Bayesian sample size re-estimation incorporating external data

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Introduction

- **Historical data on nuisance parameters** to inform design (in particular sample size) of a study
  - Historical data can be formulated as prior distribution
  - Schmidli *et al.* (2016) formalized summarizing and incorporating prior information into the sample size planning

- **Sample size re-estimation** limits the negative effect of nuisance parameter misspecification on statistical power
  - Nuisance parameter estimates can have high uncertainty when the internal pilot study is small

- Idea: Reduce uncertainty through incorporating prior information

Statistical model

- Normally distributed outcomes

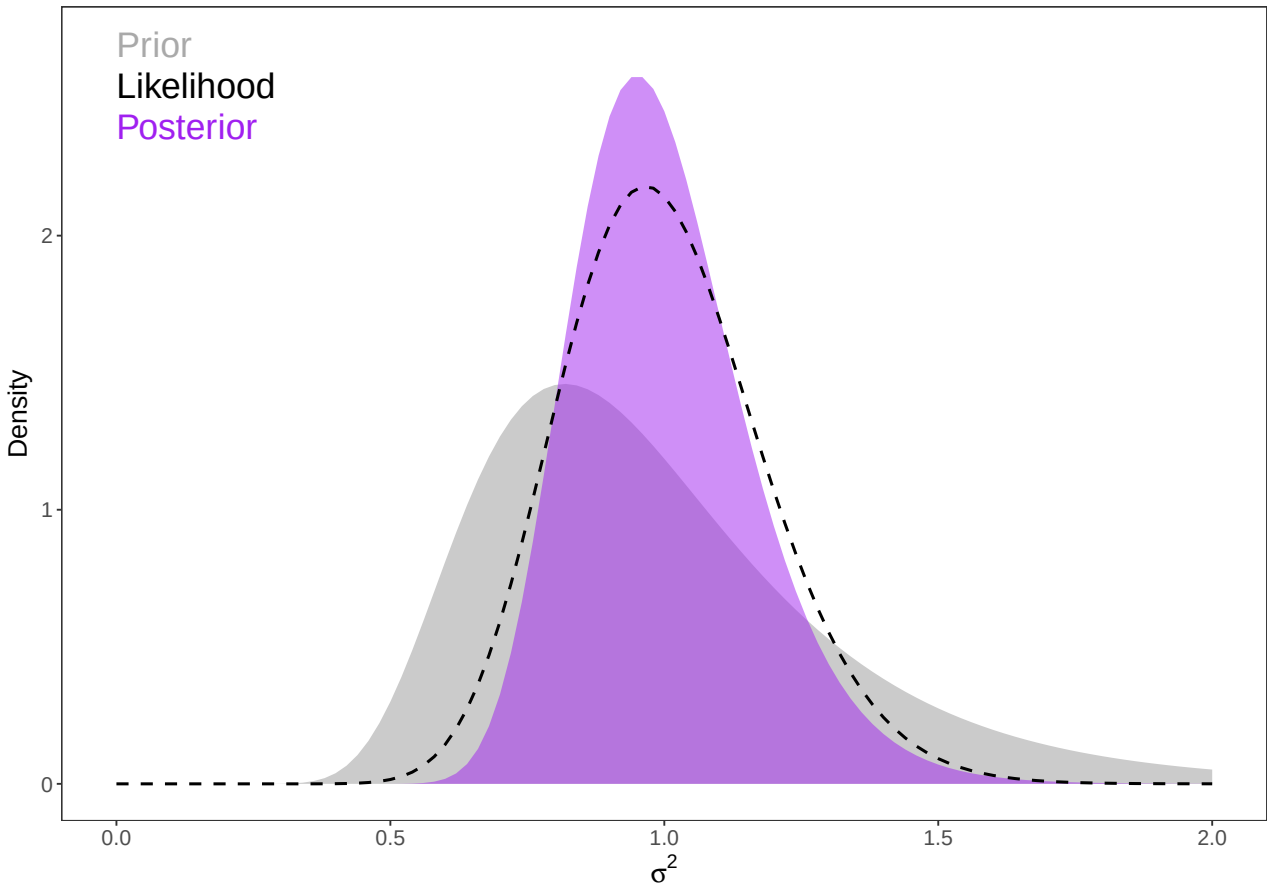
$$X_{ij}|\mu_i, \sigma^2 \sim \mathcal{N}\left(\mu_i, \sigma^2\right), \quad j = 1, \ldots, n_i,\ i = T, C$$

