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

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The overarching topic

Transparent and rational
regulatory and medical decision-making
in face of sparse data

The specific 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)
that borrows information from
existing trials in adults

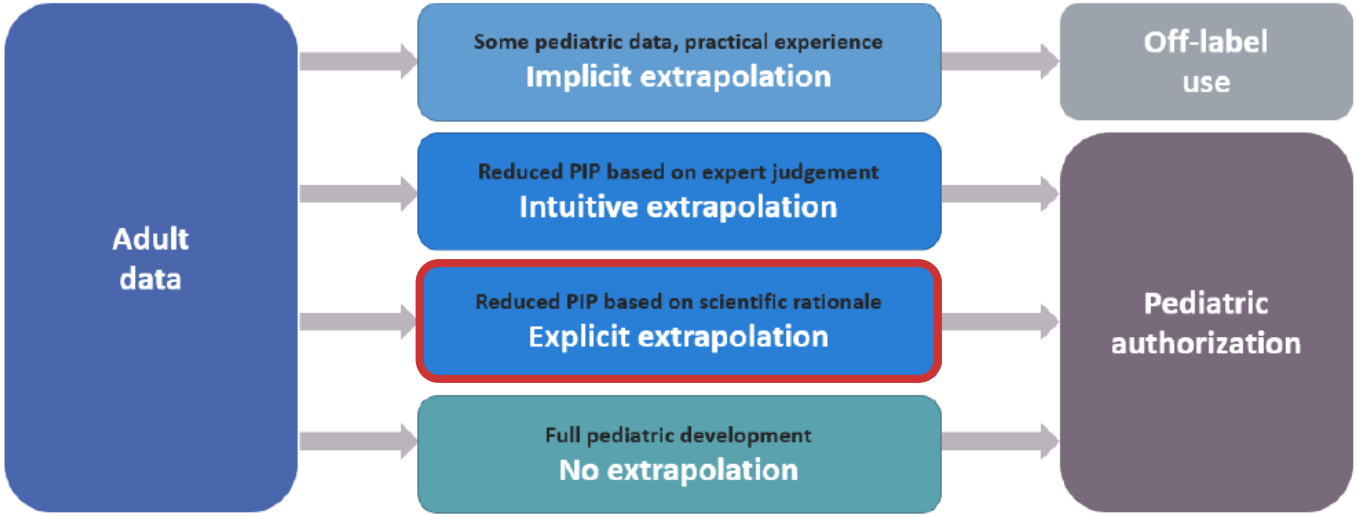
Towards a ‘default’ extrapolation approach for
pediatric drug development programs

Contents

- Introduction: extrapolation in pediatric drug development
- A case study using a Bayesian framework
  - Deriving a robust meta-analytic predictive (MAP) prior
  - A tipping point approach for analyses based on robust MAP priors
  - Expert elicitation for determination of weights
- Take-home messages

Extrapolation in pediatric drug development

Evidence base for medicine use in children



Adapted from Ollivier et al. (2019)

Extrapolation in pediatric drug development

FDA workshop (Sep 2021): ”Advancing the Development of Pediatric Therapeutics Complex Innovative Trial Design”

- Topic “Bayesian techniques in pediatric studies”
- Use of pediatric extrapolation in 21st century:
  - Ethical imperative to **minimize extent** of pediatric studies
  - Trials **more consequential** than adult trials (“one shot” only)
  - Evidence for **similarity of disease** and **similarity of treatment response**
  - Use of **innovative statistical methodologies** is encouraged
  - Generally acceptable: **raised alpha-levels** (>5%)
  - Critical: **transparency** and **increased regulatory interaction**

Extrapolation in pediatric drug development

New ICH 11 guidance

- Bayesian borrowing techniques, including mixture priors
- Importance of
  - sensitivity analysis
  - visualization
  - transparency

