Informative priors in clinical trials

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Outline

Introduction

Discussion τ prior choice

Summary

Introduction

Use of historical control data in clinical trials

Goal: reduce control group sample size while maintaining power

Design a (**future**) trial using synthesized evidence on control:

1. Collect historical (control) data from relevant literature *systematically*
2. Evaluate heterogeniety of historical data
   - data quality
   - patient population
   - trial design
3. Pre-specify trial protocol
   - what is the evidence used precisely?
   - how is the main analysis conducted?
4. Document properties of trial design using historical evidence
   - type I error
   - power

`RBesT` R package on CRAN supports steps 3-4

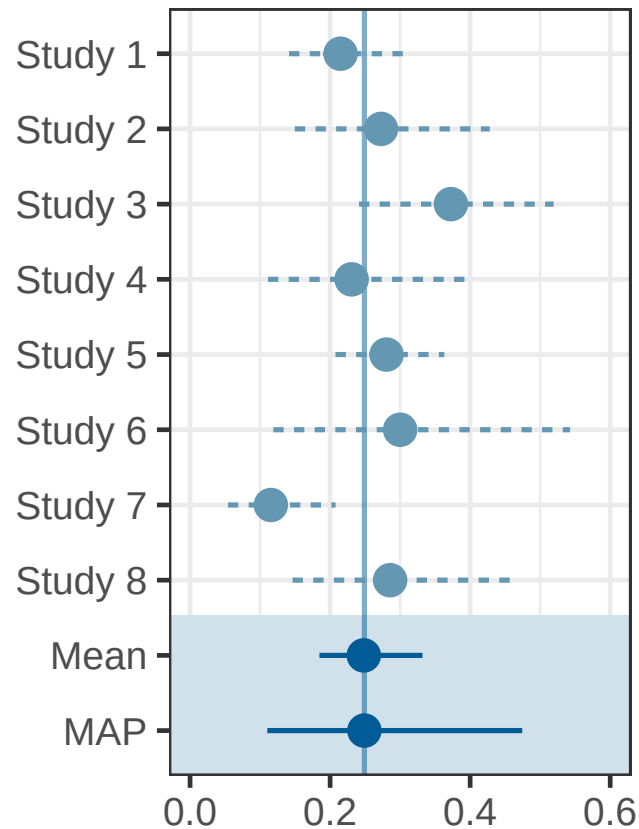
Meta-Analytic-Predictive prior approach

A MAP prior is (in essence) a data-driven prior

$$y_i|\theta_i, n_i \sim \text{Binomial}(\theta_i) \quad \& \quad \text{logit}(\theta_i)|\beta, \tau \sim \text{Normal}(\beta, \tau^2)$$

$$\beta \sim P_\beta \quad \& \quad \tau \sim P_\tau$$

- **Mean**: $p(\beta|y)$ is the population mean or the *typical trial result*
- **MAP**: $p(\theta_*|y)$ is the *predictive distribution* for the mean of a *future trial* $\Rightarrow$ model is **generative**
- **Between-trial heterogeneity** τ critically governs borrowing
  - $\tau \to 0 \Rightarrow$ pooling
  - $\tau \to \infty \Rightarrow$ stratification
  - **not informed from data alone** as often only 3, 2 or just 1 study!



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Discussion τ prior choice

Prior choices for P_τ and P_β endpoint specific

Binary and normal endpoints

Endpoint		very conservative[1] τ prior	conservative[1,2] τ prior	β prior[3]
Binary	$0.2 < \pi < 0.8$	$\mathrm{N}^+(0, 1)$	$\mathrm{N}^+(0, (1/2)^2)$	$\mathrm{N}(0, 2^2)$
Normal	known σ	$\mathrm{N}^+(0, (\sigma/2)^2)$	$\mathrm{N}^+(0, (\sigma/4)^2)$	$\mathrm{N}(\mu_0, \sigma^2)$

1. very conservative, see *Neuenschwander et al., 2010*
2. less heterogeneous data as often seen empirically in meta-analysis, see *Friede et al., 2016*
3. unit-information prior for β, see *Kass & Wasserman, 1995*
   - $\sigma_1 \approx 2$ for $\log$-odds scale
   - μ_0 set problem dependent (often 0)

These priors have been studied in the literature and are known for reasonable properties in a wide range of settings of early drug development phases.

