

A Framework for Adaptively Incorporating External Evidence in Sequentially Monitored Trials

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Motivation – Pediatric Therapeutic Development

Background

- The Pediatric Research Equity Act (PREA) and prior legislation has spurred pediatric research to inform new drug labeling by allowing the FDA to request/require trials in pediatric disease populations [Avant *et al.*, 2018].
- At this time, both the EMA/FDA require pediatric research plans at certain stages of the application for authorization of new medicines.
- Significant challenges are faced in pediatric trials necessitating timeline extensions and/or modifications to original designs developed to meet FDA post marking requirements (PMRs).
- Pediatric trials face numerous barriers (e.g., small participant pools, ethical/parental concerns related to participation [Greenberg *et al.*, 2018]) and are often unable to produce substantial evidence of efficacy.

Motivating Example – Belimumab Development Program I

- Based on data generated by two well-controlled pivotal trials in adult systemic lupus erythematosus (SLE), the BLISS-52 and BLISS-76 trials, the FDA approved belimumab for the treatment of adults with active, seropositive SLE (who are already on standard therapy).

		Study 1056			Study 1057	
	Placebo N=275	Belimumab 1 mg/kg N=271	Belimumab 10 mg/kg N=273	Placebo N=287	Belimumab 1 mg/kg N=288	Belimumab 10 mg/kg N=290
Response, n (%)	93 (34)	110 (41)	118 (43)	125 (44)	148 (51)	167 (58)
Observed difference	-	7%	9%	-	8%	14%
Odds ratio (95% CI)	-	1.3 (0.9, 1.9)	1.5 (1.1, 2.1)	-	1.6 (1.1, 2.2)	1.8 (1.3, 2.6)

Source: Review of BLA 125370 Belimumab IV dated February 18, 2011.

Figure: BLISS Trials Primary Endpoint Data: SRI Response Rate

Belimumab Development Program II

- As part of the FDA's 2011 approval of belimumab for treatment of adult SLE, a pediatric PMR was issued under PREA.
- This PMR was to conduct a phase II, multicenter study to evaluate the safety, efficacy, and pharmacokinetics of belimumab in a pediatric SLE population.
- The 2011 PMR required a trial with $N = 100$ patients but was reissued in 2016 to require $N = 70$ patients due to enrollment challenges.

	Placebo	Belimumab 10 mg/kg
Unadjusted Response n/N (%)	17/39 (43.6)	28/53 (52.8)
Observed difference	-	9.2
Odds ratio (95% CI)	-	1.5 (0.6, 3.3)

Figure: PLUTO Trial Primary Endpoint Data: SRI Response Rate

Belimumab Development Program III

- For the PLUTO trial, there could be no preconception that the trial was adequate to produce substantial evidence of efficacy on its own.
- Required sample size for 90% power $\rightarrow N = 760$.
- Nonetheless, the FDA concluded that the safety/efficacy data provided by the PLUTO trial, *taken together with the efficacy/safety data from the BLISS trials*, supported approval of belimumab for pediatric use [U.S. Food and Drug Administration, 2018].
- As a part of the multidisciplinary review, a *post-hoc* Bayesian analysis was requested that borrowed information from the BLISS trials.

Bayesian Sequential Monitoring

- Summarizing Spiegelhalter *et al.* [1994] and others, a Bayesian may monitor data continually and stop collection when any of the following criteria have been met:
 - ▶ A sufficiently skeptical observer becomes convinced H_1 is true.
 - ▶ A sufficiently enthusiastic observer becomes convinced H_1 is unlikely to be true *or* that the benefit of treatment is not what was hoped.
 - ▶ Resources allocated for the study have been exhausted.
- One can analyze accumulating data as frequently as is logistically feasible until one of these criteria is met.

Evidence from the Bayesian Perspective I

- Consider testing the hypotheses

$$H_0 : \theta \leq \theta_0 \text{ versus } H_1 : \theta > \theta_0$$

where

- ▶ θ is a parameter of interest (e.g., difference in response rates), and
 - ▶ θ_0 is a chosen constant (e.g., most commonly $\theta_0 = 0$).
- Suppose there exists a constant $\theta_1 > \theta_0$ that is thought to be a clinically meaningful and also a plausible.
 - ▶ $\theta_1 = 0.118$ based on the BLISS trial data

Evidence from the Bayesian Perspective II

- A standard Bayesian decision rule is given by

$$P_{\pi}(\theta > \theta_0 | \mathbf{D}) > 1 - \epsilon,$$

based on some prior distribution $\pi(\theta)$ and data \mathbf{D} .

