

# Towards Structured Use of Bayesian Sequential Monitoring in Clinical Trials

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## Abstract

The text of your abstract. 200 or fewer words.

*Keywords:* 3 to 6 keywords, that do not appear in the title

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# 1 Introduction

Things to discuss:

- 21<sup>st</sup> Century Cures Act (MATT)
- PDUFA VI reauthorization (MATT)
- Expansive work already done on sequential monitoring (EVAN – draft on 6/21)
- Our majors contribution (EVAN – as early as possible in introduction without having the flow appear weird – draft on 6/21)
- Outline for the remaining section of the paper (EVAN – draft on 6/21)

The theoretical foundations for the Bayesian clinical trials has been long established Cornfield (1966*a*) Cornfield (1966*b*) Neyman & Greenhouse (1967). These methods were not widely used in practice until a comprehensive framework for interpretation of results was developed through specifying prior distributions that were naturally and intuitively related to the research objectives (e.g. skeptical and enthusiastic priors) Freedman & Spiegelhalter (1989) Freedman & Spiegelhalter (1992) Spiegelhalter et al. (1993) Spiegelhalter et al. (1994) Fayers et al. (1997). (*Rewrite paragraph.*)

There is still potential for further utilization of Bayesian methods in the clinical trial setting. While the framework for interpretation of Bayesian clincial trials is well developed, the details of specifying prior distributions in a natural and intuitive way is lacking. This paper presents a structured or default way to determine prior distributions based on the trial design. Our major contribution is to present methods for the default or automatic selection of prior distributions in a way that is applicable to a wide array of clinical trial designs.

1. Bayesian methodology is widely developed.
2. It has been applied (cite).
3. The current perspective is that Bayesian methodology is only valid when Frequentist methods are insufficient, including where enrollment is challenging (rare diseases, pediatric studies)
4. Our contribution is to show that Bayesian methods are applicable to all clinical trials. This is shown by highlighting their improved interpretation and showing their use in varied and complicated situations.

## 2 Methods

As you introduce ideas that come from or extend other ideas in the literature, cite the relevant literature.

### 2.1 Monitoring versus Estimation Priors (EVAN – draft on 6/21)

#### 2.1.1 Bayesian hypothesis testing based on posterior probabilities

The Bayesian paradigm allows direct inference on a parameter of interest through specification of a model for the data generating mechanism and prior distributions for unknown quantities. Let  $\mathbf{D}$  be a random variable representing the data collected in the trial with density  $p(\mathbf{D}|\theta, \psi)$  where  $\theta$  and  $\psi$  are the unknown quantities. Let  $\theta$  be the parameter of interest and  $\psi$  be the unknown quantities that are not of primary importance (i.e. “nuisance parameters”). Define the sample spaces for the unknown quantities as  $\theta \in \Theta$  and  $\psi \in \Psi$ .

Suppose the hypotheses under consideration are  $H_0 : \theta \in \Theta_0$  versus  $H_1 : \theta \in \Theta_1$ , where  $\Theta = \Theta_0 \cup \Theta_1$  and  $\Theta_0 \cap \Theta_1 = \emptyset$ . These hypotheses are adjudicated based on posterior probabilities of  $\theta$  by evaluating its marginal likelihood  $P(\theta \in \Theta_i | \mathbf{D}) = \int_{\Theta_i} p(\theta | \mathbf{D}) d\theta$  for  $i \in \{0, 1\}$ , which is marginalized over the nuisance parameters  $p(\theta | \mathbf{D}) = \int_{\Psi} p(\theta, \psi | \mathbf{D}) d\psi$ .

Define  $\delta \in [0, 1]$  as a threshold for *a compelling level of evidence* as it relates to  $\theta$ . We say that an individual is “all but convinced” that  $H_i$  is true given the observed data if  $P(\theta \in \Theta_i | \mathbf{D}) \geq \delta$  for  $i \in \{0, 1\}$ . The quantity  $1 - \delta$  reflects *residual uncertainty* of  $H_i$  being true relative to the competing hypothesis. For example, an individual would be “all but convinced” of the truth of the alternative hypothesis if  $P(\theta \in \Theta_1 | \mathbf{D}) \geq \delta$ .

