

Bayesian borrowing for pediatric extrapolation is easy. Not.

Bayesian Biostatistics Conference Bayes 2025

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Disclaimer

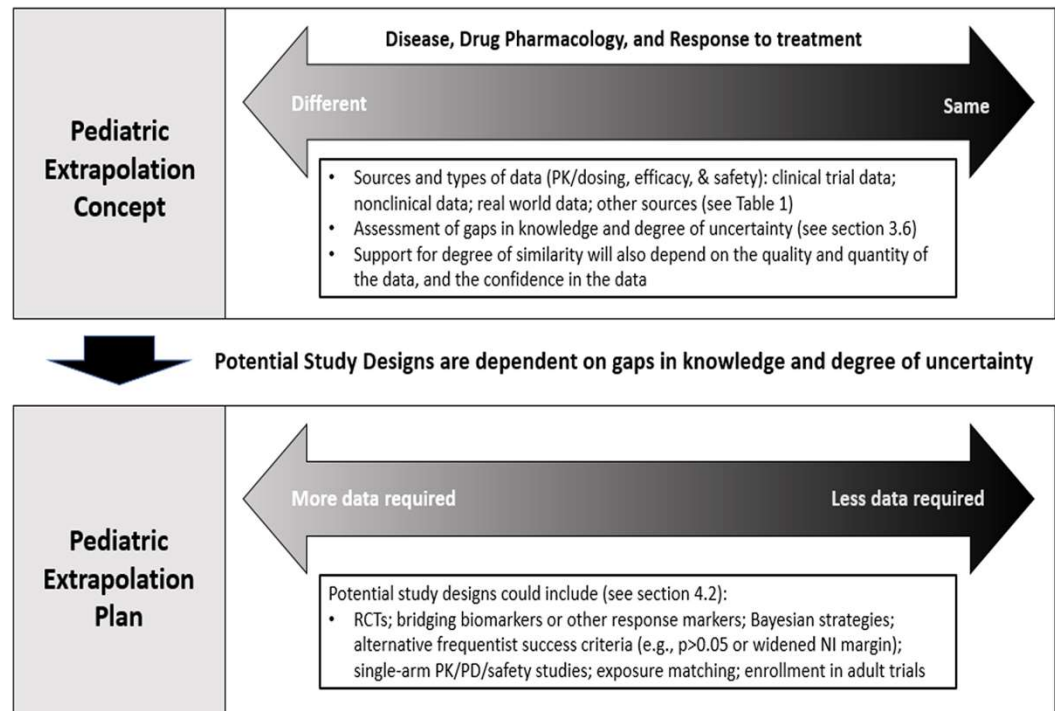
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Bayesian borrowing for pediatric efficacy analysis

ICH Guidance on pediatric extrapolation

- “**Pediatric extrapolation**” is an approach to providing evidence in support of effective and safe 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 and reference (adult or other pediatric) population

Figure 1: Pediatric extrapolation as a continuum



ICH E11(R1)

ICH E11A

ICH E11A Guideline on pediatric extrapolation

- Incorporate information from the reference population in the analysis of the target population, for example, through **Bayesian approaches**
- **Combine data from reference and target populations**, weighting the contribution of the reference data based on an evaluation of similarity between reference and target populations
- Consider the **trade-off** between bias, power (false negative), and type I error (false positive) rate
- Methods exist to **limit borrowing** if the data generated are not similar to the prior belief about them
- Prior weight of informative component of the mixture prior considered as the prior belief about the plausibility and acceptability of the extrapolation concept. The closer the value to 1, the more confidence there is.

ICH E11A Guideline on pediatric extrapolation

- Document how uncertainty has been defined. Specify any relevant assumptions with respect to the definition or expression of uncertainty.
- Evaluate the study design including under scenarios inconsistent with planning assumptions such as where there is a prior-data conflict. This is especially important when Bayesian designs are used.
- Establish operating characteristics (OC) of the design (e.g., false positive and false negative error rates), properties of the estimator (bias, variance), and properties of intervals (e.g., frequentist coverage of confidence or Bayesian credible intervals).
- When the sample size limited, relative importance of false positive and false negative error rates may be modified from convention
- If Bayesian design uses an informative prior, strict control of the type I error rate is not possible.