- Larger values of μ_i better
- Superiority hypothesis testing problem

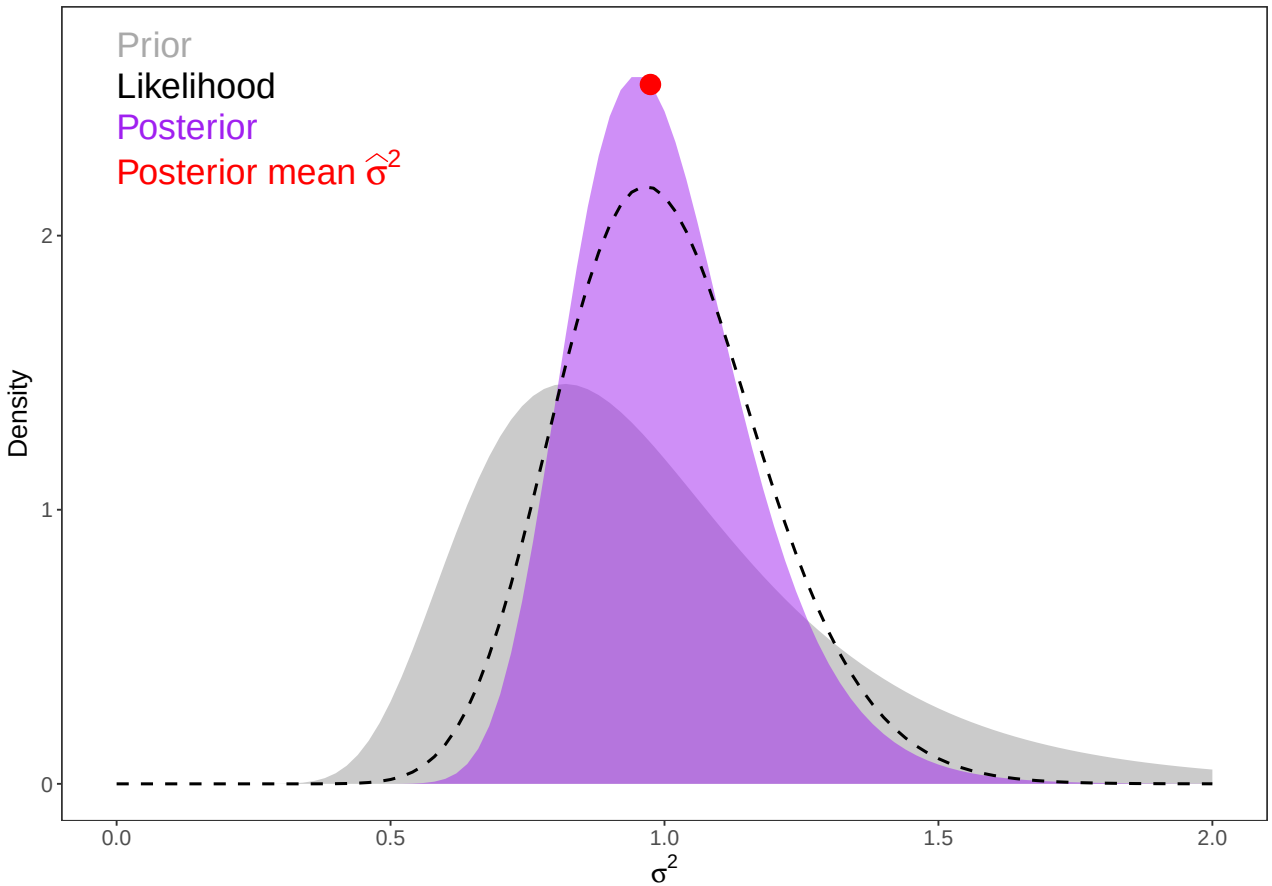
$$H_0 : \mu_T \leq \mu_C \qquad \text{vs.} \qquad H_1 : \mu_T > \mu_C.$$

