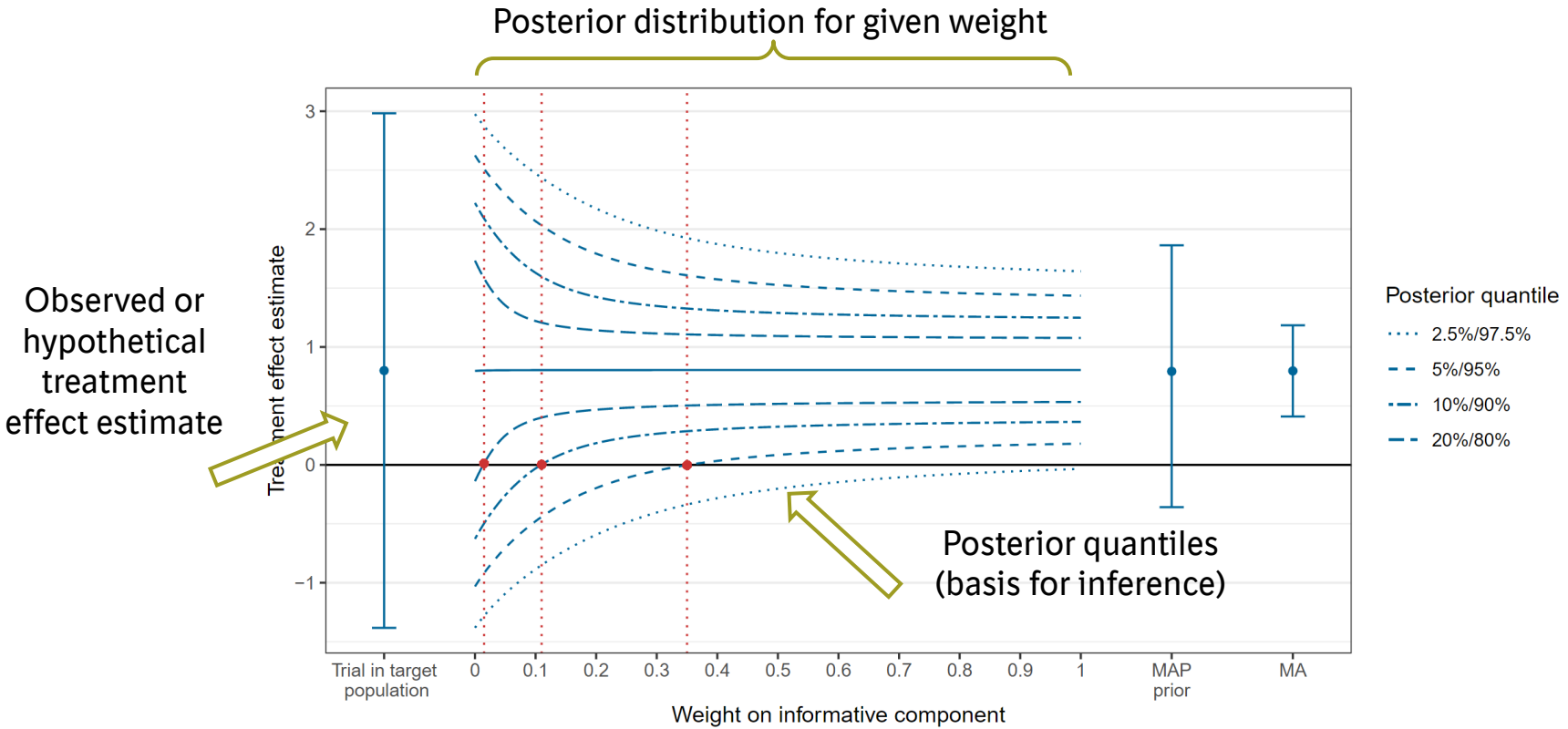
	Comp 1	Comp 2	Comp 3	Comp 4
Weight	0.63**w**	0.33**w**	0.03**w**	**(1 - w)**
Mean	0.78	0.79	0.80	**0**
SD	0.27	0.71	1.85	**Large**

