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

Evan Kwiatkowski[1], Eugenio Andraca-Carrera[2], Mat Soukup[2], Matthew A. Psioda[1]

[1] Department of Biostatistics, University of North Carolina at Chapel Hill
[2]Division of Biometrics VII, Office of Biostatistics, Center for Drug Evaluation and Research, US Food and Drug Administration

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Motivation

- We present a structured framework for specifying monitoring priors and stoppage criteria for a Bayesian sequentially monitored clinical trial that is based on intuitive justification for the design quantities rather than being motivated by having pre-specified frequentist operating characteristics.

Enthusiastic Monitoring Prior

- Consider again the hypotheses $H_0 : \theta \leq \theta_0$ versus $H_1 : \theta > \theta_0$ where θ_0 represents a treatment effect of interest and let $\theta_1 > \theta_0$ represent a plausible, clinically meaningful effect.
- Define an enthusiastic prior, denoted as $\pi_E(\theta)$, as a prior consistent with θ_1 being the most likely value of θ (i.e., the prior mode) and that reflects the belief of an observer who is *all but convinced* that H_1 is true a priori.
- Formally, this is defined as satisfying (i) $\text{argmax}_\theta \, \pi_E(\theta) = \theta_1$ and (ii) $P_E(\theta > \theta_0) = 1 - \epsilon$, where the subscript E indicates that the probability is based on $\pi_E(\theta)$.

Skeptical Monitoring Prior

- Similarly, define a skeptical prior, denoted as $\pi_S(\theta)$, as a prior consistent with θ_0 being the most likely value of θ and that reflects the belief of an observer who is *all but convinced* that $\theta < \theta_1$ is true a priori.
- Formally, this is defined as the prior $\pi_S(\theta)$ satisfying (iii) $\text{argmax}_\theta \, \pi_S(\theta) = \theta_0$ and (iv) $P_S(\theta < \theta_1) = 1 - \epsilon$. In what follows we refer to (i) and (iii) as *mode value constraints* and (ii) and (iv) as *tail-probability constraints*, respectively.

Generalized Normal Distribution

- The density for a generalized normal distribution $\mathcal{GN}(\mu, \alpha, \beta)$ is

$$f(\theta) = \frac{\beta}{2\alpha\Gamma(1/\beta)} \exp\left\{-\left(\frac{|\theta - \mu|}{\alpha}\right)^{\beta}\right\}$$

  where μ is a location parameter, $\alpha > 0$ is a scale parameter, and $\beta > 0$ is a shape parameter.
- A monitoring prior in the generalized normal family of distributions can have density at the mode equal to $k \times \frac{1}{\sqrt{2\pi}\sigma}$, with $k < 1$ indicating a more flattened distribution and $k > 1$ indicating a more peaked distribution at the mode, relative to the default normal distribution.

