A Structured Framework for Adaptively Incorporating External Evidence in Sequentially Monitored Clinical Trials

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Skeptical Monitoring Prior

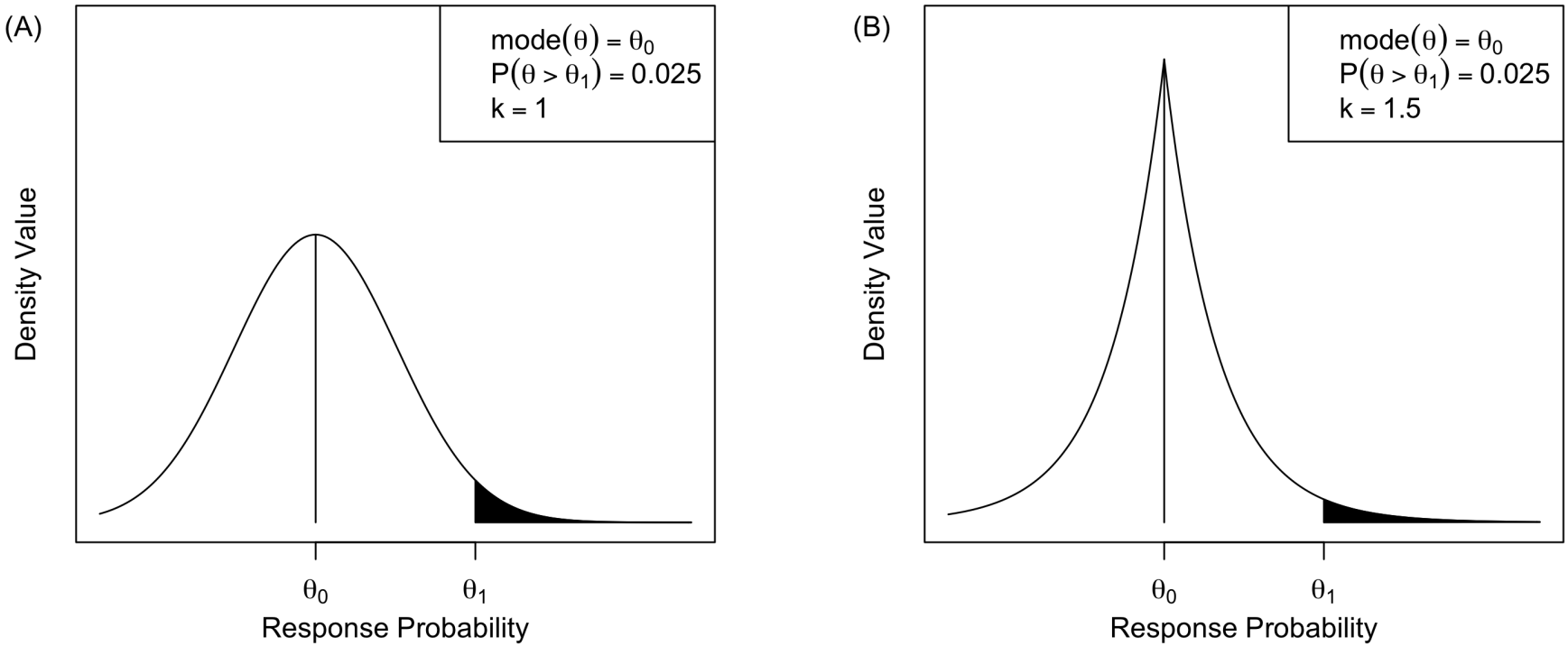

Figure: A, Default skeptical prior. B, Concentrated skeptical prior.