Informative component of weight = **w**

Robust component

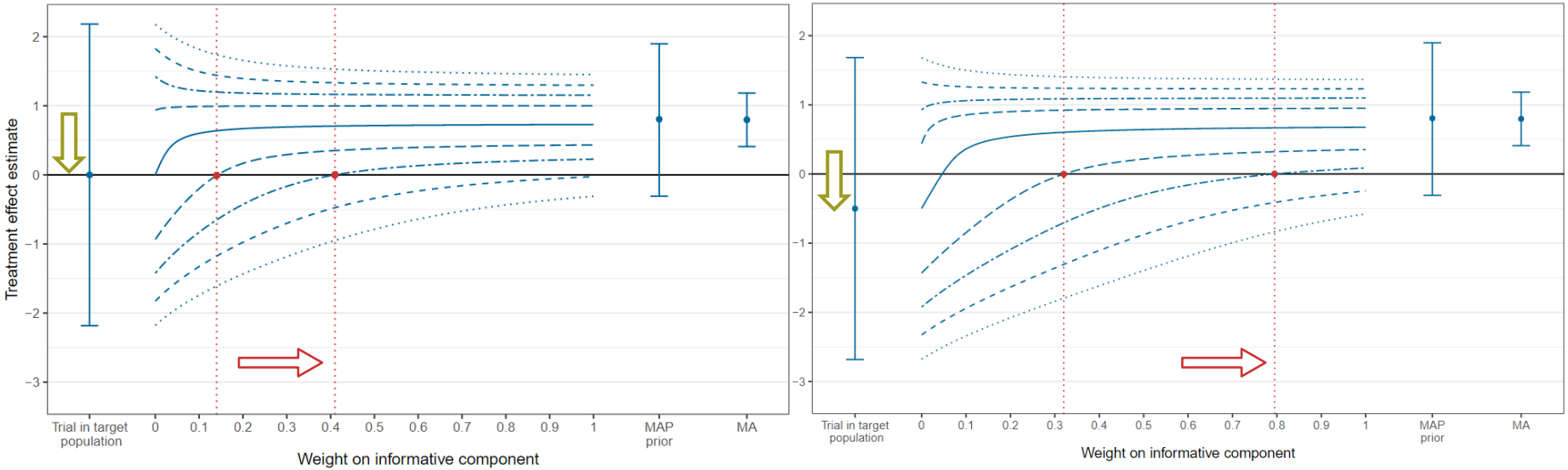
- Borrowing becomes dynamic
- Weight **w** is the belief in target and source being exchangeable
- How do we pre-specify **w** ?

Tipping point analysis



Motivated by Best et al. (*Pharm Stat*, 2021)

Illustration of dynamic borrowing



Uses of the tipping point analysis

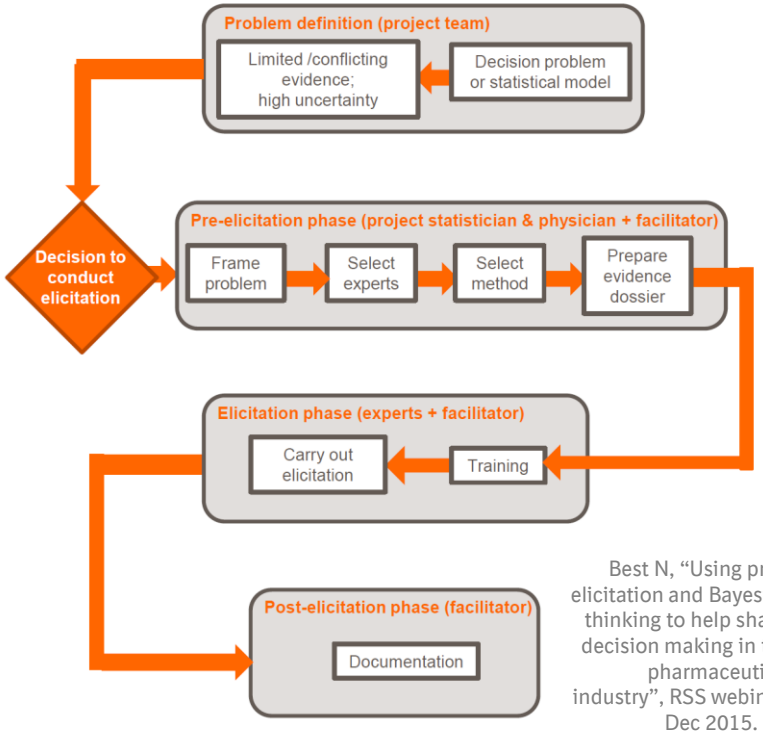
- Use in the trial planning
  - to explore hypothetical scenarios
  - to pre-specify a primary weight of the informative MAP prior component
  - in expert elicitation exercises

- Use in the interpretation of observed results
  - “reverse-Bayes” method
  - Sensitivity analysis

Expert elicitation

- Expert judgment can be formally considered for statistical inference and decision-making
- Process of expressing expert knowledge about uncertain quantities as subjective probability distributions
- Practically desirable since it allows for realistic inferences in face of sparse data