Skeptical Monitoring Prior

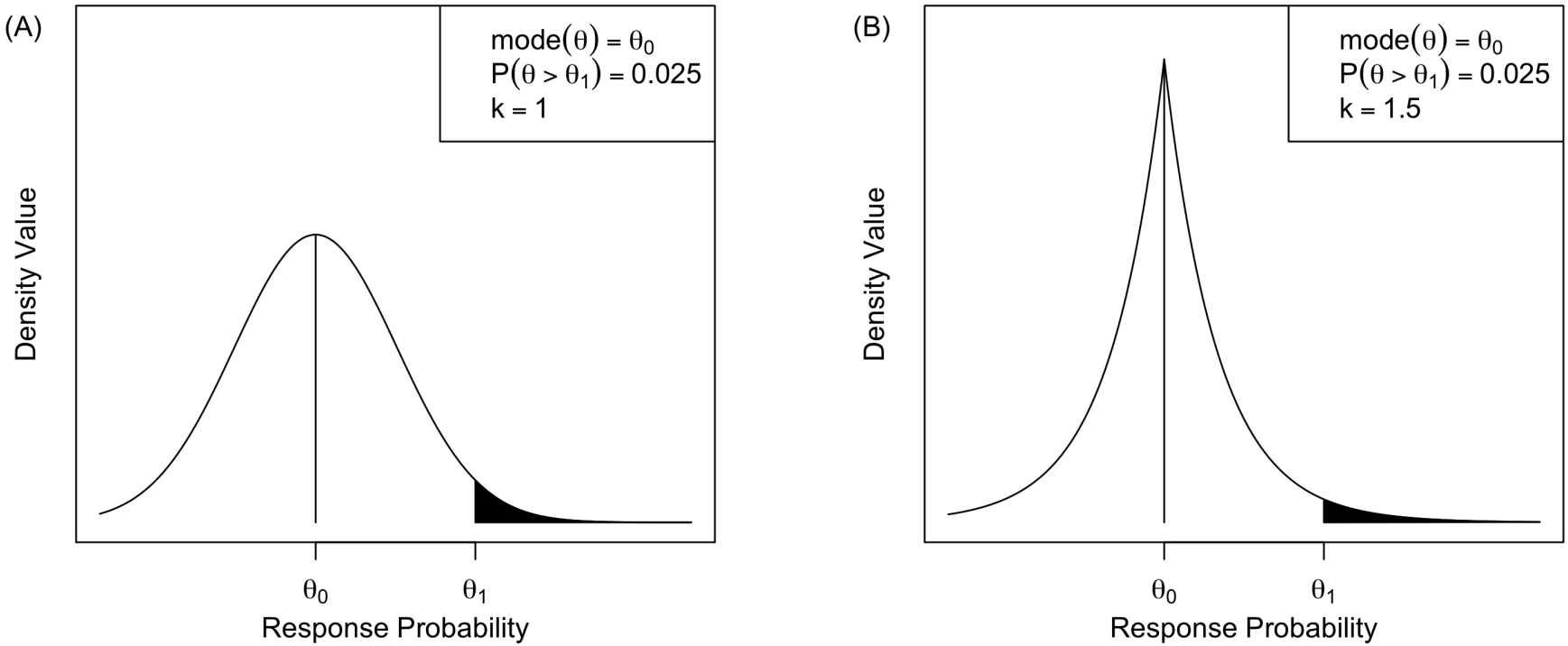

Figure: A, Default skeptical prior. B, Concentrated skeptical prior.