ICH harmonisation for better health

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

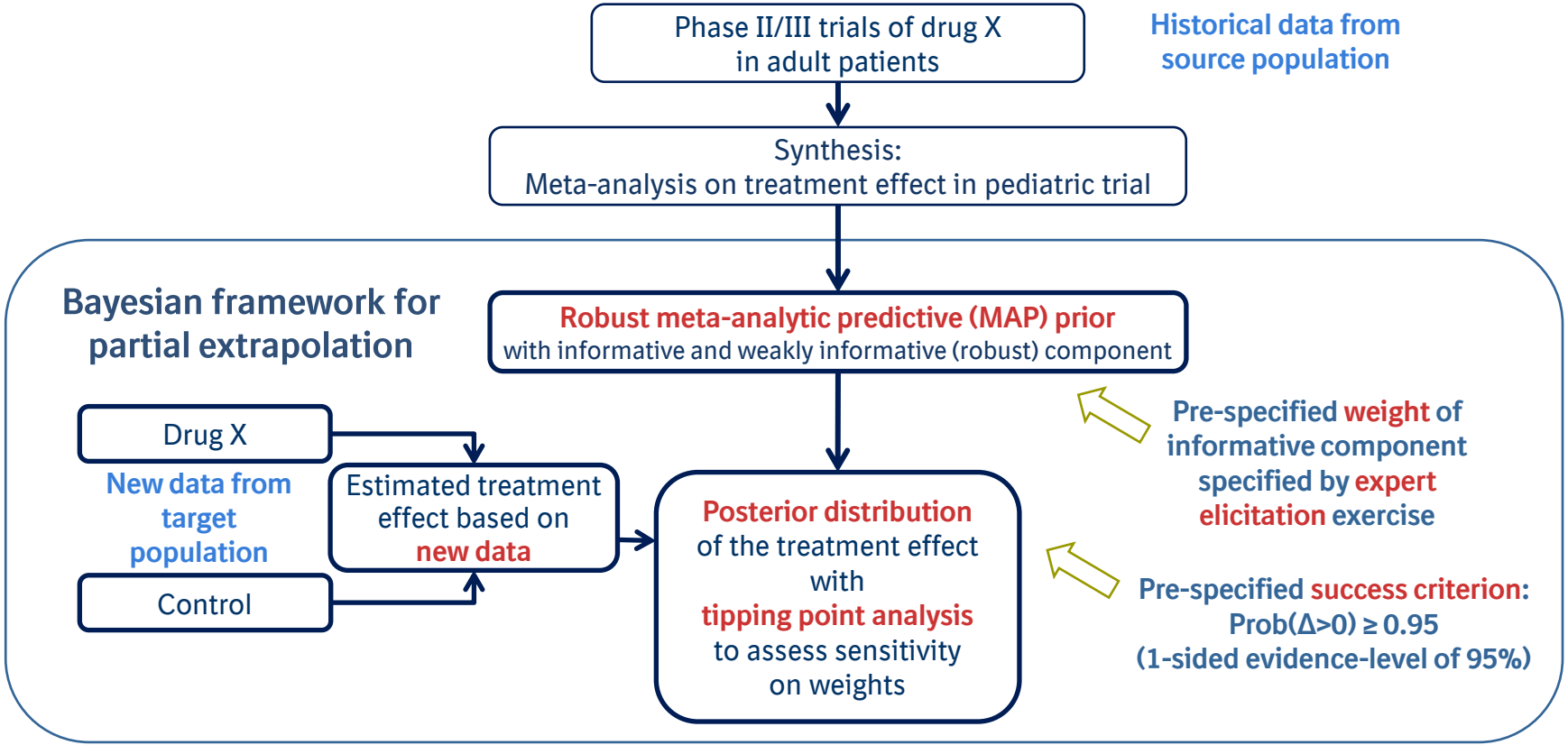
06 April 2022
EMA/CHMP/ICH/205218/2022
Committee for Medicinal Products for Human Use

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

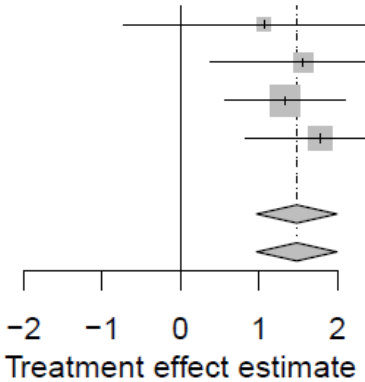
Bayesian statistics and meta-analytic predictive (MAP) priors



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

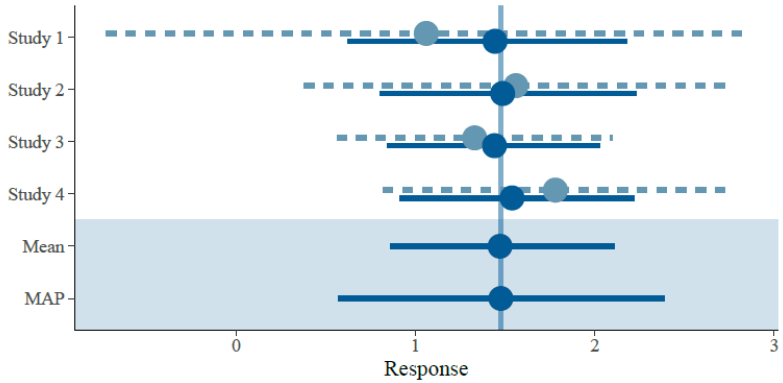
Study	TE	seTE	95%−CI	Weight (common)	Weight (random)
Study 1	1.06	0.9100	1.06 [−0.72; 2.84]	8.2%	8.2%
Study 2	1.56	0.6020	1.56 [0.38; 2.74]	18.8%	18.8%
Study 3	1.33	0.3920	1.33 [0.56; 2.10]	44.5%	44.5%
Study 4	1.78	0.4900	1.78 [0.82; 2.74]	28.4%	28.4%
Common effect model			**1.48 [0.97; 1.99]**	**100.0%**	**--**
Random effects model			**1.48 [0.97; 1.99]**	**--**	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.86$