IQWiG analysis: data-driven prior derivation

Analysis of meta-analyses

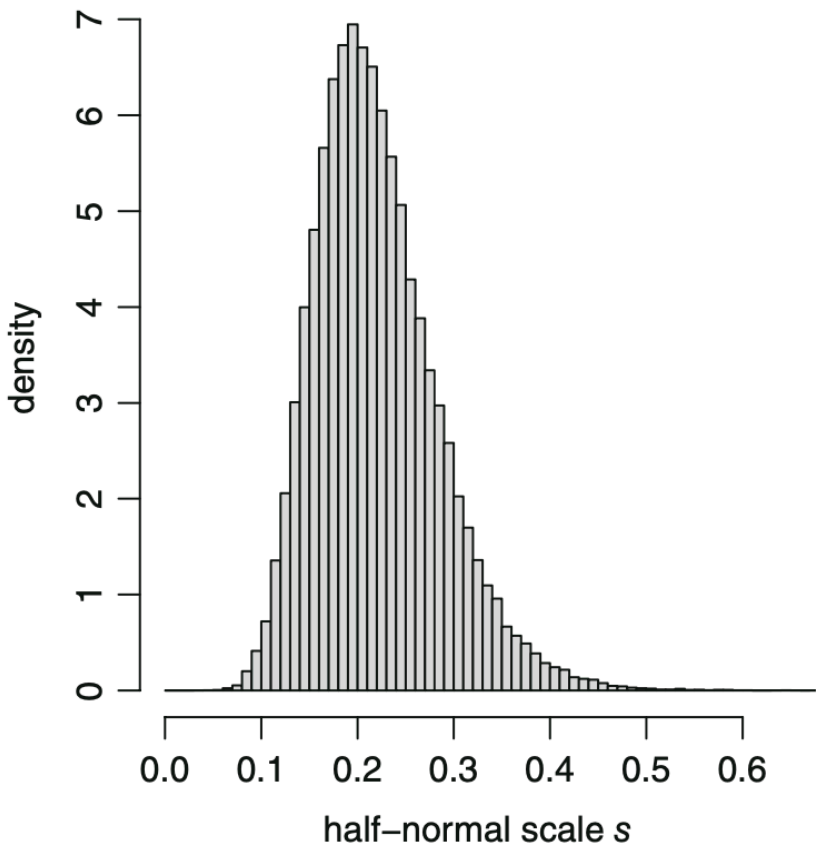
$$y_{ij}|\mu_j, \tau_j \sim \text{Normal}(\mu_j, \sigma_{ij}^2 + \tau_j^2)$$
$$\mu_j|\mu_p, \sigma_p \sim \text{Normal}(\mu_p, \sigma_p^2)$$
$$\tau_j|s \sim P_\tau(s)$$
$$s \sim \text{Uniform}(0, b)$$