- Frequentist analysis: one-sided Student's t-test to test H_0 at level α
- Blinded one-sample variance estimator recommended for sample size re-estimation

Incorporating prior information into sample size re-estimation



Incorporating prior information into sample size re-estimation



$$\hat{n} = 4\frac{(q_{1-\alpha} + q_{1-\beta})^2}{(\mu_T^* - \mu_C^*)^2}\hat{\sigma}^2$$

Incorporating prior information into sample size re-estimation

- Prior distribution of variance
  - MAP approach: meta-analysis of historical data to obtain prior distribution of study parameters
  - MAP approach motivates inverse Gamma prior for σ^2 (Schmidli et al., 2016)
- Unblinded sample size re-estimation: closed form expression of posterior and posterior mean
- Focus on unblinded sample size re-estimation first; extension to blinded sample size re-estimation later

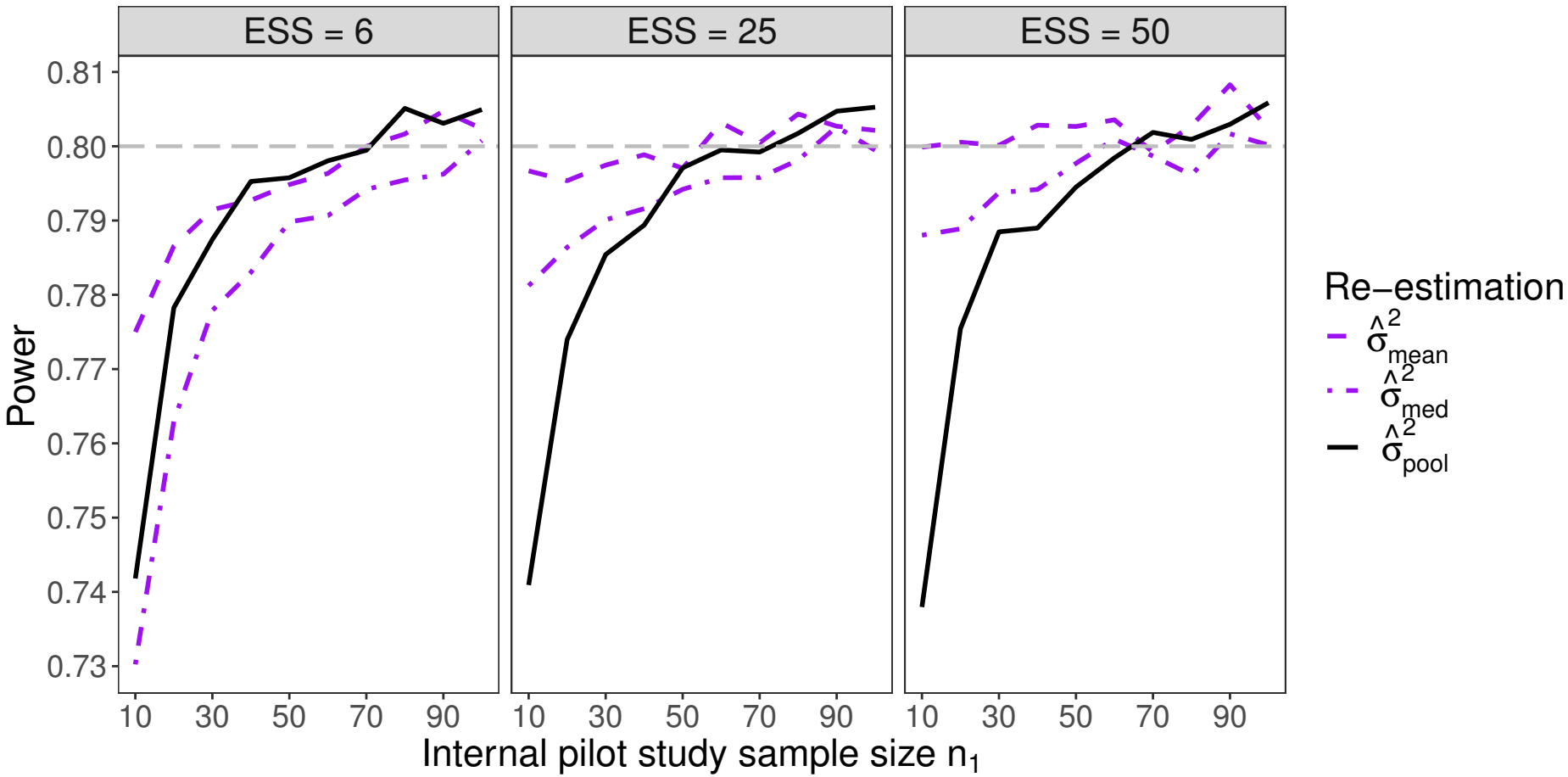
Simulation study - Scenarios

Parameter	**No prior-data conflict**	**Prior-data conflict**
One-sided significance level α	0.025	0.025
Target power $1-\beta$	0.8	0.8
Assumed treatment effect δ^* under the H_1	0.5	0.5
Internal pilot study size n_1	$10, 20, \ldots, 100$	$10, 20, \ldots, 100$
Sample size ratio k	1	1
True variance σ^2	1	1
Expected value of prior $p_{\sigma^2}(\cdot)$	1	0.49
Effective sample size ESS of prior $p_{\sigma^2}(\cdot)$	$6, 25, 50$	$6, 25, 50$