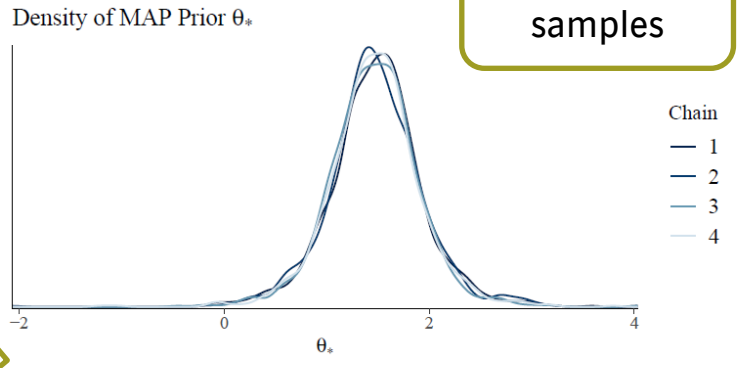


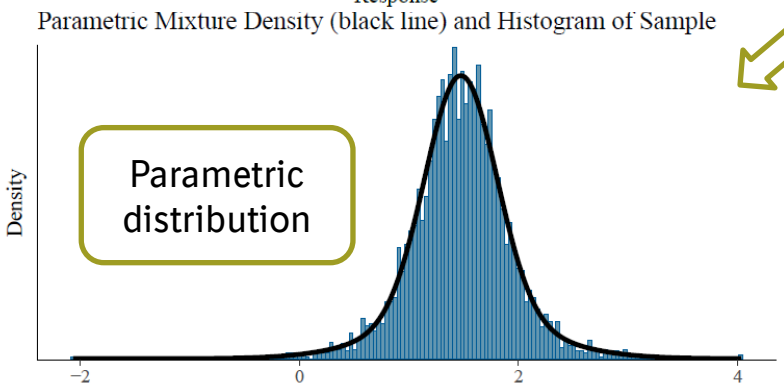
⇨ Down-weighting the evidence will be required

Bayesian meta-analysis and MAP prior derivation



MCMC samples



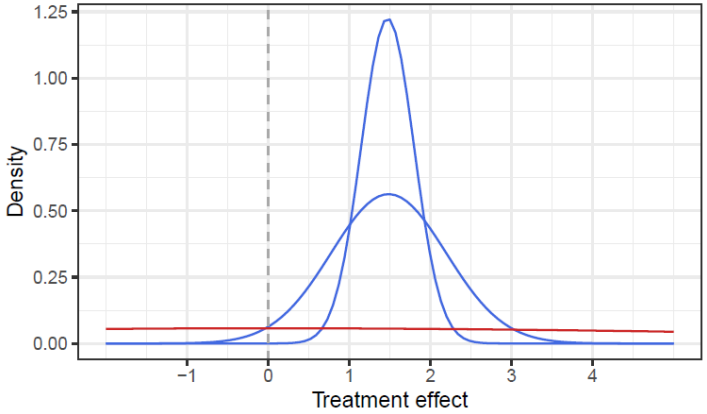


Parametric distribution

2-component mixture of normals:

	Comp 1	Comp 2
Weight	0.75	0.25
Mean	1.47	1.49
SD	0.33	0.71

Robustification of the MAP prior



3-component mixture of normals:

	Comp 1	Comp 2	Comp 3
Weight	0.75**w**	0.25**w**	**(1 - w)**
Mean	1.47	1.49	**0**
SD	0.33	0.71	**Large**