Some examples

- FDA (2018): Multi-disciplinary Review and Evaluation Benlysta® (belimumab) for Intravenous Infusion in Children 5 to 17 Years of Age with SLE.
 - Best et al. (2025): Beyond the Classical Type I Error: Bayesian Metrics for Bayesian Designs Using Informative Priors
- Maher et al. (2024): Estimating the effect of nintedanib on forced vital capacity in children and adolescents with fibrosing interstitial lung disease using a Bayesian dynamic borrowing approach
- Sailer et al. (2025): Pharmacometrics-Enhanced Bayesian Borrowing for Pediatric Extrapolation - A Case Study of the DINAMO Trial.

So why don't we always do Bayesian borrowing for pediatric extrapolation?

- Sometimes exposure matching sufficient, no efficacy study required
- Sometimes the disease is not sufficiently similar between adults and children or doubts regarding comparable outcomes exist
- Sometimes there is no relevant data to borrow from
- Otherwise it's deceptively easy to perform the extrapolation
- Let's look at a few potential statistical questions that may come up

Model

Consider a new pediatric development project

- Hypothetical example based on actual clinical trial in published literature
- Benlysta: sBLA 125370/S-064 for belimumab (Benlysta) IV formulation for use in children aged 5–17 years
 - Best et al. 2025 Statistics in Biopharmaceutical Research
 - Response at week 52 on the SLE responder index
 - log odds ratio Benlysta vs. Placebo in adult trials: $N(0.48, 0.121^2)$ in 1125 patients (ESS=562.5)
 - New pediatric trial: N = 100 total (1:1 randomised, ESS=50), sample size limited by feasibility
 - Decision rule: Declare new trial positive if $P(\theta_{pediatric} > 0 | y_{pediatric}) \geq \gamma = 0.975$
 - Should we borrow from adult data?
 - What is the prior for the pediatric trial efficacy?

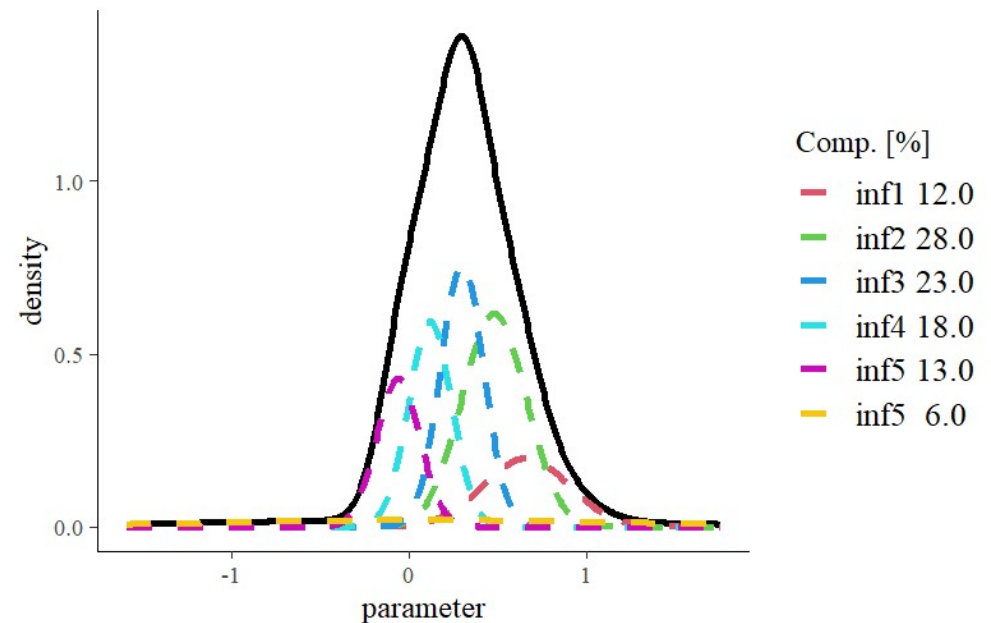
Data generating process: relationship adult, pediatric data

- **Robust mixture prior** for pediatric effect 1
- Same distribution as adults ($1-w$)
- or robust component (w)
- plausible design prior?
- tuning parameter: robust component to achieve dynamic borrowing, more favorable OC?
- Ratta et al 2025: robust component with small w & ESS may have better OC and be more plausible than unit info prior

- **Meta-analytic predictive prior** (Schmidli et al., 2014) 2
- Hierarchical model to relate adult, pediatric trial outcomes
- Robustification inbuilt, could add robust component on top
- Pediatric trial not just another trial in adults: use differential heterogeneity?