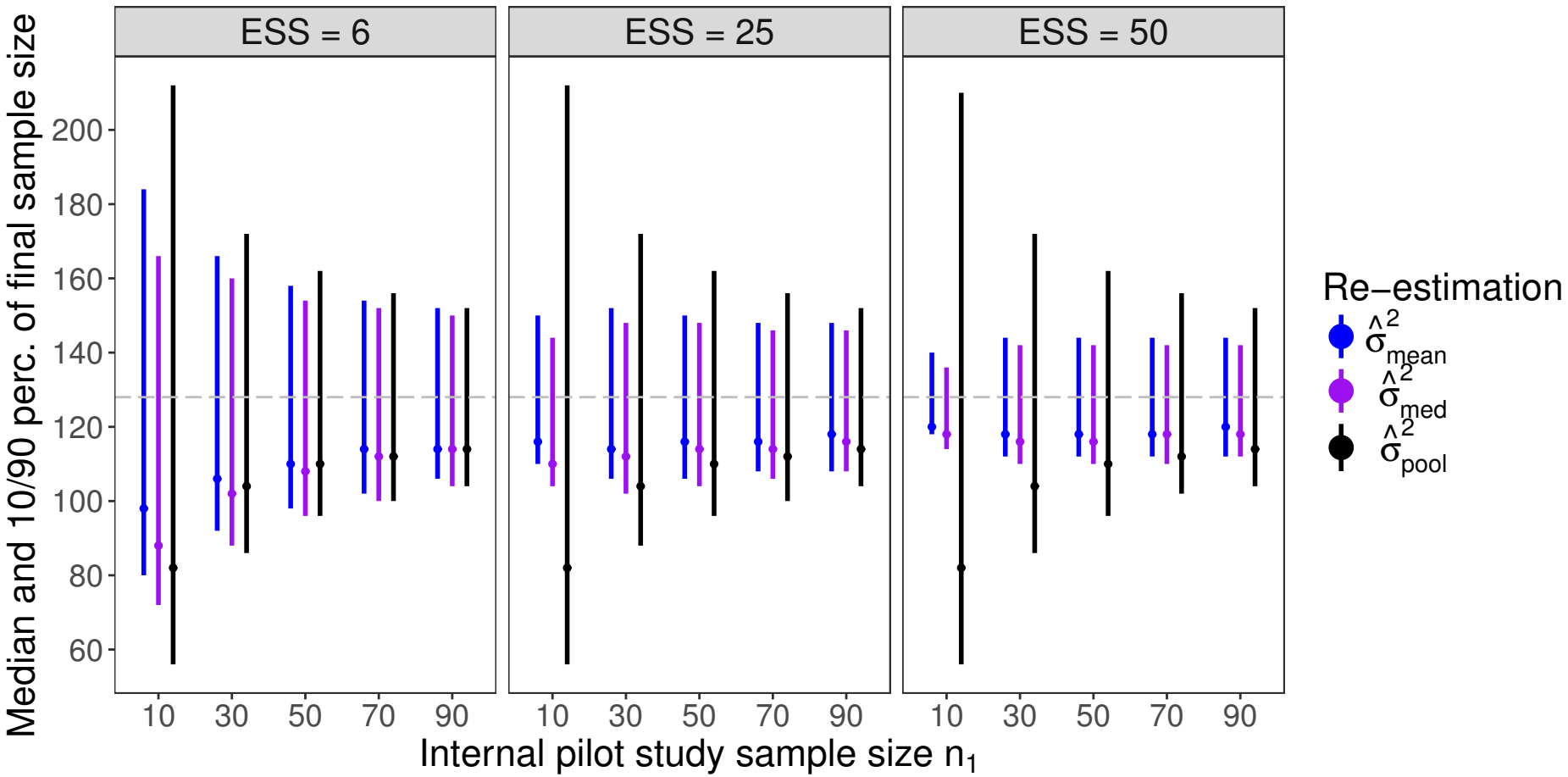
- Comparison of three sample size re-estimation approaches based on
  - unblinded pooled sample variance $\hat{\sigma}^2_{pool}$ (frequentist approach)
  - posterior median $\hat{\sigma}^2_{med}$
  - posterior mean $\hat{\sigma}^2_{mean}$