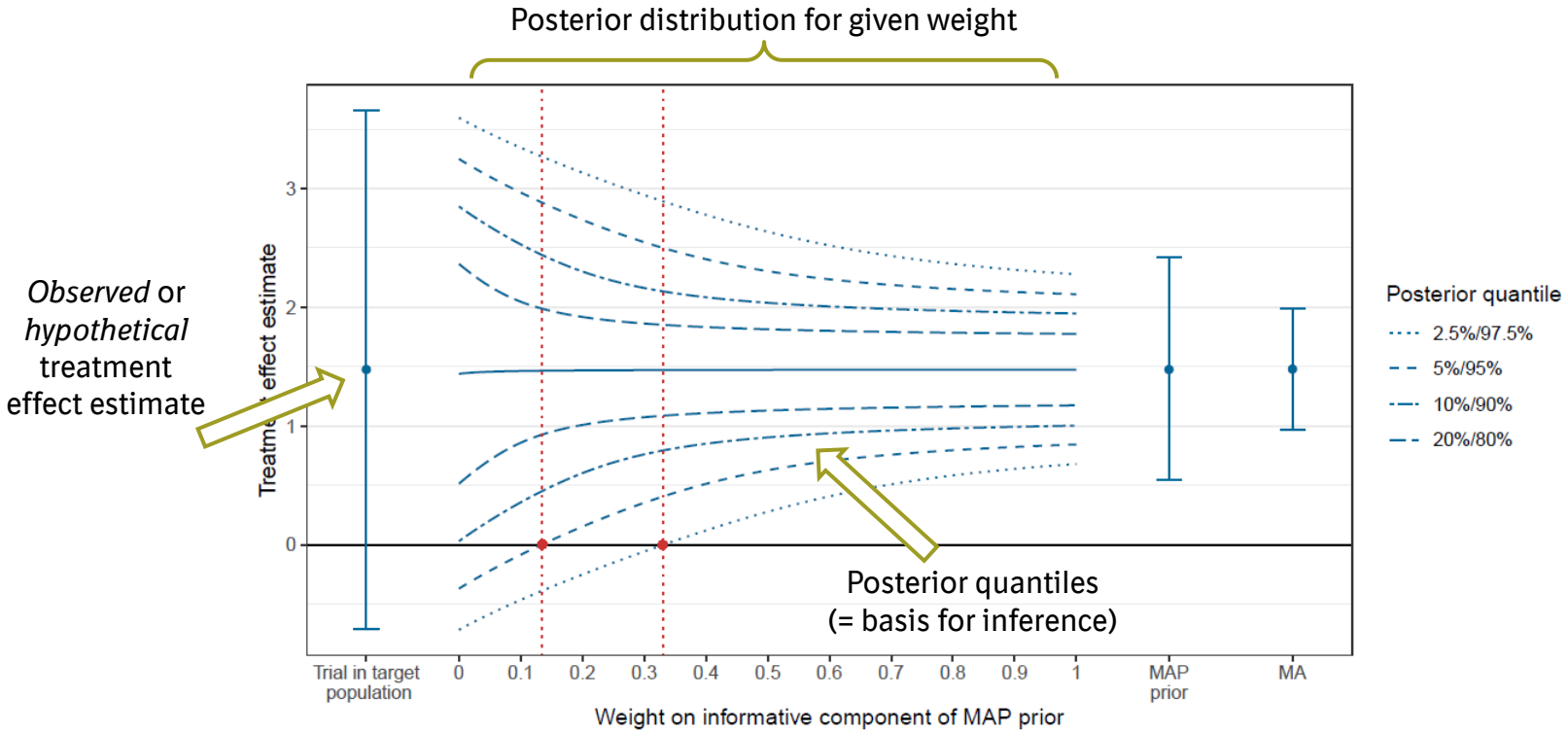
Informative component of weight = **w**

Robust component

- Borrowing becomes dynamic → less information borrowed with larger prior-data conflict
- The weight **w** is the probability of the target and source data being exchangeable
- How do we pre-specify **w** ?

A tipping point approach for analyses based on robust MAP priors

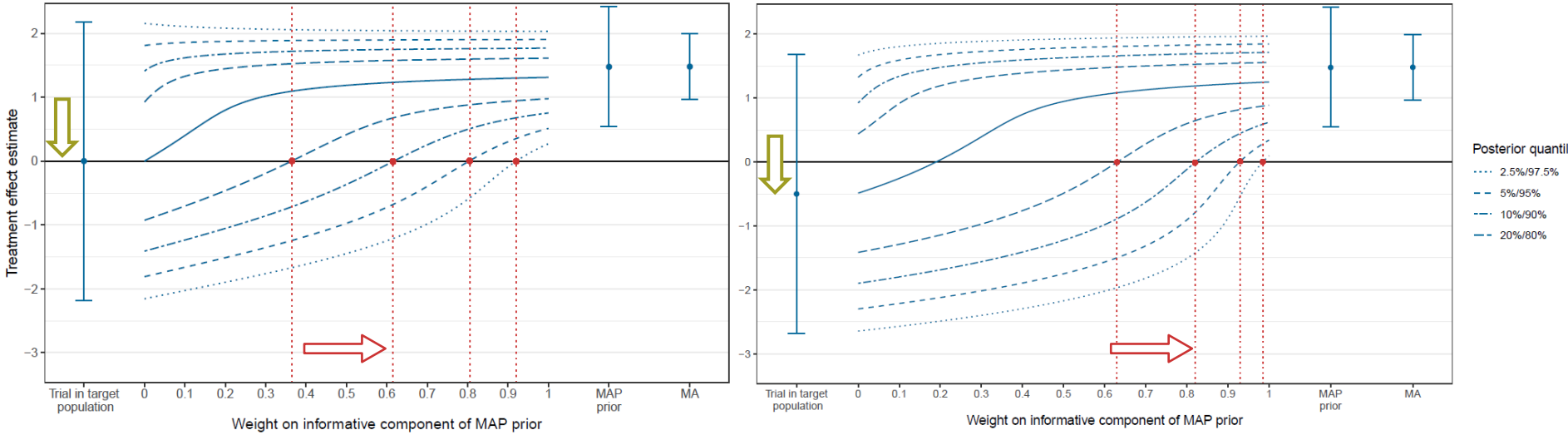
Tipping point analysis



Motivated by Best et al. *Pharm Stat* 2021; 20(3): 551-562

A tipping point approach for analyses based on robust MAP priors

Illustration of dynamic borrowing



A tipping point approach for analyses based on robust MAP priors

Uses of the tipping point analysis

Retrospectively

- Use in the interpretation of observed results
  - "reverse-Bayes" method (see Held et al., 2022)