Enthusiastic Monitoring Prior

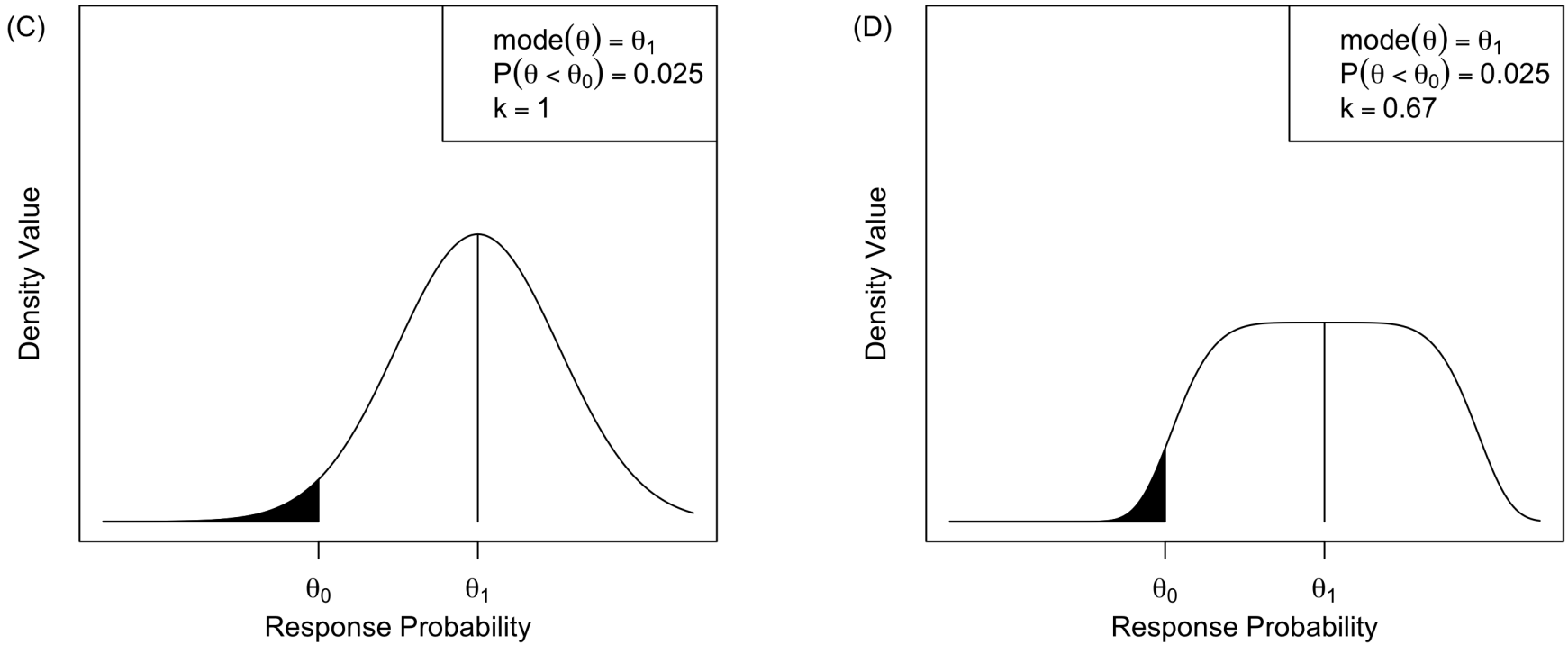

Figure: C, Default enthusiastic prior. D, Flattened enthusiastic prior.

Box's *p*-value

The prior-predictive distribution for data D (also called the marginal likelihood) reflects the probability of observing D given the assumed prior distribution for θ and is defined formally as

$$p(\mathrm{D}) = \int p(\mathrm{D}|\theta)\pi(\theta)d\theta. \tag{1}$$

Let $\mathrm{D}_{\mathrm{obs}}$ be the observed data at some point in time in an ongoing trial. *Box's p-value* is defined as the following:

$$\psi(\mathrm{D}_{\mathrm{obs}}) = \int p(\mathrm{D})1[p(\mathrm{D}) \leq p(\mathrm{D}_{\mathrm{obs}})]d(\mathrm{D}) \tag{2}$$

where $1[A]$ is an indicator that the event A is true.

Adaptive Monitoring Prior

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

$$\pi_{AE}(\theta) = \omega \cdot \pi_E(\theta) + (1 - \omega) \cdot \pi_S(\theta) \tag{3}$$

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

$$\omega = (1 - \delta) \cdot \psi^{(E)}(\mathrm{D}_{\mathrm{obs}}) \tag{4}$$

- This mixture weight achieves the goal of favoring the enthusiastic component if the trial data are compatible with that prior, and otherwise assigning a higher weight to the skeptical component.
- The minimum possible mixing weight δ assigned to the *skeptical* prior is achieved when $\psi^{(E)}(\mathrm{D}_{\mathrm{obs}}) = 1$ and is equal to δ.
- Choices of δ in $\{0, 0.05, 0.10, 0.15, 0.20, 0.25\}$ are explored.

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 study population was comprised of patients ages 5 though 17 with active systemic lupus erythematosus (SLE), defined as a baseline SELENA SLEDAI score of 6 or above on a scale of 0-105, where higher scores indicate more severe disease activity.
- Patients were randomized to monthly dosing of either belimumab 10mg/kg or placebo, while continuing to receive standard of care therapy regardless of assignment.
- The primary endpoint was a dichotomous variable reflecting a 4-point or greater reduction in SELENA SLEDAI score from baseline to week 52.

External Evidence & Power

- An estimate for the pediatric response probability is denoted by $\eta_0 = 0.39$ (i.e. the sample proportion of responders from the pooled adult studies), and for purposes of monitoring, a plausible, clinically meaningful difference in response probabilities is $\theta_1 = 0.12$ (i.e. based on the pooled adult study's treatment response probability of 0.51).
- Using these values for the null and hypothesized response probabilities for the treatment group and assuming a response probability of 0.39 for the control group, a frequentist two-sided hypothesis test with confidence level 95% and 80% power would require 266 patients per group.