Power - no prior-data conflict

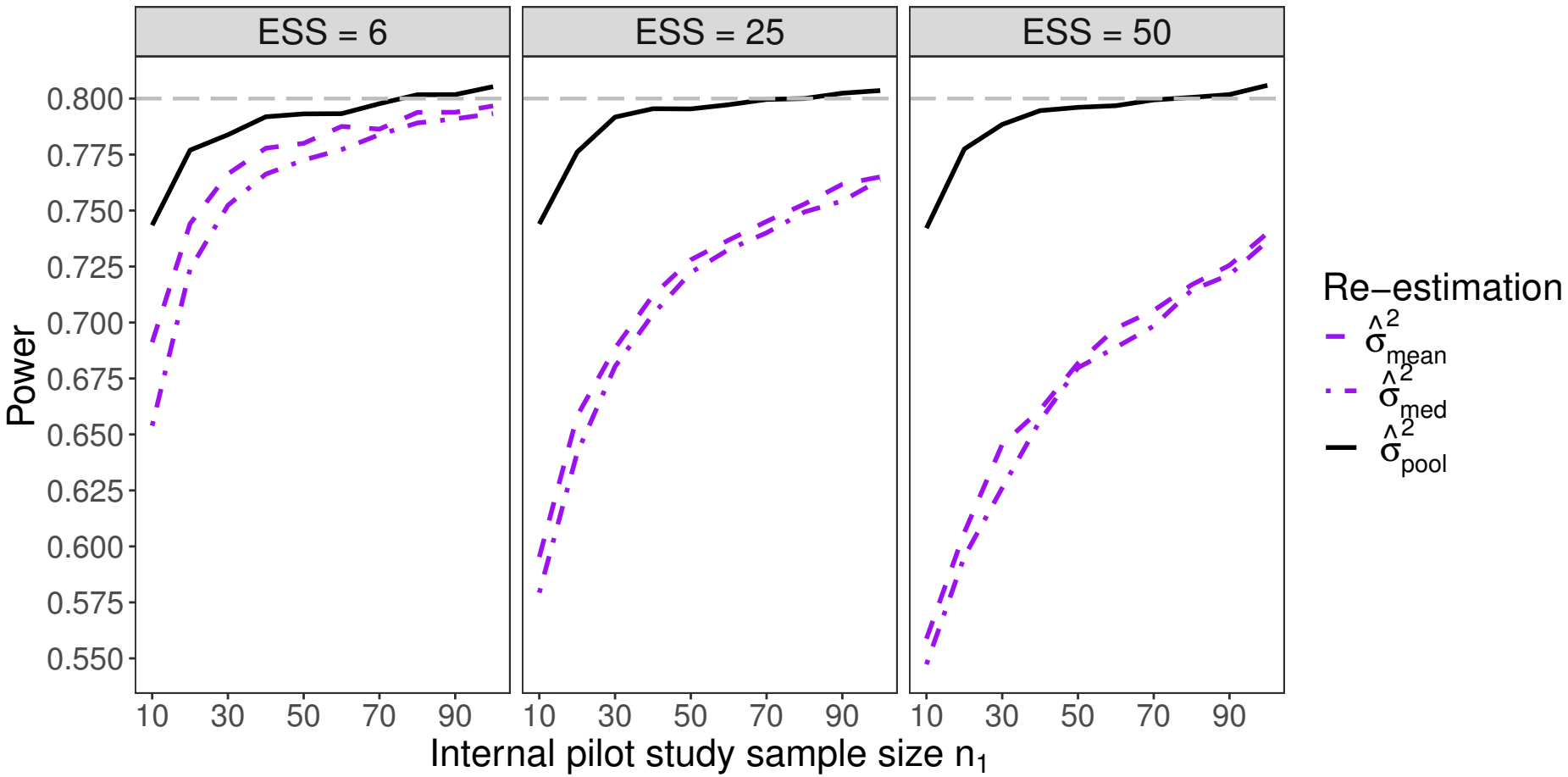
- Increasing weight of prior across panels