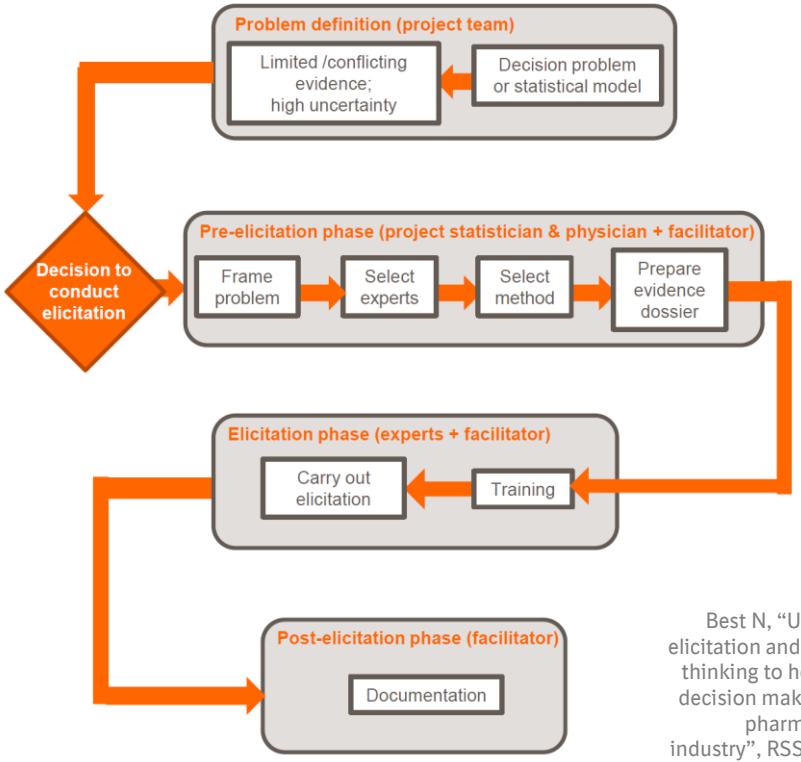
- Use in the trial planning to explore hypothetical scenarios and to pre-specify a primary weight of the informative MAP prior component
  - Can be used in expert elicitation exercises to determine prior weights

Prospectively

The role of expert elicitation

What is expert elicitation?

- A way through which **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

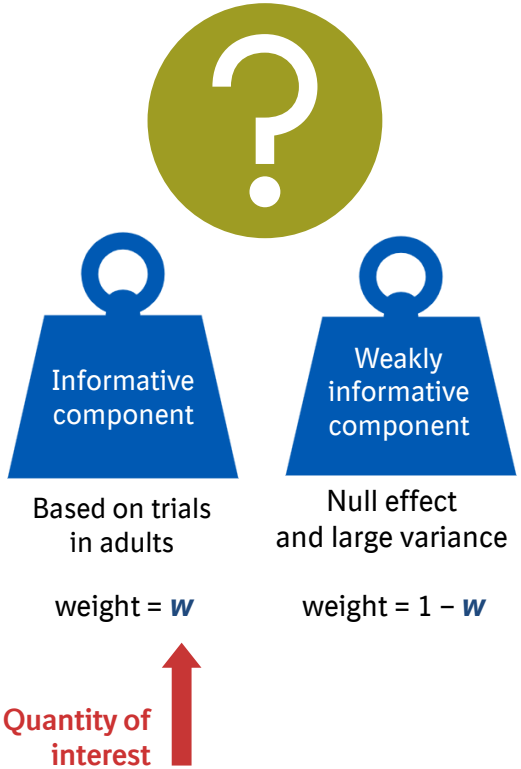


Best N, "Using prior elicitation and Bayesian thinking to help shape decision making in the pharmaceutical industry", RSS webinar, Dec 2015. [#]