Data generating process: relationship adult, pediatric data

- Formal definition of joint distribution of effects?
- Sometimes: Expectation that effect differs but still is related, e.g.
 - Covariate adjusted effects
 - **Asymmetry**: If effect in adults large: 3 pediatric effect large or less, if no effect in adults: no effect in children
 - **Attenuated effect likely**, 15% no/negative effect in children, 33% effect larger than observed in adults *skeptical prior?*



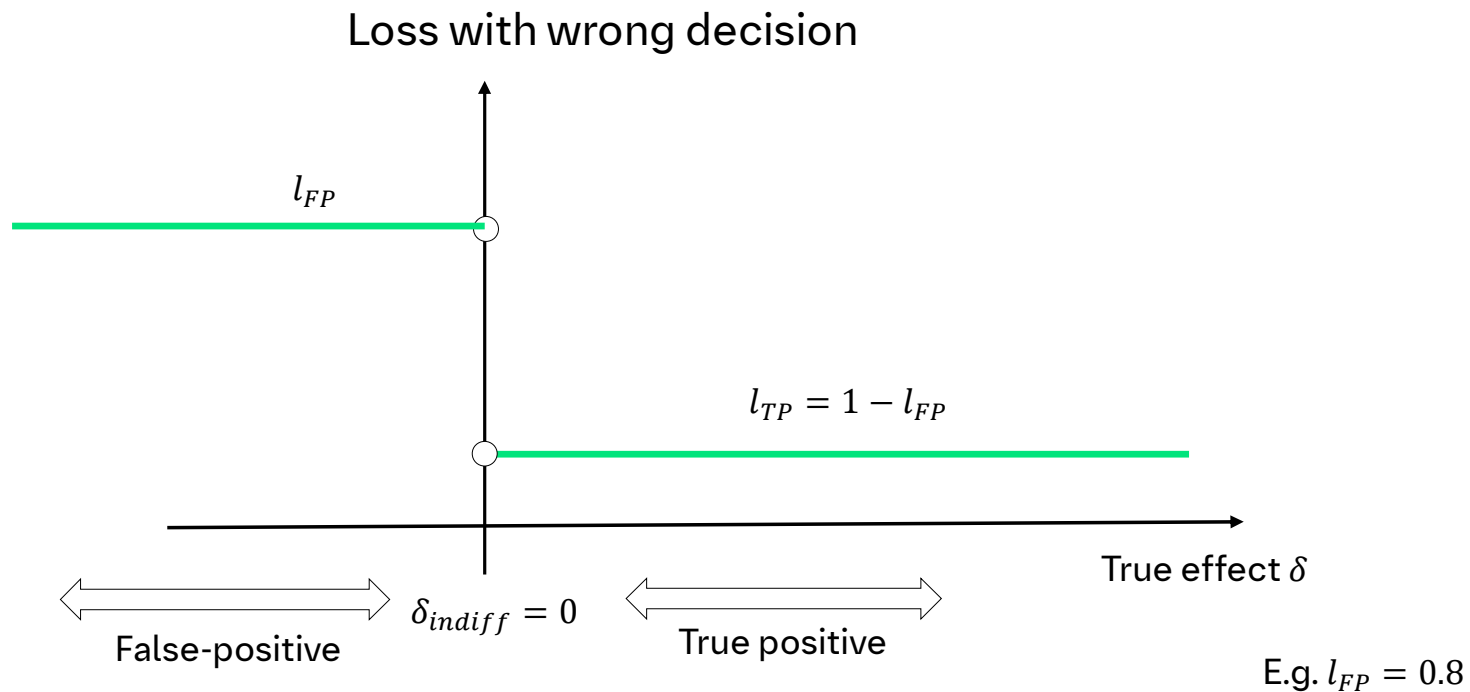
Mixture prior representing asymmetric, attenuated effect likely.
ESS=102