Joint Enthusiastic Monitoring Prior

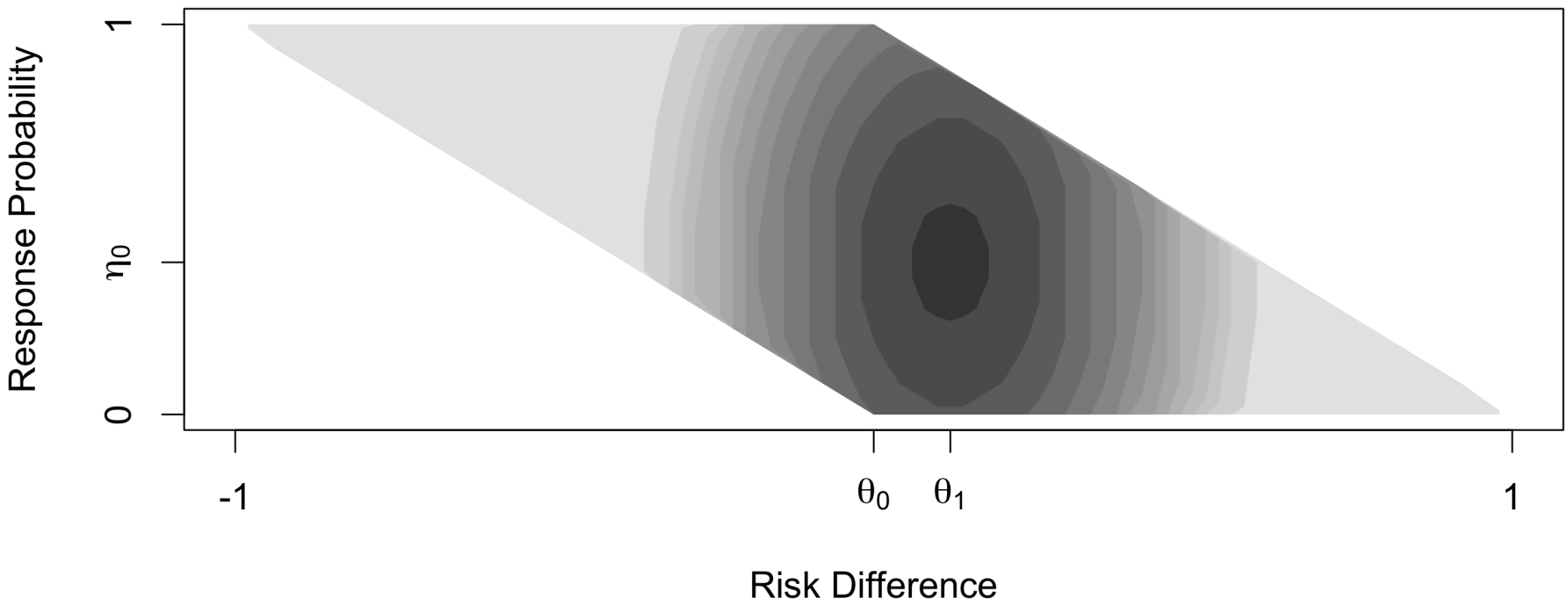

Figure: Joint prior $\pi(\theta, \eta) = \pi(\theta) \times \pi(\eta|\theta)$ truncated based on the conditions $-1 < \theta < 1$ and $0 < \theta + \eta < 1$.