The role of expert elicitation

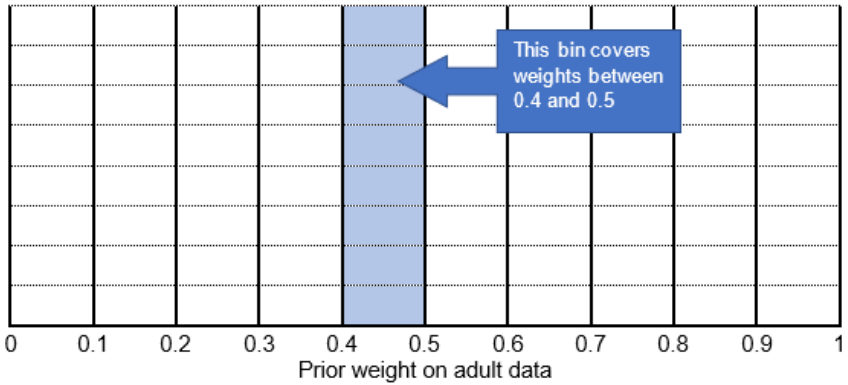
Basis for decision on pre-specified weight

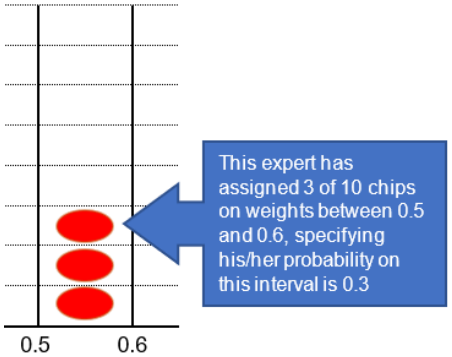
- Pre-clinical evidence
- Clinical evidence
- Personal clinical experience and opinion
- **Personal inferences in hypothetical scenarios**
  - **For given point and variance estimate, and one-sided evidence level**
  - **Tipping point analysis as a tool**
- Operating characteristics



Expert elicitation for determination of weights

Task description for elicitation via the ‘roulette’ method





10 chips need to be placed to create histogram-like data.

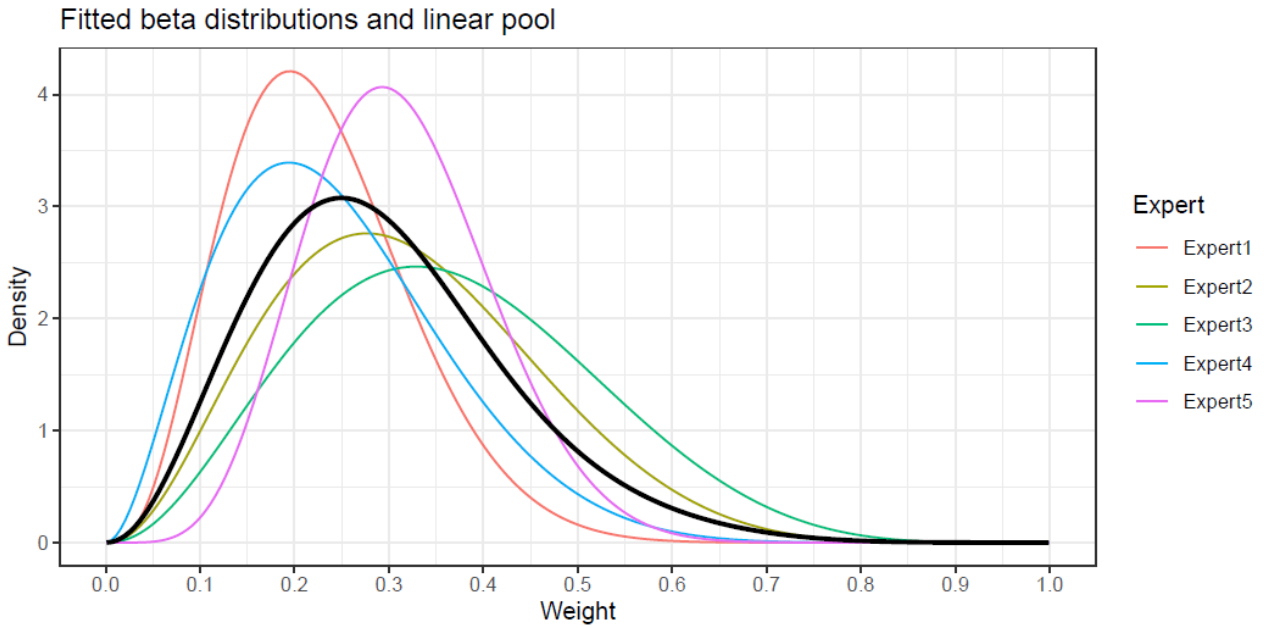
No particular shape or symmetry is needed.