Operating characteristics

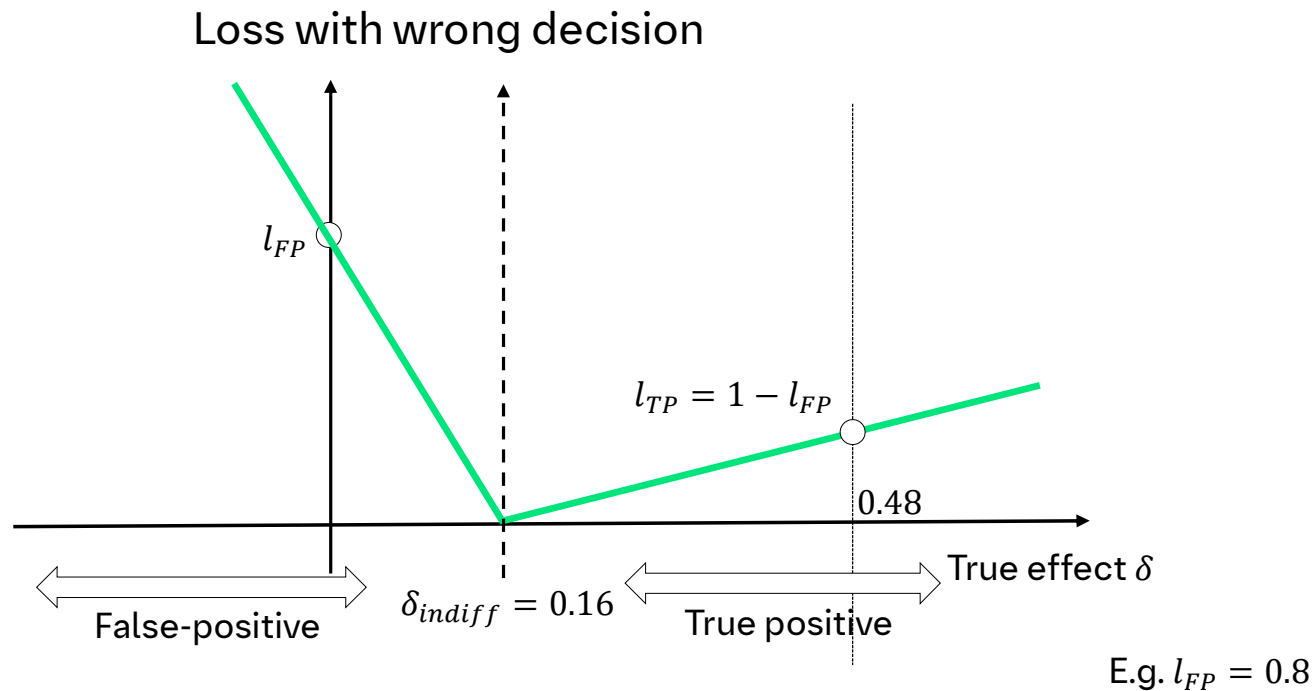
Operating characteristics

- Type I error
- Power
- OC related to estimation: bias, MSE, coverage of interval estimates
- We know we can't beat power of frequentist design with same type I error rate (Kopp-Schneider et al. 2020)
- Should we then not also look at Bayesian OC related to decision making if we want to borrow information? (e.g. utility metrics in Calderazzo et al. 2022)
- Let's look at some expected loss criteria