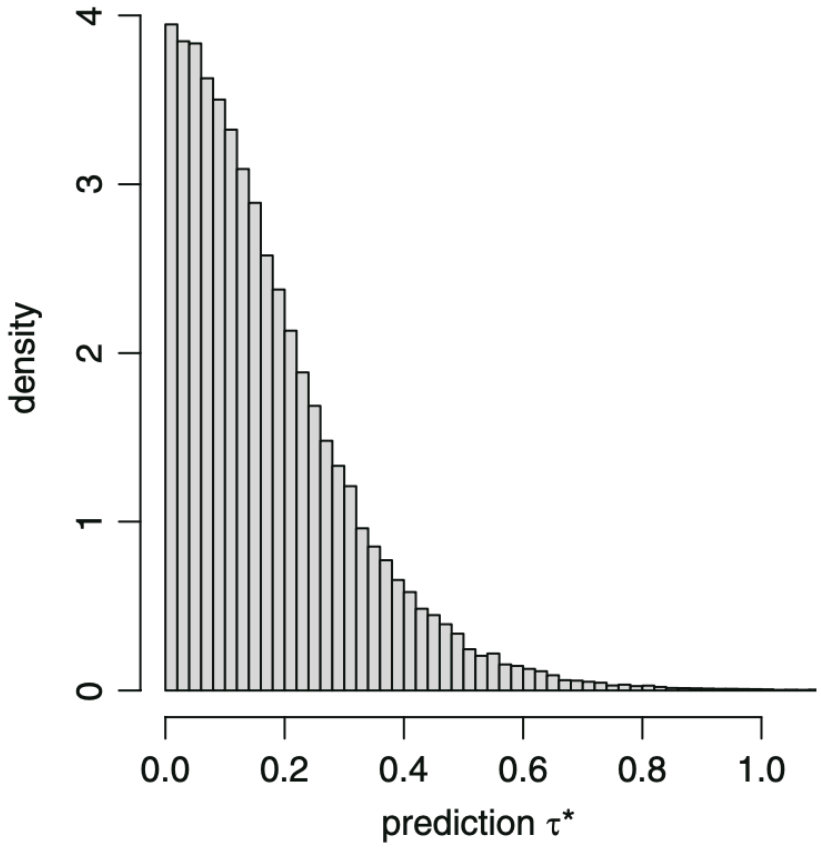
- j meta-analysis, $i = 1, ..., k_j$ study within meta-analysis j
- model aimed at common τ prior P_τ with scale parameter s
- $\log$-OR analysis uses $\mu_p = 0$, $\sigma_p = 100$, $b = 10$
  - The choice of $s \sim \text{Uniform}(0, b)$ with large b *can* make results depend on the choice of b. As the data-set seems to be large, this is likely not an issue, but can become relevant for smaller data-sets. Refer to Gelman (2006) or Gelman et al., BDA3, section 5.7, p.128.

Refer to *Röver et al., 2023*

IQWiG analysis results

Figure 1, Röver et al., 2023, log-OR, P_τ = HalfNormal





$p(s|y)$ posterior distribution s

$p(\tau^\star|y)$ predictive distribution $\tau^\star$ (marginalizes over $p(s|y)$)