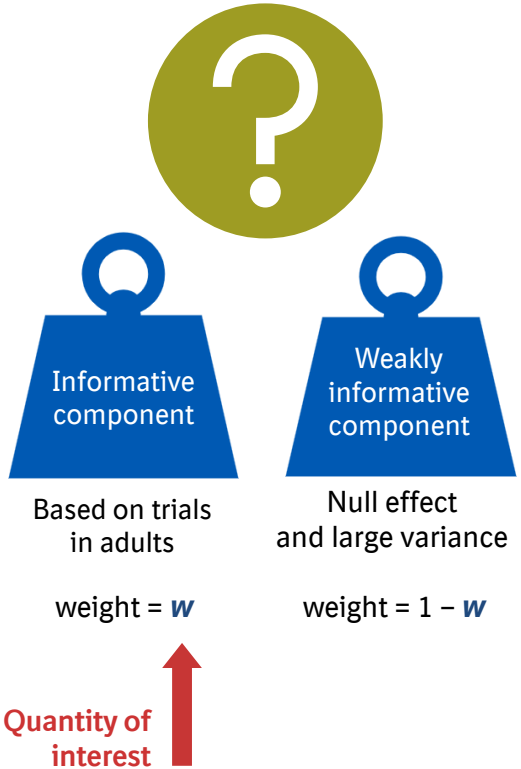
Sheffield Elicitation Framework (SHELF)



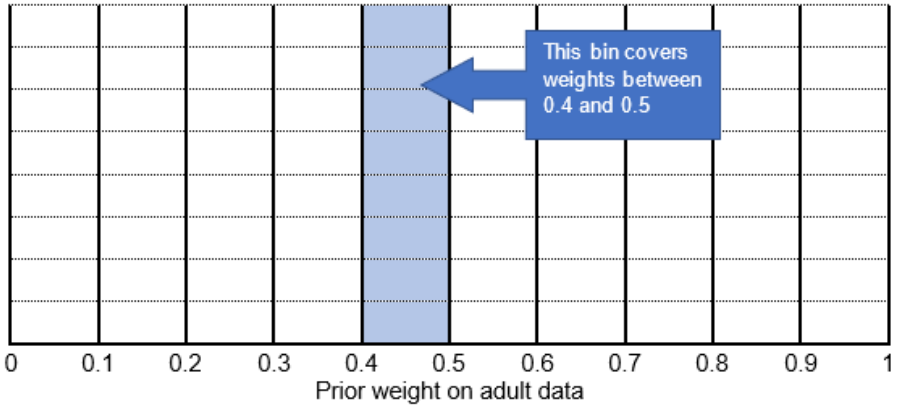
Best N, "Using prior elicitation and Bayesian thinking to help shape decision making in the pharmaceutical industry", RSS webinar, Dec 2015. [#]

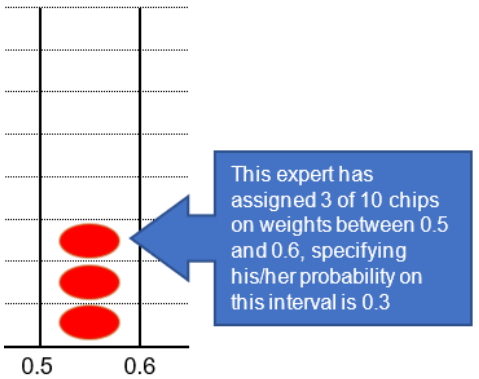
Basis for individual decision on weight

- Pre-clinical and clinical evidence
- Clinical experience and opinion
- Inferences in hypothetical scenarios
  - For given point and variance estimate, and one-sided evidence level
  - Tipping point analysis as a tool
- Operating characteristics (type I error, power, bias)