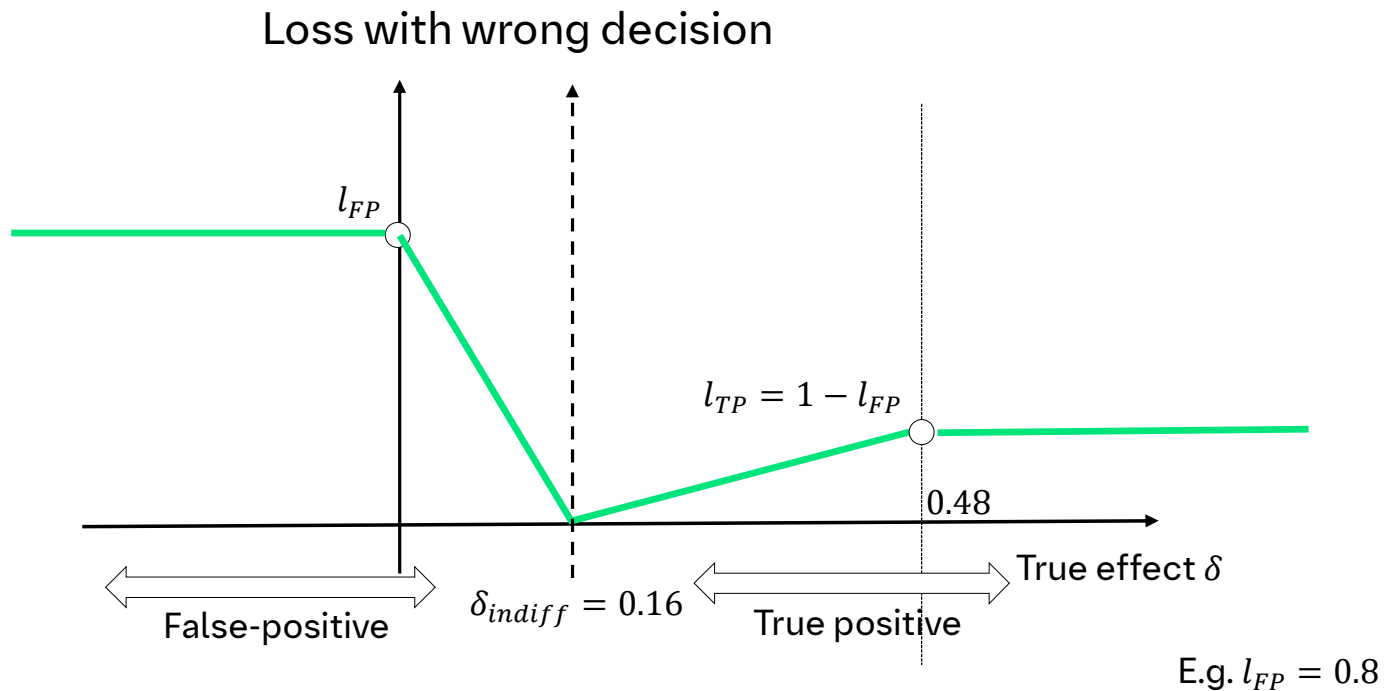
Loss functions – Constant loss