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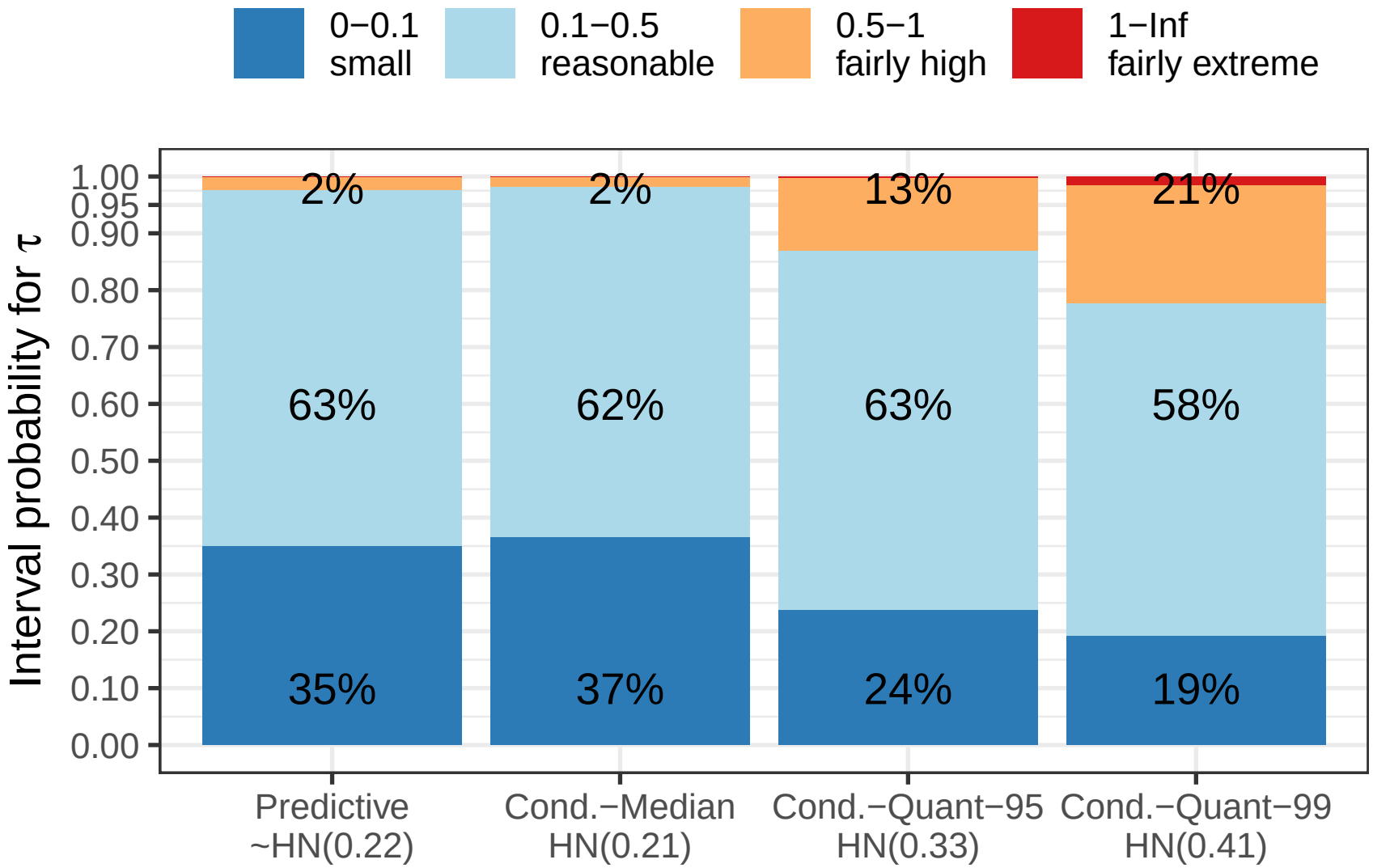
Derived τ prior with a half normal distribution

Heterogeneity classification for log-OR by Spiegelhalter



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Summary

Summary historical control data
Informative MAP priors are widley in use

- Attractive for patients
  - Avoids unnecessary enrollement to control treatment
  - Unequal randomization (higher chance to recieve active treatment)
- Faster trial conduct
- Broad application in drug development (early phases, pediatrics, rare diseases)

- Data missing for other endpoints
- Study results become dependent on analysis assumptions
- Requirement to align all stakeholders

Summary empirical heterogeneity prior

Data-driven basis for heterogeneity prior P_τ

- Analysis model accounts for full uncertainty
- $p(\tau^\star|y)$ is "best" for IQWiG compiled data set y
- Prior evaluation shows mostly *small to moderate* degree of heterogeneity (in line with PICO framework used for trial inclusion criteria)
- Publication of full data-set & programs desirable for full transparency
- Extension of model to by-arm estimates could result in applications of borrowing historical controls
- Choice of final $p(\tau)$ should be based on predictive from a Bayesian perspective (marginalizes out uncertainty)

Backup

Use of informative priors in biostatistics
Applications in drug development

- **historical control** data
  - **sample size reduction in control group** while maintaining statistical power
  - aid in trial design to define true effect
  - aid in assessment of design parameters like variability
  - probability of success
- pediatric extrapolation
  - predicting pediatric outcomes based on adult data
    Are children like small adults?
  - combine discounted adult evidence with pediatric data
- historical treatment effect data (network meta-analysis)
  - support futility decisions at interim analysis
  - derivation of non-inferiority margins
  - sample size reduction for head-to-head comparison trials