Task description



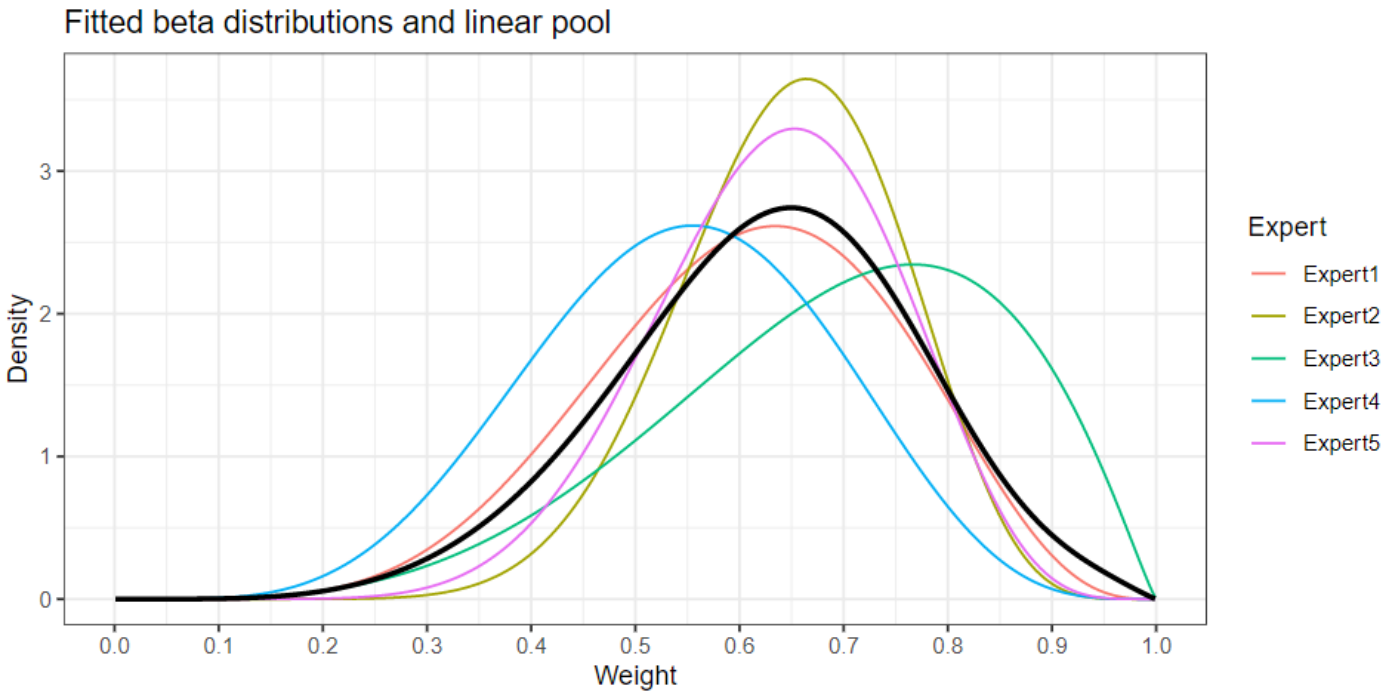


- 10 chips need to be placed to create histogram-like data
- No particular shape or symmetry needed

Elicitation results

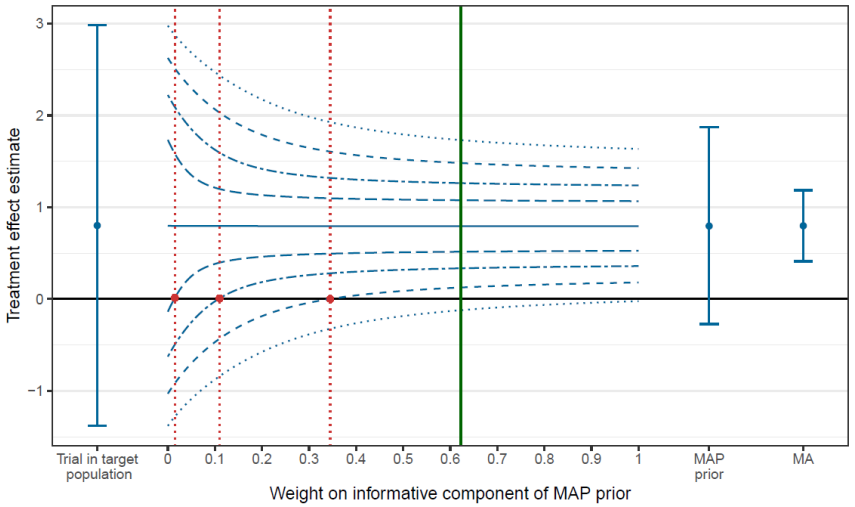
Descriptive statistics of linear pool:

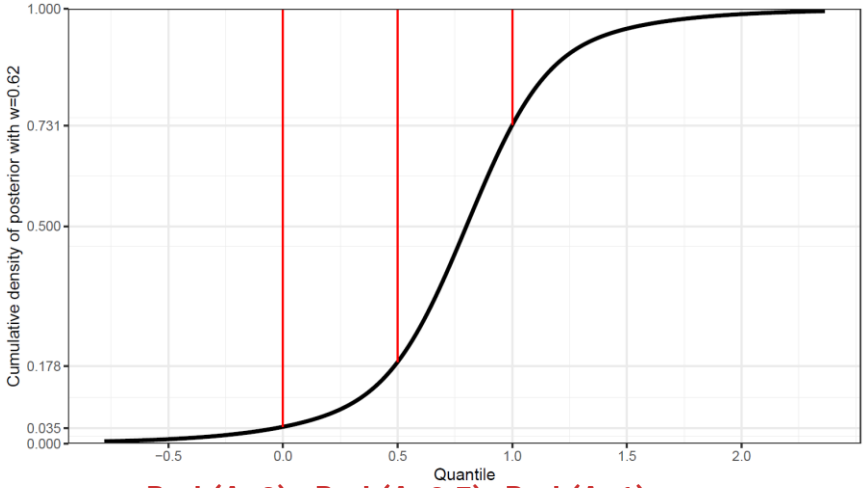
Mean	0.62
Q1	0.54
Median	0.64
Q3	0.73



Posterior with expert-elicited weight of trials in adults

Pre-specified primary weight (=0.62) [fully specified prior]