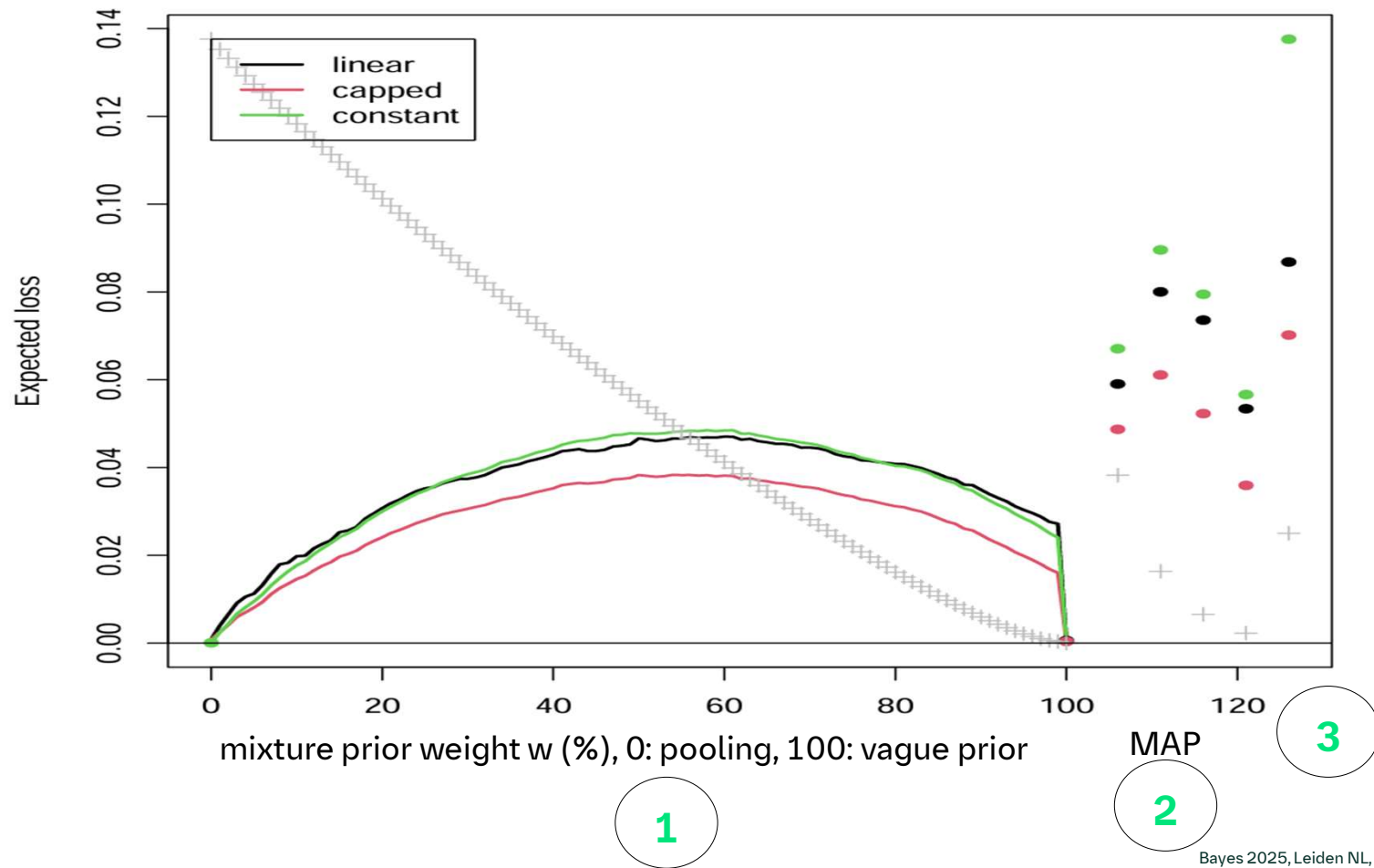
Loss functions – Linear loss with risk-benefit boundary