Enthusiastic Monitoring Prior

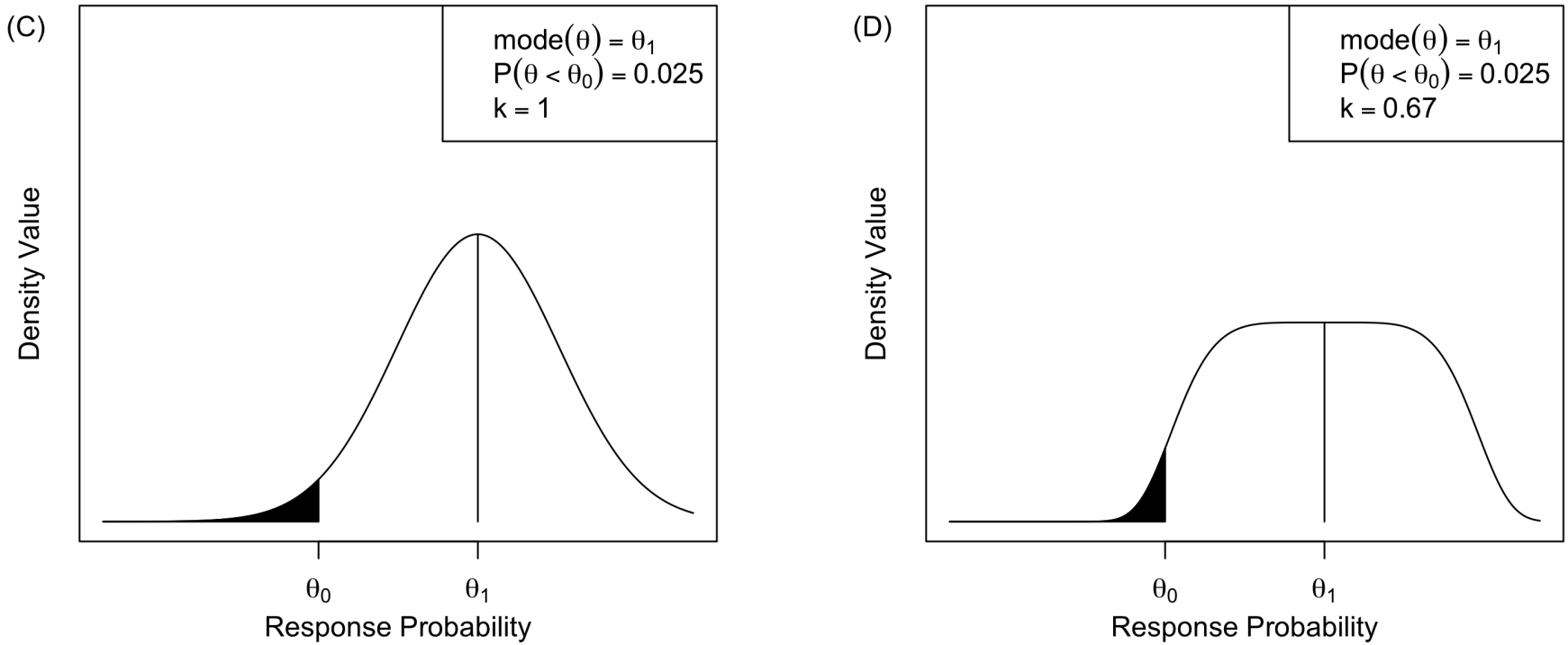

Figure: C, Default enthusiastic prior. D, Flattened enthusiastic prior.

Adaptive Monitoring Prior

- Let D_{obs} be the observed data at some point in time in an ongoing trial, and let $p(\mathrm{D}) = \int p(\mathrm{D}|\theta)\pi(\theta)d\theta$ be the prior-predictive distribution for the data.
- *Box's p-value* is defined as the following:

$$\psi(\mathrm{D}_{\text{obs}}) = \int p(\mathrm{D})1[p(\mathrm{D}) \leq p(\mathrm{D}_{\text{obs}})]d(\mathrm{D}) \tag{1}$$

- We define the *adaptive monitoring prior* for efficacy evaluations as the mixture distribution

$$\pi_{AE}(\theta) = \omega \cdot \pi_E(\theta) + (1 - \omega) \cdot \pi_S(\theta) \tag{2}$$

- Define the mixing weight ω given to the *enthusiastic* prior as

$$\omega = \psi^{(E)}(\mathrm{D}_{\text{obs}}) \tag{3}$$

PLUTO Trial

- We consider the trial "The Pediatric Lupus Trial of Belimumab Plus Background Standard Therapy (PLUTO)" (NCT01649765) which was conducted between September 2012 and January 2018 [Brunner *et al.*, 2020].
- The primary endpoint was a dichotomous variable reflecting a 4-point or greater reduction in SELENA SLEDAI score from baseline to week 52.
- External data is used to identify $\eta_0 = 0.39$, $\theta_1 = 0.12$, using $\theta_0 = 0$ as the null value.
- A frequentist two-sided hypothesis test with confidence level 95% and 80% power would require 266 patients per group.

Trial Result

- Ultimately, 93 patients were enrolled over approximately 52.5 months (approximately 1 patient enrolled per 17 days).
- Clinical response was observed in 28 of 53 (52.8%) of patients randomized to belimumab and in 17 of 40 (43.6%) of patients randomized to placebo (95% CI [-0.1122, 0.2962]).
- The data for 1 patient was not available for re-analysis due to a protocol violation.
- Analyze the data as if it was sequentially monitored after every 2 completed outcomes using the adaptive enthusiastic monitoring prior.