Enthusiastic Prior Mixing Weight ω

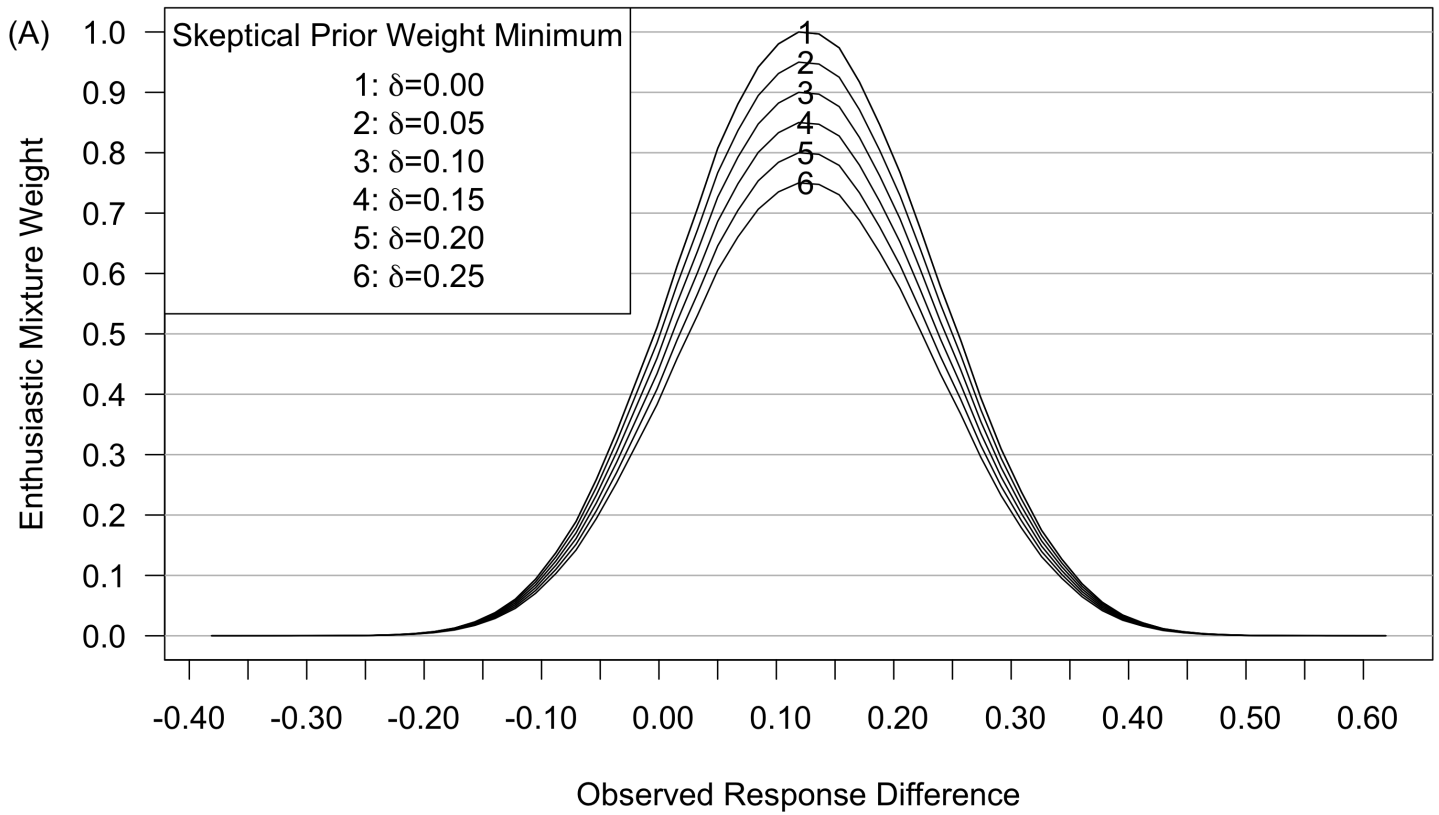

Figure: A, Enthusiastic prior mixing weight ω associated with skeptical prior weight minimum δ in (4) by observed response difference between IP and PC groups, when the PC response rate is fixed at 38% (16/42 responses).

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])

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.