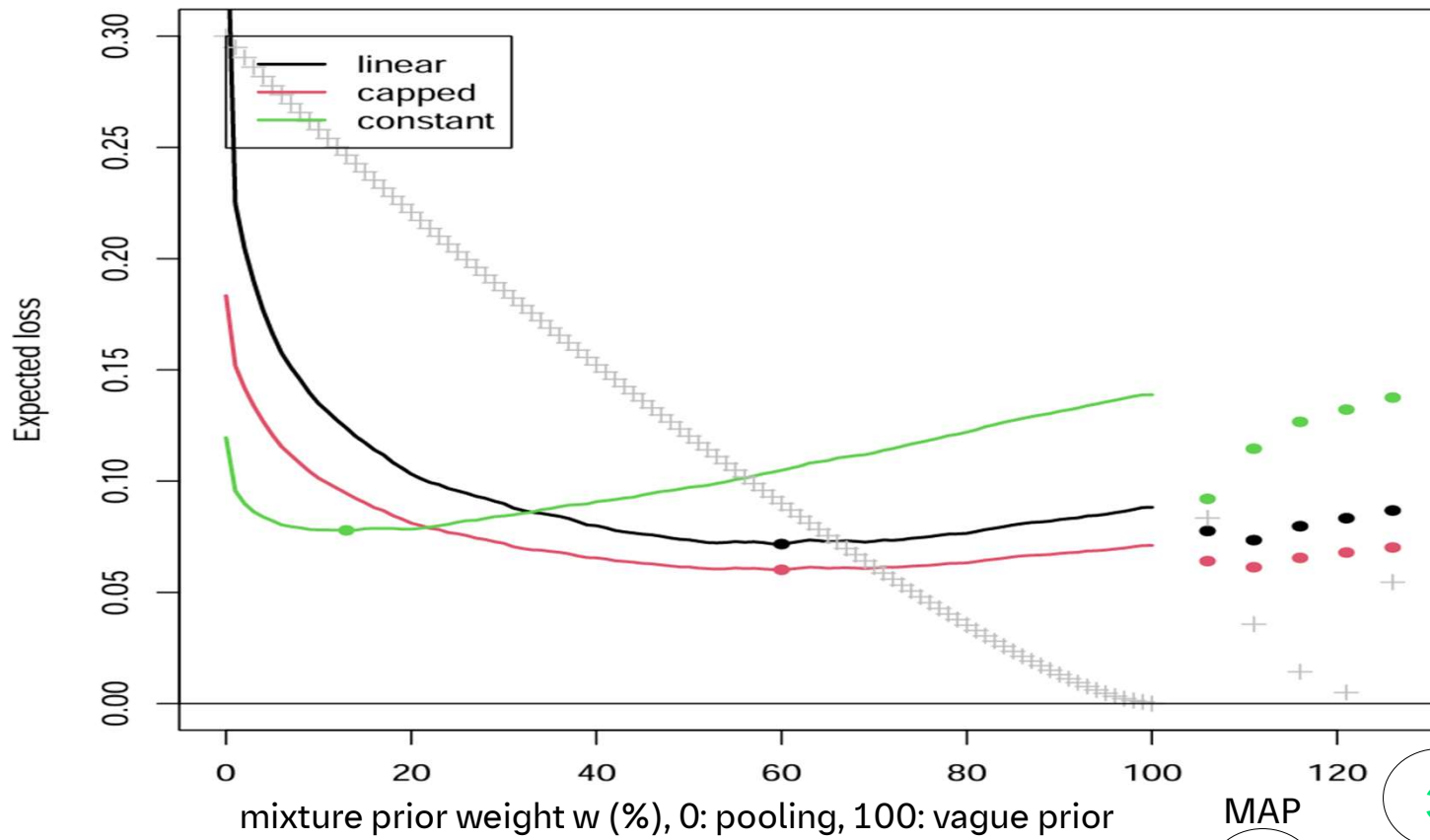
Loss functions – Capped loss with risk-benefit boundary



Expected loss: design prior = analysis prior



Expected loss: design prior = prior 3



ESS, expected loss, power and type I error rate

Analysis prior	ESS prior	E(const. loss) with prior 3	E(linear loss) with prior 3	Power ($\theta_{ped.} = 0.48$)(%)	Type I error prob.(%)
Adult data (full borrowing)	562.5	0.120	0.368	100	100
Robust mixture (unit-info centered at 0.48 with weight 0.14)	455	0.078	0.124	89.5	53.3
Robust mixture (unit-info centered at 0.48 with weight 0.61)	163	0.105	0.072	53.0	13.4
Vague, centered at 0.48 (no borrowing)	0.0008	0.139	0.088	21.6	2.5
MAP ($\tau = \sigma/8$)	71	0.115	0.073	43.6	9.1
Prior 3	102	0.138	0.089	22.8	2.8

ESS, expected loss, power and type I error rate

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Vague, centered at 0.48 (no borrowing)	0.0008	0.139	0.088	21.6	2.5
Vague, decision rule: $P(\theta_{ped} > 0 y) \geq 0.866$	0.0008	0.105	0.072	53.2	13.4

Discussion

- Evaluation beyond type I error rate, power rarely used in clinical practice
 - Many options, no standards
- Specification of design prior: plausible / mechanistic DGP / subjectivity vs. simplicity, restricted degrees of freedom in specification
- Specification of loss function: what loss, for whom; plausible / subjectivity vs. simplicity, restricted degrees of freedom in specification
- Compare candidate analysis priors for „same“ decision rule $P(\theta_{pediatric} > 0 | y_{pediatric}) \geq \gamma = 0.975$ or optimize over all possible analysis priors, decision rules?
- What's a good quantitative answer to „Will borrowing lead to better decisions in the planned trial?“

Questions?

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