Re-analysis of PLUTO trial

Table: Summary characteristics of re-analysis of PLUTO trial. SS = Sample Size, I/F = Interim/Final, $\psi^{(E)}(D_{obs})$ = Box's p-value using enthusiastic prior, ω = Enthusiastic mixing weight in adaptive monitoring prior, Efficacy Post Prob = Posterior probability of treatment efficacy.

SS (I/F)	$\psi^{(E)}(D_{obs})$ (I/F)	ω (I/F)	Efficacy Post Prob (I/F)
62 / 90	0.914 / 0.965	0.914 / 0.965	0.980 / 0.979

Box's P-value Using Enthusiastic Prior $\psi^{(E)}(\mathrm{D}_{\mathrm{obs}})$

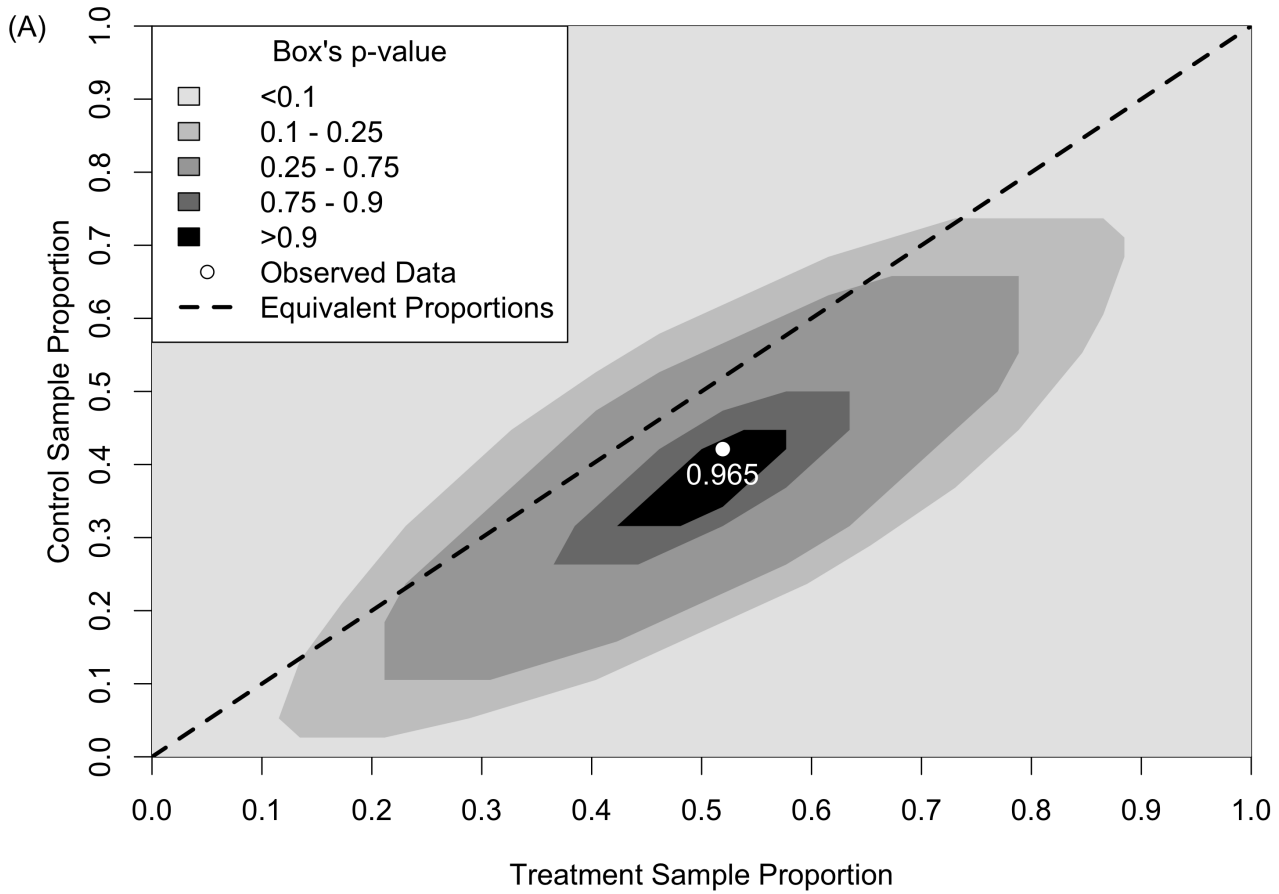

Figure: A, Box's p-value by control and treatment sample proportions at the final analysis with 90 subjects when $\delta = 0$ is used (3) for the adaptive monitoring prior.