Generalized Meta-Analytic-Predictive model

Hierarchical model to obtain predictive of mean parameter

Y is the (control) group summary data for H historical trials

$$Y_h|\theta_h \sim f(\theta_h) \qquad \forall\ h \in [1, H]$$
$$Y_*|\theta_* \sim f(\theta_*) \qquad \text{for new trial (generative)}$$

Exchangeability assumption:

$$g(\theta_h)|\beta, \tau \sim \text{Normal}(\beta, \tau^2) \qquad \forall\ h \in [1, H]$$
$$g(\theta_*)|\beta, \tau \sim \text{Normal}(\beta, \tau^2) \qquad \text{for new trial (generative)}$$

- f likelihood / g link function
  Binomial/logit, Normal (known σ)/identity or Poisson/log
- β population mean with prior Normal(m_β, s_β^2)
- τ between-trial heterogeneity with prior P_τ

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The hierarchical model: A data driven prior

The normal-normal hierarchical model with known σ and τ with n_h measurements per group is:

$$y_h|\theta_h, \sigma \sim \text{Normal}(\theta_h, \sigma^2)$$
$$\theta_h|\beta, \tau \sim \text{Normal}(\beta, \tau^2)$$

Then the *conditional* posterior on y_h for θ_h is (β & τ known):

$$\theta_h|\beta, \tau, y_h \sim \text{Normal}(\hat{\theta}_h, V_h)$$

$$\hat{\theta}_h = \frac{\frac{1}{\tau^2}\beta + \frac{1}{se_h^2}\bar{y}_h}{\frac{1}{V_h}} \text{ and } \frac{1}{V_h} = \frac{1}{\tau^2} + \frac{1}{se_h^2}$$

The per-group mean $\hat{\theta}_h$ is a precision weighted average of the data-mean $\bar{y}_h$ and the population mean β

References

Gelman, A. (2006) Prior distributions for variance parameters in hierarchical models (comment on article by browne and draper). *Bayesian Analysis*, **1**, 515–534.

Gelman, A., Carlin, J.B., Stern, H.S., Dunson, D.B., Vehtari, A. and Rubin, D.B. (2014) *Bayesian Data Analysis*, Third edit.

Neuenschwander, B., Capkun-Niggli, G., Branson, M. and Spiegelhalter, D.J. (2010) Summarizing historical information on controls in. *Clin Trials*, **7**, 5–18.

Röver, C., Bender, R., Dias, S., Schmid, C.H., Schmidli, H., Sturtz, S., et al. (2021) On weakly informative prior distributions for the heterogeneity parameter in Bayesian random-effects meta-analysis. *Research Synthesis Methods*, **12**, 448–474.

Röver, C., Sturtz, S., Lilienthal, J., Bender, R. and Friede, T. (2023) Summarizing empirical information on between-study heterogeneity for bayesian random-effects meta-analysis. *Statistics in Medicine*, **42**, 2439–2454.

Schmidli, H., Gsteiger, S., Roychoudhury, S., O'Hagan, A., Spiegelhalter, D. and Neuenschwander, B. (2014) Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biom*.

Spiegelhalter, D.J., Abrams, K.R. and Myles, J.P. (2004) *Bayesian Approaches to Clinical Trials and Health-Care Evaluation: Spiegelhalter/Clinical Trials and Health-Care Evaluation*. John Wiley & Sons, Ltd, Chichester, UK.

Weber, S., Li, Y., Seaman III, J.W., Kakizume, T. and Schmidli, H. (2021) Applying Meta-Analytic-Predictive Priors with the R Bayesian Evidence Synthesis Tools. *Journal of Statistical Software*, **100**, 1–32.

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