- One may formally define the concept of **substantial total evidence** in favor of a claim (e.g., $\theta > \theta_0$) as the posterior probability of the claim exceeding $1 - \epsilon$.
- **Total information** = **information from likelihood** + **prior information**
- Sequential monitoring rationale:
 - ▶ Skeptic: substantial total evidence that $\theta > \theta_0 \implies$ enrollment stop.
 - ▶ Enthusiast: substantial total evidence that $\theta < \theta_1 \implies$ study stop.

Skeptical and Enthusiastic Priors I

- Define a skeptical observer as someone whose belief satisfies:
 - (i) The observer believes θ_0 is the most likely value of θ .
 - (ii) Belief consistent with substantial total evidence that $\theta < \theta_1$.
 - (iii) Formally, this is defined as the prior $\pi_S(\theta)$ satisfying $\operatorname{argmax}_{\theta} \pi_S(\theta) = \theta_0$ and $P_S(\theta < \theta_1) = 1 - \epsilon$.
- Define an enthusiastic observer as someone whose belief satisfies:
 - (i) The observer believes θ_1 is the most likely value of θ .
 - (ii) Belief consistent with substantial total evidence that $\theta > \theta_0$.
 - (iii) Formally, this is defined as the prior $\pi_E(\theta)$ satisfying $\operatorname{argmax}_{\theta} \pi_E(\theta) = \theta_1$ and $P_E(\theta > \theta_0) = 1 - \epsilon$.

Skeptical and Enthusiastic Priors II

- For prior construction, we propose the flexible family of generalized normal distributions – $\mathcal{GN}(\mu, \alpha, \beta)$

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

where

- ▶ μ is a location parameter,
 - ▶ α is a scale parameter, and
 - ▶ $\beta > 0$ is a shape parameter.
- This family of distributions accommodates a variety of shapes – both very peaked and very flat – and includes the normal distribution as a special case.

Skeptical and Enthusiastic Priors III

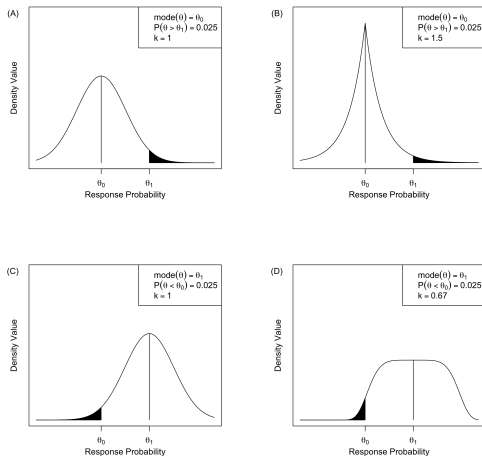


Figure: A, Default skeptical prior. B, Concentrated skeptical prior. C, Default enthusiastic prior. D, Flattened enthusiastic prior.

Adaptive Monitoring Prior

- One may define the *adaptive monitoring prior* for efficacy monitoring as the mixture distribution

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

- We define $\omega_0 = (1 - \delta)\psi^{(E)}(\mathbf{D}_{\text{obs}})$, where
 - ▶ $\psi^{(E)}(\mathbf{D}_{\text{obs}}) \in [0, 1]$ is a measure of congruency between the pediatric data (i.e., \mathbf{D}_p) and the enthusiastic prior, and
 - ▶ $\delta \in [0, 1]$ provides a limit regarding how much the adaptive monitoring prior can “shift” away from the skeptical perspective and towards the enthusiastic one.
- $\delta = 1 \rightarrow \pi_{AMP}(\theta) = \pi_S(\theta)$ regardless of $\psi^{(E)}(\mathbf{D}_{\text{obs}})$

Box's p -value

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

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

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

$$\psi(\mathbf{D}_{\text{obs}}) = \int p(\mathbf{D})1[p(\mathbf{D}) \leq p(\mathbf{D}_{\text{obs}})]d(\mathbf{D}) \quad (2)$$

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

- 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 through 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