δ	SS (I/F)	$\psi^{(E)}(D_{obs})$ (I/F)	ω (I/F)	Efficacy Post Prob (I/F)
0.00	62 / 90	0.914 / 0.965	0.914 / 0.965	0.980 / 0.979
0.05	64 / 92	0.876 / 0.934	0.833 / 0.887	0.976 / 0.962
0.10	76 / 92	0.941 / 0.934	0.847 / 0.841	0.975 / 0.951
0.15	92 / 92	0.934 / 0.934	0.794 / 0.794	0.940 / 0.940
0.20	92 / 92	0.934 / 0.934	0.747 / 0.747	0.928 / 0.928
0.25	92 / 92	0.934 / 0.934	0.701 / 0.701	0.917 / 0.917

Box's *P*-value Using Enthusiastic Prior $\psi^{(E)}(D_{obs})$

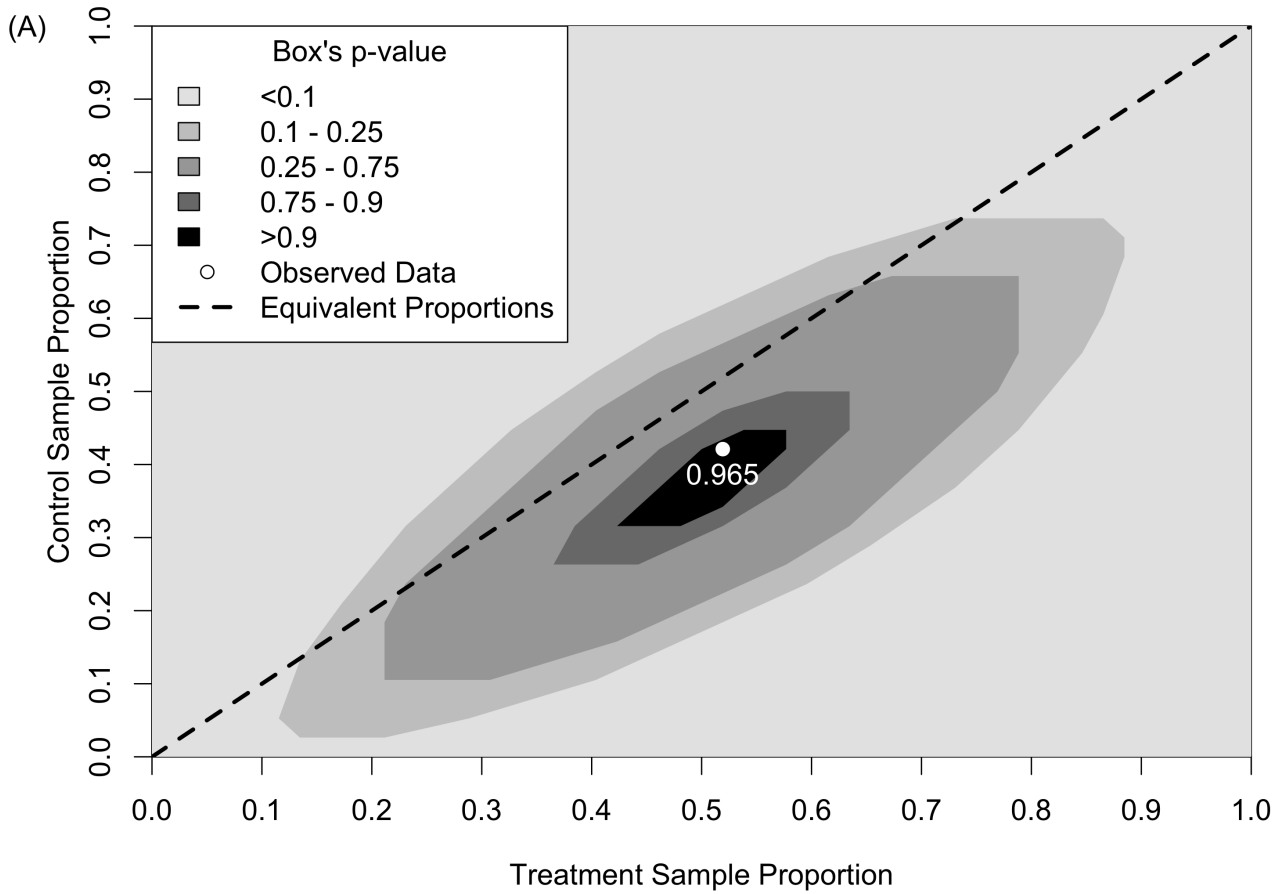

Figure: A, Box's p-value by control and treatment sample proportions at the final analysis with 90 subjects when $\delta = 0$ is used (4) for the adaptive monitoring prior.