Expert elicitation for determination of weights

Aggregated results

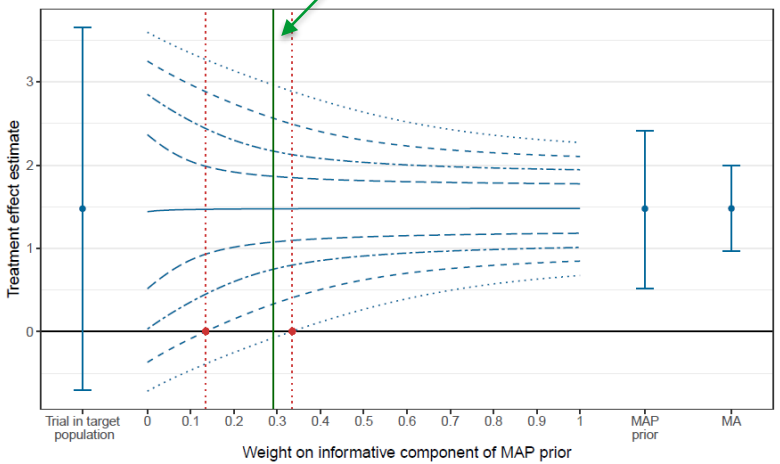
Descriptive statistics of linear pool:

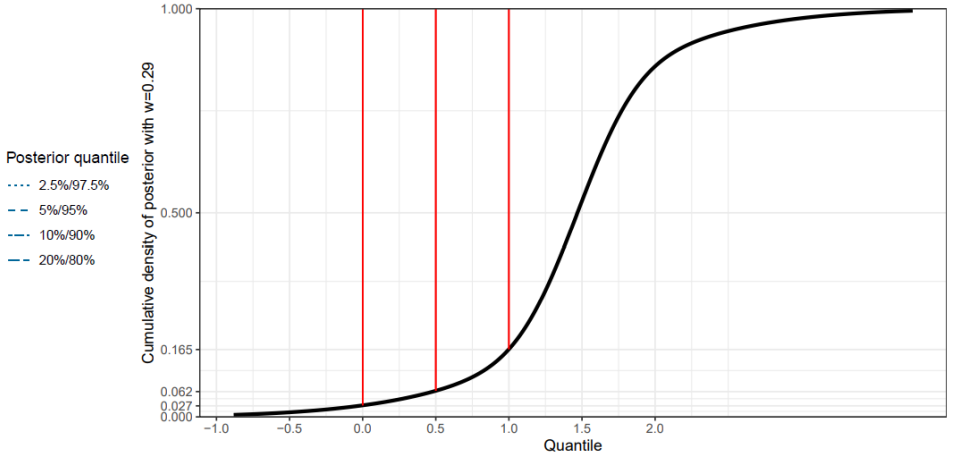
Mean	0.29
Q1	0.20
Median	0.28
Q3	0.37



Expert elicitation for determination of weights

Pre-specified primary weight (=0.29) → fully specified prior





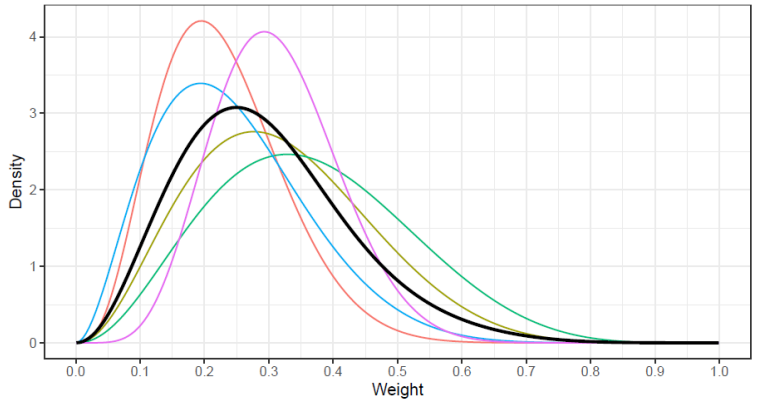
Prob(Δ>0) = 0.973 **Prob(Δ>0.5) = 0.938** **Prob(Δ>1) = 0.835**

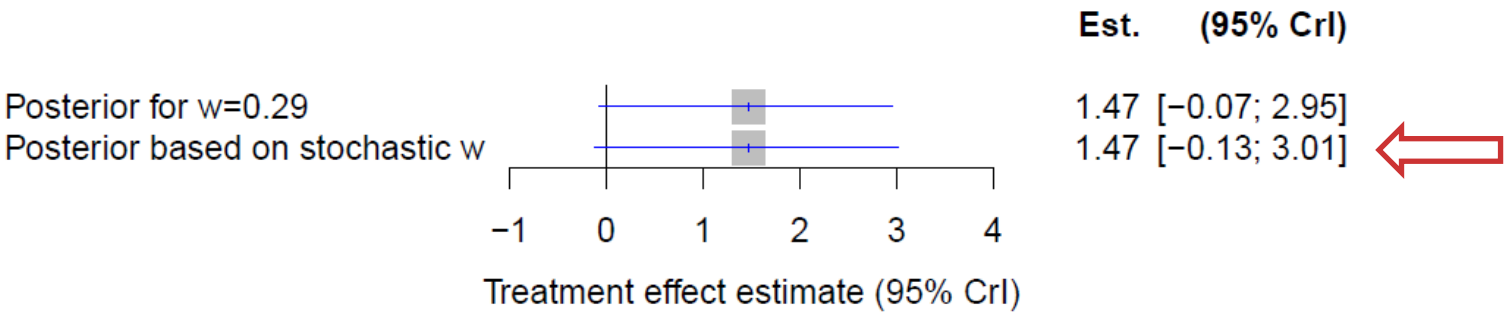
Pre-specified success criterion Prob(Δ>0) ≥ 0.95 is fulfilled
Importantly, any efficacy claim is conditional on acceptable safety and PK/PD results