Sample size distribution - no prior-data conflict



Power - prior-data conflict

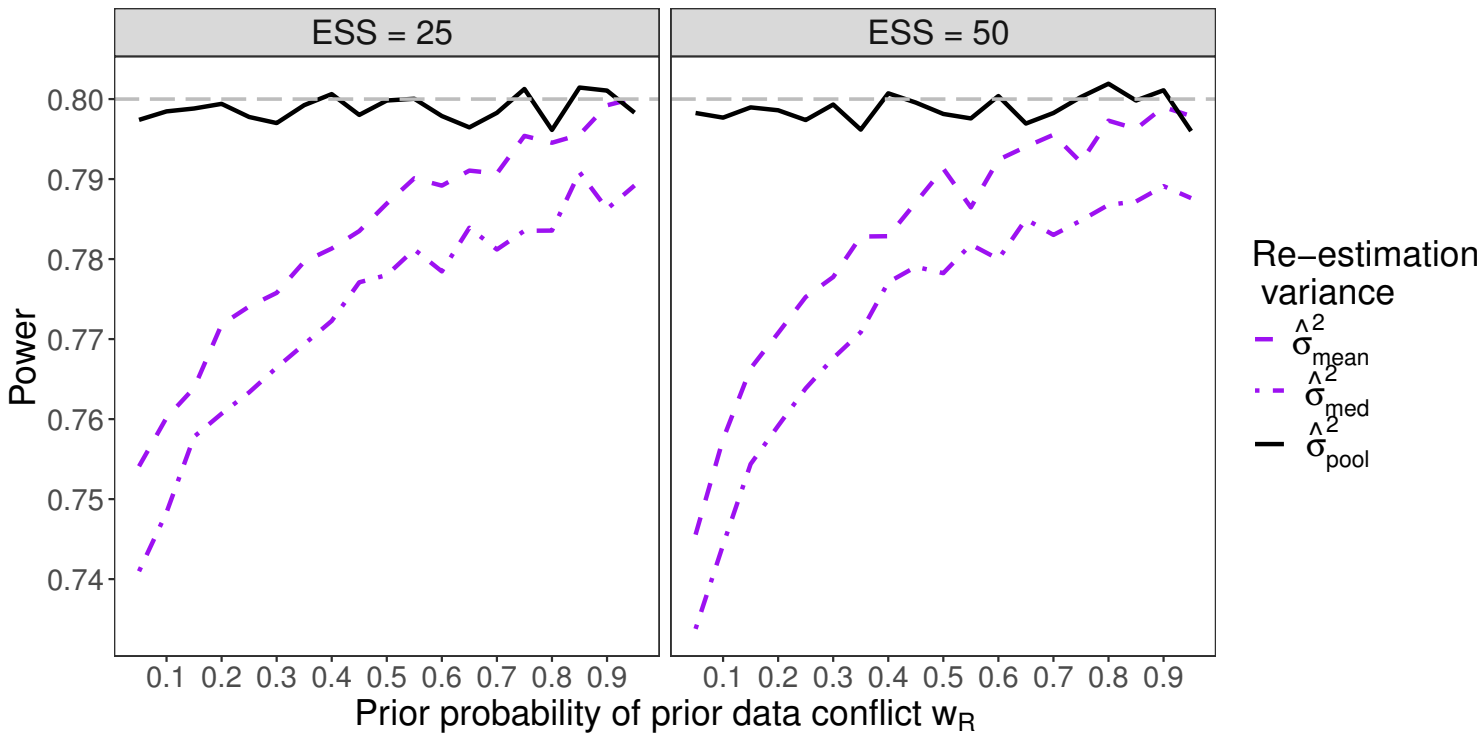


Robustifying the prior

- Robustify prior from historical data by mixing it with vague prior (Schmidli et al., 2014)

$$w_R \text{ InvGamma}(2, 1) + (1 - w_R) \text{ InvGamma}(a, b)$$

- The larger w_R, the smaller the influence and benefit of incorporating prior information



Extension to blinded data

- Various approaches for updating the variance prior based on blinded information:
  - blinded one-sample variance estimator
  - model the data of the internal pilot study as a mixture of two normal distributions
  - randomized block design: update prior information based on distribution of block sums (Xing & Ganju, 2005)

$\Rightarrow$ All methods face same issue concerning prior-data conflict

- Internal pilot study too small to dominate prior and thereby resolve prior-data conflict

Discussion and outlook

- Incorporating prior information into sample size re-estimation
  - reduces variability of re-estimated sample size
  - bears risk of under- or overpowered clinical trials in the case of prior-data conflict
- Other methods for selecting final sample size such as decision theoretic approaches (Stallard, 1998)
- Not considered here: incorporating prior information into effect-based sample size re-estimation

For further reading


Mütze T, Schmidli H, Friede T. Nuisance parameter based sample size re-estimation incorporating prior information. `https://arxiv.org/abs/1703.06957`.


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**:1023–1032.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Xing B, Ganju J. A method to estimate the variance of an endpoint from an on-going blinded trial. *Statistics in Medicine* 2005; **24**:1807–1814.


Stallard N. Sample size determination for phase II clinical trials based on Bayesian decision theory. *Biometrics* 1998; **55**:279–294.