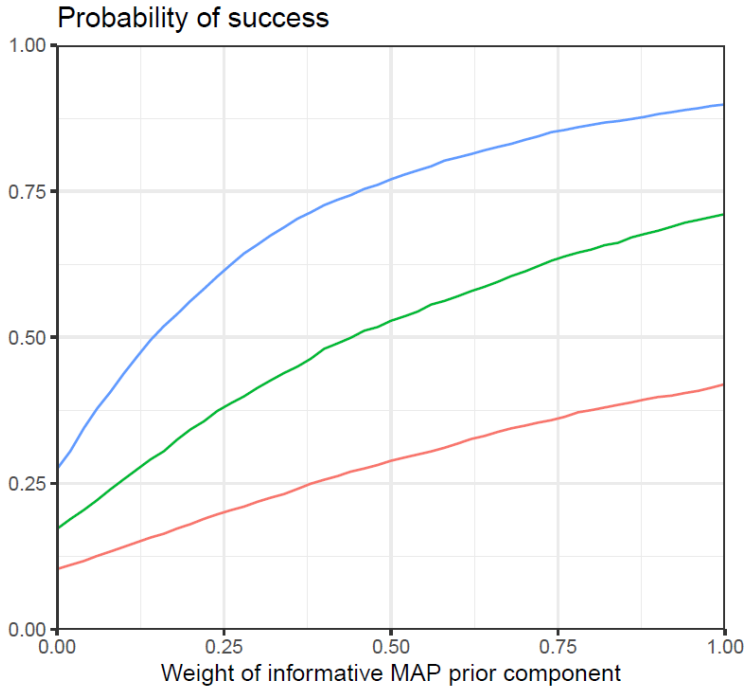


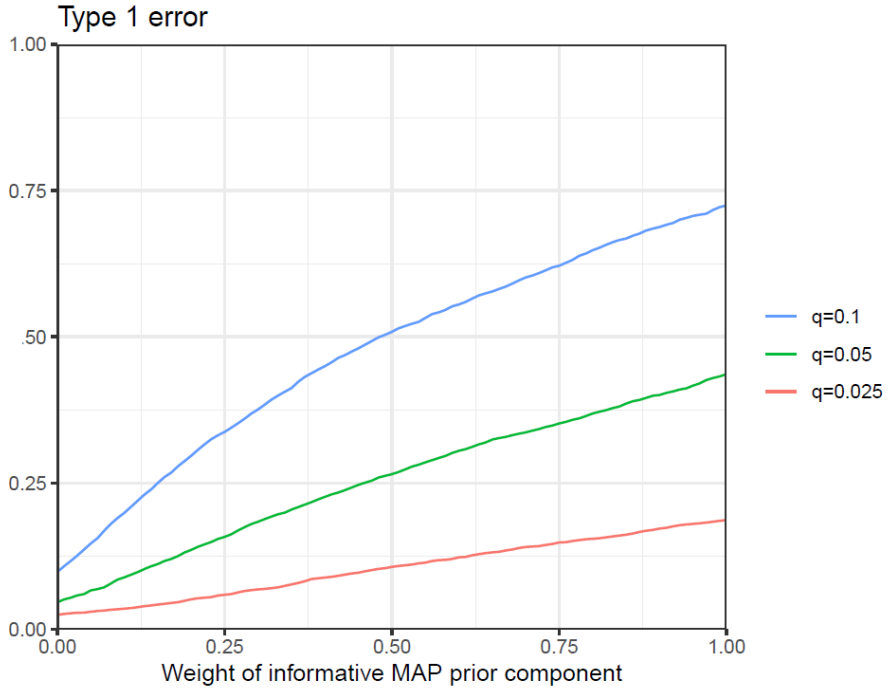


Prob(Δ>0) = 0.97 Prob(Δ>0.5) = 0.82 Prob(Δ>1) = 0.27

Pre-specified success criterion Prob(Δ>0) ≥ 0.95 is fulfilled
(Importantly, any efficacy claim requiring acceptable safety and PK/PD results)

Operating characteristics





Discussion points

- Expert elicited weights and constraints from operating characteristics

- Prior effective sample size

- What is the influence of the adult data when making inferences based on the total evidence?

R package ‘tipmap‘

tipmap: Tipping Point Analysis for Bayesian Dynamic Borrowing

Tipping point analysis for clinical trials that employ Bayesian dynamic borrowing via robust meta-analytic predictive (MAP) priors. Further functions facilitate expert elicitation of a primary weight of the informative component of the robust MAP prior and computation of operating characteristics. Intended use is the planning, analysis and interpretation of extrapolation studies in pediatric drug development, but applicability is generally wider.