Uncertainty propagation with elicited weights

Computing posteriors that reflect uncertainty in weights

- Expectation remains the same
- But CrI becomes wider
- Here based on 1000 weights drawn from beta mixture





Discussion points

- Validity
  - Complexity of ’statistical questions’ imposed on clinical 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

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. Mainly an implementation of an approach proposed by Best and colleagues (2021) is provided <doi:10.1002/pst.2093>. Further functions facilitate the specification of the robust MAP prior via expert elicitation (using the roulette method) and computation of the posterior distribution of the treatment effect with either fixed or stochastic expert-elicited weights. Intended use is the planning, analysis and interpretation of extrapolation studies in pediatric drug development, but applicability is generally wider.

Version:	0.3.9
Depends:	R (≥ 3.5.0)
Imports:	dplyr, purrr, ggplot2, RBesT
Suggests:	knitr, rmarkdown, testthat (≥ 3.0.0)
Published:	2022-12-07
Author:	Morten Dreher [aut], Christian Stock [aut, cre], Emma Torrini [ctb]
Maintainer:	Christian Stock <christian.stock at boehringer-ingelheim.com>
License:	GPL (≥ 3)
NeedsCompilation:	no
Materials:	README NEWS
CRAN checks:	tipmap results

Documentation:

Reference manual:	tipmap.pdf
Vignettes:	Introduction to the R package 'tipmap'

https://cran.r-project.org/web/packages/tipmap/index.html

Take-home messages

- In pediatric drug development it is often particularly challenging to make statistical inferences on efficacy and safety
- Bayesian techniques are increasingly used and recommended to incorporate evidence from trials in adults
- *Dynamic borrowing via mixture priors* in combination with *tipping point analysis* and *expert elicitation* to pre-specify priors, is a promising and guideline-compatible approach to partial extrapolation
- The proposed approach formalizes and brings transparency into a process that is often done informally and implicity

Thank you for your interest and attention

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Subjectivity of judgement

- “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

Role of facilitator

- Guides the experts, manages the process to ensure that all viewpoints are shared and debated, and, at the end, delivers the fitted probability distribution(s) representing the experts' beliefs
- Prompts the experts to explore areas of disagreement
- Needs to concentrate on language of experts and the scientific rationale for their beliefs, and challenge the experts if necessary to ensure ***the 'what they want to see'-aspect*** does not creep into the process."
- Needs familiarity with the possible sources of bias

Appendix

Risk of bias (I/III)

- Experts having a stake in the trial (KOLs, internal experts) clearly are at risk of conscious or unconscious biases

- Recommendation
  - Some experts should be independent
  - Plus a statistician

- More on biases in expert elicitation
  - Kynn (2008), The 'heuristics and biases' bias in expert elicitation. *J R Stat Soc Ser A Stat Soc*, 171: 239-264.
  - Dallow et al. (2018), Better decision making in drug development through adoption of formal prior elicitation. *Pharm Stat*, 17: 301– 316.

Risk of bias (II/III)

- Aspiration vs belief
  - Experts struggle with eliciting “true” treatment effects: effects wanted to be observed vs effects that would be clinically relevant vs realistic treatment effects
  - Make these distinction: the “what they want to see”-aspect should not creep into the process

- Over-optimism
  - Document potential sources of known bias (eg, conflicts of interest) to create transparency
  - Ensure that experts provide justification for their beliefs
  - “Portfolio priors” can be helpful: sharing success rates for assets at a particular stage with either disease or broader industry levels can help calibrate risks of novel mechanisms not translating to clinical efficacy

Risk of bias (III/III)

- Anchor-and-adjustment heuristic
  - People tend to stick to closely to an initial anchor and do not adjust sufficiently, leading to anchoring bias in their judgements
- Risk of misunderstanding statistical quantities
  - Good understanding of probability and other terms (eg, quartiles) is needed
  - Quartile approach: experts required to give their median, lower 25% and upper 75% quartiles for the true value of the quantity of interest.
  - May result in distributions not matching experts belief
  - Preferred method roulette approach is more intuitive and less prone to misunderstanding
    - Bringing sampling uncertainty into elicited prior
- And several others
  - Risk of experts providing symmetrical “bell-shaped” distributions
  - Risk of biased information