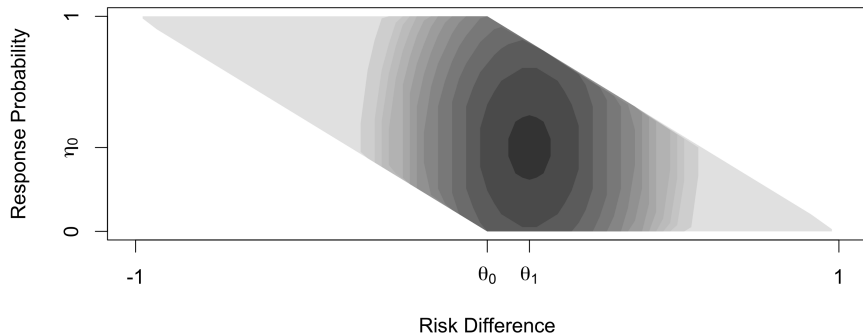


Figure: Joint prior $\pi(\theta, \eta) = \pi(\theta) \times \pi(\eta|\theta)$ truncated based on the conditions $-1 < \theta < 1$ and $0 < \theta + \eta < 1$.

Enthusiastic Prior Mixing Weight ω

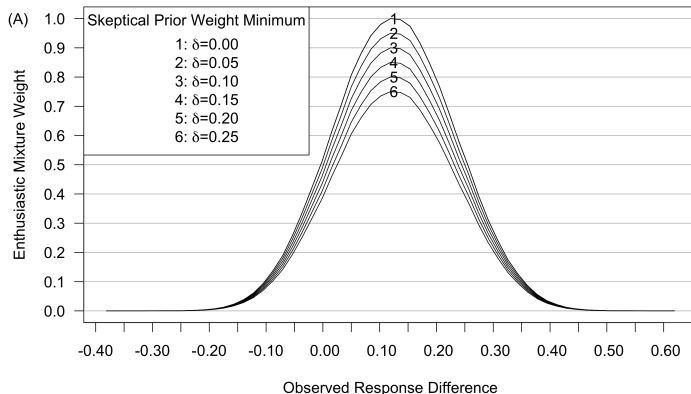


Figure: A, Enthusiastic prior mixing weight ω associated with skeptical prior weight minimum δ in (??) by observed response difference between IP and PC groups, when the PC response rate is fixed at 38% (16/42 responses).

- 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, $\psi^{(E)}(\mathbf{D}_{\text{obs}})$ = 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)	$\psi^{(E)}(\mathbf{D}_{\text{obs}})$ (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 $\psi^{(E)}(\mathbf{D}_{\text{obs}})$

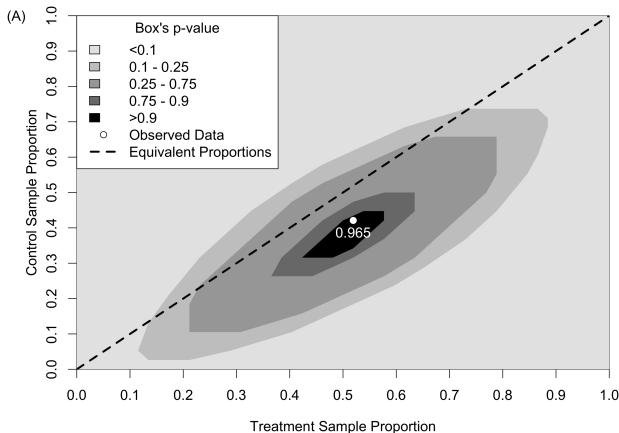


Figure: A, Box's p -value by control and treatment sample proportions at the final analysis with 90 subjects when $\delta = 0$ is used (??) for the adaptive monitoring prior.

Posterior Probability of Treatment Efficacy

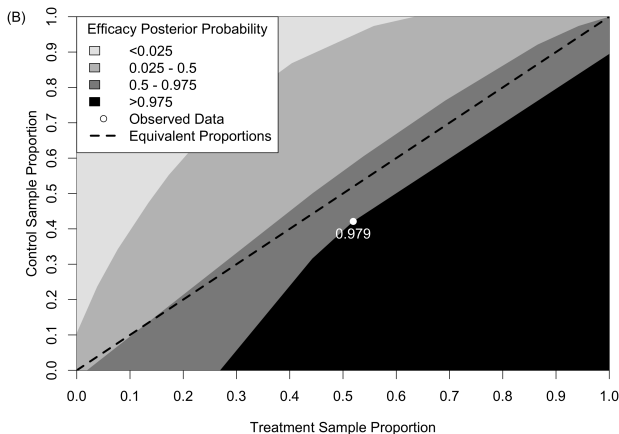


Figure: B, Posterior probability of efficacy by control and treatment sample proportions.

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