Version:	0.5.2
Depends:	R (≥ 3.5.0)
Imports:	dplyr, magrittr, purrr, ggplot2, RBesT, assertthat, stats, furrr, future
Suggests:	knitr, rmarkdown, tidyr, tibble, testthat (≥ 3.0.0)
Published:	2023-08-14
Author:	Christian Stock [aut, cre], Morten Dreher [aut], Emma Torrini [ctb], Boehringer Ingelheim Pharma GmbH & Co. KG [cph, fnd]
Maintainer:	Christian Stock <christian.stock at boehringer-ingelheim.com>
BugReports:	https://github.com/Boehringer-Ingelheim/tipmap/issues
License:	Apache License 2.0
URL:	https://github.com/Boehringer-Ingelheim/tipmap
NeedsCompilation:	no
Materials:	README NEWS
CRAN checks:	tipmap results

Documentation:

Reference manual:	tipmap.pdf
Vignettes:	Determining a weight of the informative prior component Introduction to the 'tipmap' package

Take-home messages

- In drug development for rare pediatric diseases, it is particularly challenging to make inferences on efficacy (and safety).
- Bayesian extrapolation techniques are increasingly used and recommended to incorporate evidence from trials in adults.
- **Dynamic borrowing via mixture priors combined with tipping point analysis and expert elicitation to pre-specify priors, can help to formalize and bring transparency into a process that is often done informally and implicity.**

Credit

- Developers of rMAP prior approach and RBesT package
- Best et al. (Pharm Stat, 2021)
- SHELF team

Thank you for your interest and attention

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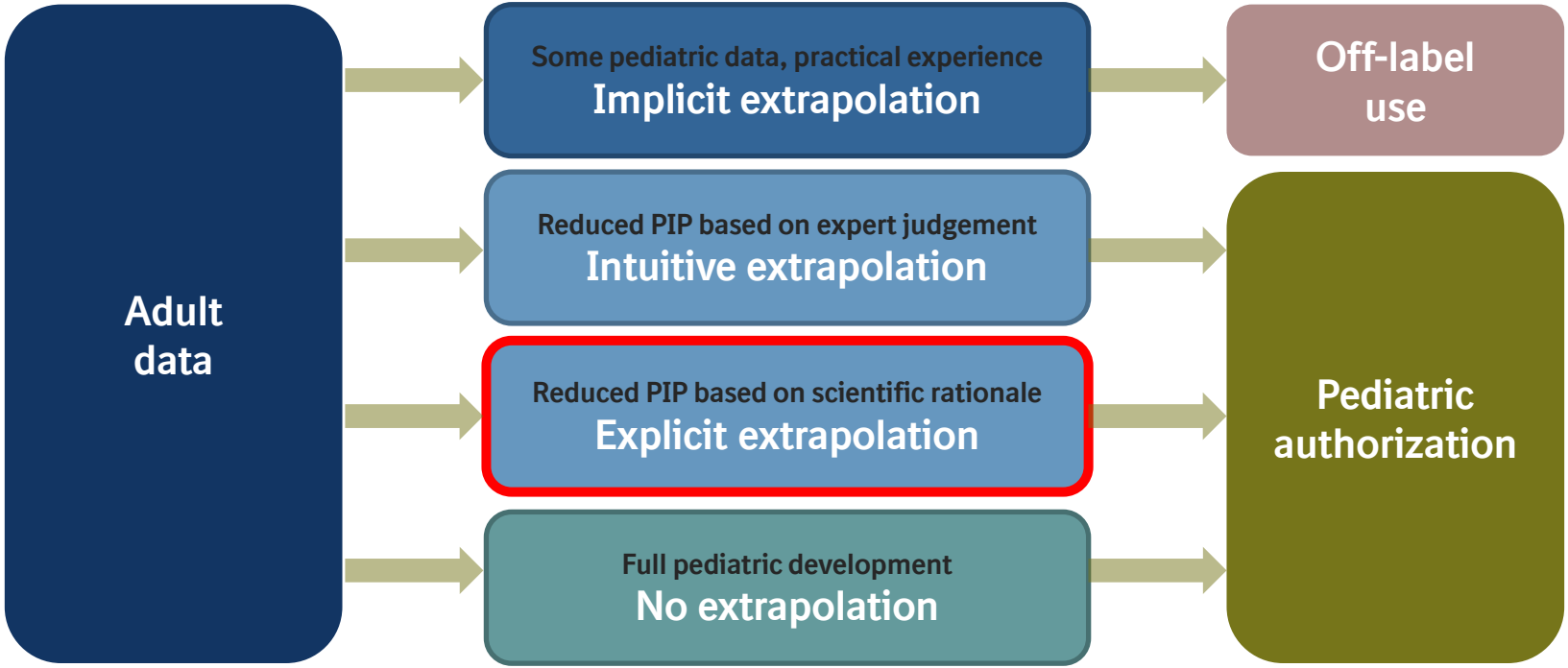
Literature