Posterior Probability of Treatment Efficacy

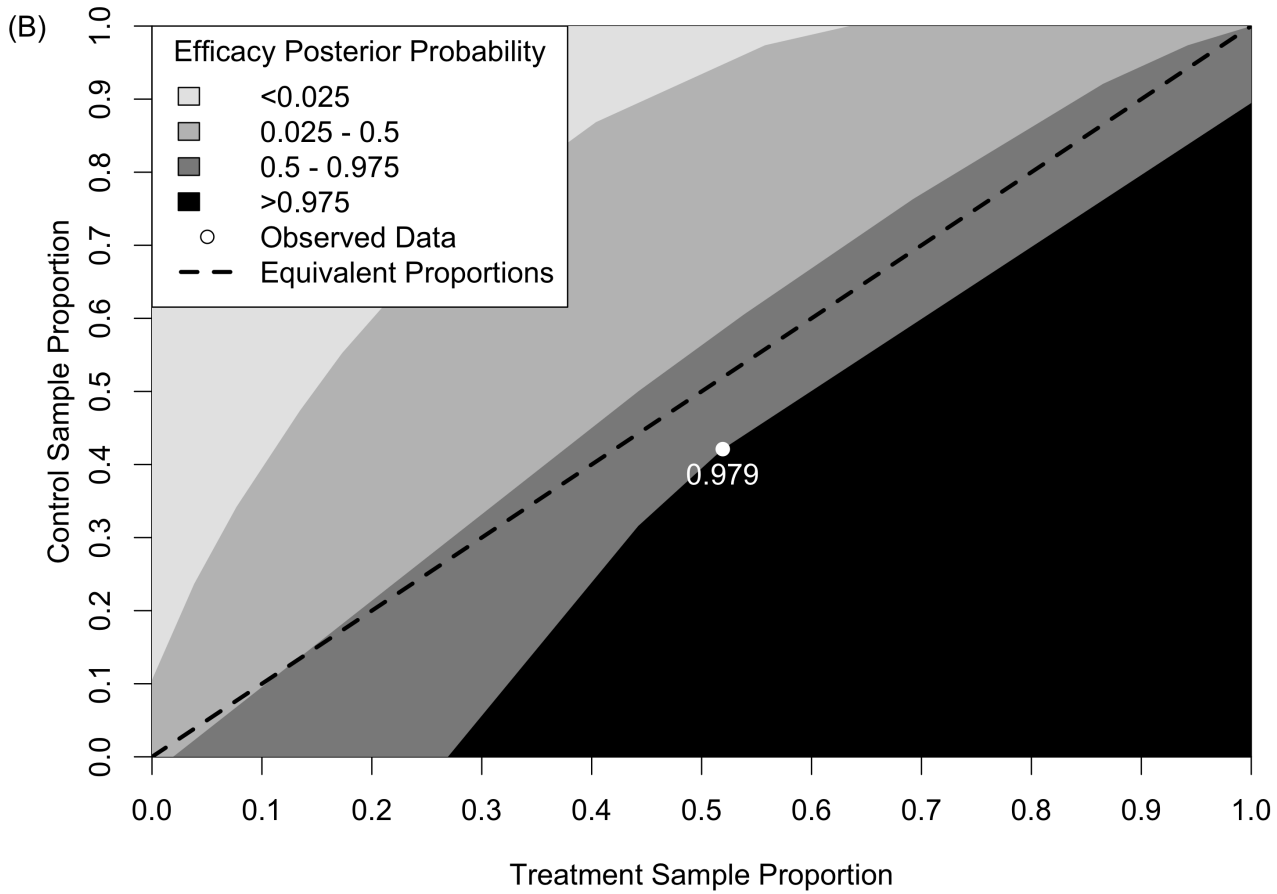

Figure: B, Posterior probability of efficacy by control and treatment sample proportions.

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.

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