Posterior Probability of Treatment Efficacy

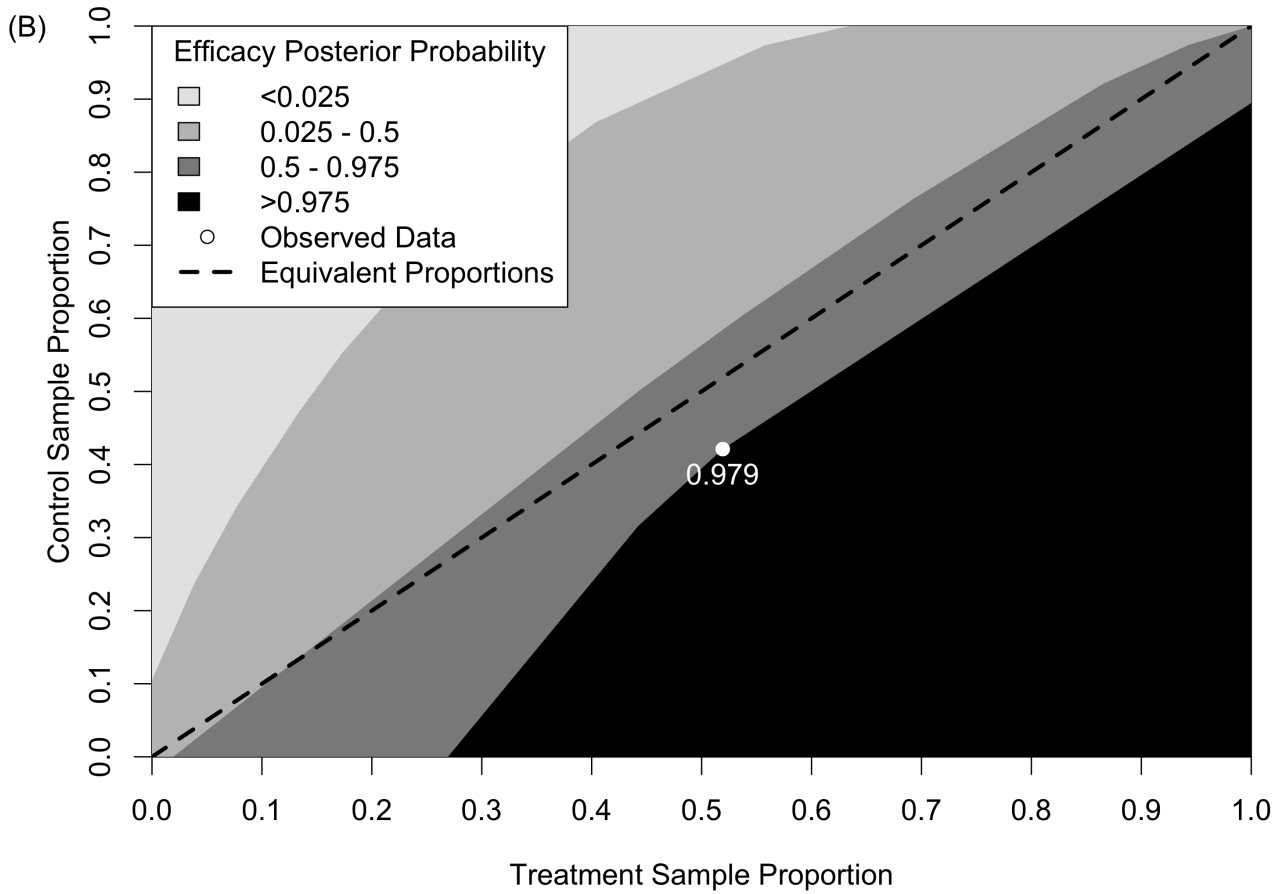

Figure: B, Posterior probability of efficacy by control and treatment sample proportions.

References

Brunner, H. I., Abud-Mendoza, C., Viola, D. O., Calvo Penades, I., Levy, D., Anton, J., and et al. (2020). Safety and efficacy of intravenous belimumab in children with systemic lupus erythematosus: results from a randomised, placebo-controlled trial. *Annals of the Rheumatic Diseases*, **79**(10), 1340 LP – 1348.