- Best N, Price RG, Pouliquen IJ, Keene ON. Assessing efficacy in important subgroups in confirmatory trials: an example using Bayesian dynamic borrowing. *Pharm Stat*. 2021;20:551–562.
- Brownstein NC, Louis TA, O'Hagan A, Pendergast J. The Role of Expert Judgment in Statistical Inference and Evidence-Based Decision-Making. *Am Stat*. 2019;73(1):56-68.
- Calderazzo S, Wiesenfarth M, Kopp-Schneider A. A decision-theoretic approach to Bayesian clinical trial design and evaluation of robustness to prior-data conflict. *Biostatistics*. 2022; 23(1):328-344.
- Dallow N, Best N, Montague TH. Better decision making in drug development through adoption of formal prior elicitation. *Pharm Stat*. 2018; 17(4): 301-316.
- Gamalo M, Bucci-Rechtweg C, Nelson RM, Vanh L, Porcalla A, Thackray H, Cooner F, Cutler L, Friend D, Portman R. Extrapolation as a Default Strategy in Pediatric Drug Development. *Ther Innov Regul Sci*. 2022; 56(6): 883-894.
- Gosling JP. SHELF: The Sheffield Elicitation Framework. In: Dias L C, Morton A, Quigley J (eds.). Elicitation: The science and art of structuring judgement. Springer International Publishing, 2018.
- O'Hagan A. Expert Knowledge Elicitation: Subjective but Scientific. *Am Stat*. 2019; 73: sup1, 69-81.
- Neuenschwander B, Capkun-Niggli G, Branson M, Spiegelhalter DJ. Summarizing historical information on controls in clinical trials. *Clin Trials*. 2010;7:5-18.

Literature

- Neuenschwander B, Schmidli H. Use of historical data. In: Lesaffre E, Baio G, Boulanger B (editors). Bayesian methods in pharmaceutical research. CRC Press, 2020.
- Neuenschwander B, Weber S, Schmidli H, O'Hagan A. Predictively consistent prior effective sample sizes. Biometrics. 2020; 76(2): 578-587.
- Ollivier C, Thomson A, Manolis E, Blake K, Karlsson KE, Knibbe CAJ, Pons G, Hemmings R. Commentary on the EMA Reflection Paper on the use of extrapolation in the development of medicines for paediatrics. *Br J Clin Pharmacol*. 2019; 85(4): 659-668.
- Schmidli H, Gsteiger S, Roychoudhury S, O'Hagan A, Spiegelhalter D, Neuenschwander B. Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics*. 2014;70:1023-32.
- Travis J, Rothmann M, Thomson A. Perspectives on informative Bayesian methods in pediatrics. *J Biopharm Stat*. 2023; in press.
- Weber S, Li Y, Seaman JW, Kakizume T, Schmidli H. Applying Meta-Analytic-Predictive Priors with the R Bayesian Evidence Synthesis Tools. *J Stat Softw*. 2021; 100(19): 1-32.

Evidence base for medicine use in children



Adapted from Ollivier et al. (2019)

Subjectivity

- “We must accept that there is subjectivity in every stage of scientific inquiry, but objectivity is nevertheless the fundamental goal. Therefore, we should base judgments on evidence and careful reasoning, and seek wherever possible to eliminate potential sources of bias.”

  Brownstein et al. (2019)

- “Judgment is necessarily subjective, but should be made as carefully, as objectively, and as scientifically as possible.”

  O’Hagan (2019)

Further discussion points

- Validity
  - Complexity of ’statistical questions’ to experts
  - Degree of subjectivity and cognitive biases
- Regulatory aspects
  - Internal decision-making ↔ regulatory decision-making
  - Clinical experts’ perspective ↔ regulatory perspective
- Statistical
  - Propagation of uncertainty
  - Effective sample size
- Feasibility and scalability

Application

Estimating the effect of nintedanib on forced vital capacity in children and adolescents with fibrosing interstitial lung disease: extrapolation using a Bayesian borrowing approach

Toby M Maher,[1] Kevin K Brown,[2] Steven Cunningham,[3] Emily M DeBoer,[4,5] Robin Deterding,[4,5] Elizabeth K Fiorino,[6] Matthias Griese,[7] Nicolaus Schwerk,[8] David Warburton,[1,9] Lisa R Young,[10] Martina Gahlemann,[11] Florian Voss,[12] Christian Stock[12] on behalf of the InPedILD trial investigators

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INTRODUCTION

- Nintedanib has a consistent effect on slowing decline in forced vital capacity (FVC) in adults with different types of fibrosing ILD.[1]
- In the InPedILD trial in children and adolescents with fibrosing ILD, a weight-based dosing regimen for nintedanib resulted in exposure similar to adults and had an acceptable safety and tolerability profile.[2]
- The InPedILD trial was not powered to show an effect of nintedanib on change in FVC.
- A Bayesian dynamic borrowing approach is a statistical method that enables the effects of therapy in a target population (here, children and adolescents) to be estimated by extrapolating evidence from a source population (here, adults).[3,4]

AIM

- To use a Bayesian dynamic borrowing approach, incorporating data on the effect of nintedanib in adults, to estimate the effect of nintedanib on FVC in children and adolescents with fibrosing ILDs.

METHODS

InPedILD trial[2]

- Children or adolescents aged 6–17 years with fibrosing ILD on HRCT and clinically significant disease were randomized to receive nintedanib or placebo.
- Change in FVC % predicted at week 24 was analysed based on a mixed model for repeated measures.

Pre-specified Bayesian framework for partial extrapolation

- Data on changes in FVC % predicted at week 24 from six placebo-controlled trials of nintedanib in adults with fibrosing ILDs were included in a meta-analysis.
- The data from adults were incorporated into a Bayesian framework for partial extrapolation. Dynamic borrowing was applied through a robust meta-analytic predictive (MAP) prior distribution of the treatment effect.[5] This was a weighted mixture of an informative component, based on the adult data, and a weakly informative component, implying a null effect, that led to less borrowing the more the adult and pediatric data were in conflict.
- The weight was determined in an elicitation exercise involving nine experts in the treatment of adult or paediatric ILD, using the SHELF process.[6]
- The prior distribution was updated with the FVC data from the InPedILD trial to calculate a "posterior distribution" of the treatment effect of nintedanib in children and adolescents with fibrosing ILD based on all the evidence.
- Tipping point analyses were performed to assess the sensitivity of the results across the range of weights that could be placed on the relevance of adult data.[7]

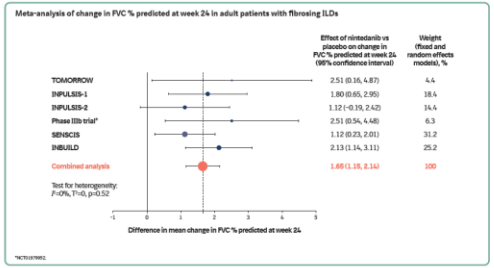
CONCLUSIONS

- Pre-specified analyses based on a Bayesian borrowing approach suggested a benefit of nintedanib on change in FVC in children and adolescents with fibrosing ILDs similar to that observed in adults.
- These findings, together with the safety findings from the InPedILD trial, support the use of nintedanib in children and adolescents with fibrosing ILDs.

RESULTS

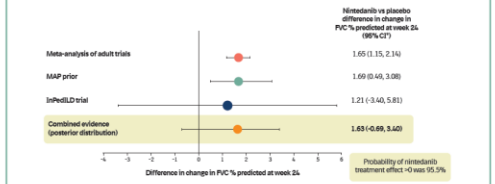
Baseline characteristics of patients in the InPedILD trial (n=39)

Meta-analysis of change in FVC % predicted at week 24 in adult patients with fibrosing ILDs

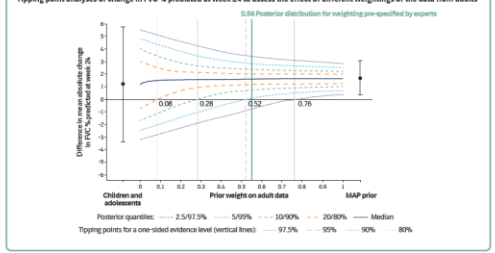


Mean prior weight on adult data from expert elicitation exercise

Nintedanib versus placebo difference in change in FVC % predicted at week 24 across datasets



Tipping point analyses of change in FVC % predicted at week 24 to assess the effect of different weightings of the data from adults



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REFERENCES
1. Borella F et al. Adv Ther 2022;39:3392–3402.
2. Deterding R et al. Eur Respir J 2022;2201512.
3. Garnaio-Siebers M et al. Ther Innov Regul Sci 2019;53:567–578.
4. Rubing SJ et al. Nat Rev Drug Discov 2023;22:239–250.
5. Schmidli H et al. Biometrics 2014;70:1023–1032.
6. Gosling JP. SHELF: The Sheffield Elicitation Framework. In: Dias LC et al (eds.). Elicitation: The Science and Art of Structuring Judgment. Springer International Publishing, 2018.
7. Best N et al. Pharm Stat 2021;20:551–562.

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