The posterior distribution of  $\theta$  depends on the choice of prior distribution  $\pi(\theta, \psi)$  since  $p(\theta, \psi | \mathbf{D}) = p(\mathbf{D} | \theta, \psi) \pi(\theta, \psi) / p(\mathbf{D})$  by Bayes rule. The specification of the prior distribution depends on the research objective. An *inference prior* is a prior that is used when the research objective is to make final analysis after data collection is complete. A *monitoring prior* is a prior that is used when the research objective is to consider the impact of interim analyses on subject enrollment, with the potential for early termination (or less commonly prolongation).

It has been said that “the purpose of a trial is to collect data that bring to conclusive consensus at termination opinions that had been diverse and indecisive at the *outset*” (Kass and Greenhouse (1989), emphasis added). These opinions manifest as priors  $\pi(\theta, \psi)$  for which their relation to  $P(\theta \in \Theta_i | \pi(\theta, \psi))$   $i \in \{0, 1\}$  is examined. Note this quantity does not depend on the data  $\mathbf{D}$  and therefore reflects a-priori opinion. A skeptical prior is an informative or subjective prior that gives substantial preference to  $H_0$  such that it is “all but convinced” that  $H_0$  is true a-priori. This prior  $\pi_S(\theta, \psi) \equiv \pi_S$  has the property that  $P(\theta \in \Theta_0 | \pi_S) \geq \delta$  (equivalently  $P(\theta \in \Theta_1 | \pi_S) < 1 - \delta$ ). The choice of  $\delta \in [0, 1]$  is

motivated by *a compelling level of evidence* as it relates to  $\theta$ , although in this setting the “evidence” reflects a theoretical opinion rather than empirical judgement. For example, if  $\delta = 0.95$ , then this choice of skeptical prior places 95% prior probability that  $\theta \in \Theta_0$ . An enthusiastic prior  $\pi_E(\theta, \psi) \equiv \pi_E$  similarly gives preference to  $H_1$  through the property that  $P(\theta \in \Theta_1 | \pi_E) \geq \delta$  (equivalently  $P(\theta \in \Theta_0 | \pi_E) < 1 - \delta$ ). For purposes of interpretation, a *skeptical person* is someone whose a-priori opinions of  $\theta$  are reflected through a skeptical prior and a *enthuastic person* is someone whose a-priori opinions of  $\theta$  are reflected through an ethuastic prior. The prior distributions discussed are generally “non-informative” over the nuisance parameters.

The use of monitoring based on changing the opinion of skeptical and enthuastic priors has been described as overcoming a handicap (Freedman & Spiegelhalter (1989)) and providing a brake (Fayers et al. (1997)) on the premature termination of trials, or constructing “an adversary who will need to be disilusioned by the data to stop further experimentation” (Spiegelhalter et al. (1994)).

Early termination of the trial is appriopriate if diverse prior opinions about  $\theta$  would be in agreement given the interim data (e.g. the skeptical and enthuastic person reach the same conclusion). It is then reasonable to stop data collection if, upon seeing the data, a *skeptical person* changes their opinion to be “all but convinced” that  $H_1$  is true ( $P(\theta \in \Theta_1 | \mathbf{D}, \pi_S) \geq \delta$ ), or an *enthuastic person* becomes “all but convinced” that  $H_1$  is false ( $P(\theta \in \Theta_0 | \mathbf{D}, \pi_E) \geq \delta$ ).

Final inference on  $\theta$  is made once enrollment is stopped based on the monitoring priors or at the planned end of the trial. An inference prior  $\pi_I(\theta, \psi) \equiv \pi_I$  is often non-informative or objective in the sense that it does not show a-priori preference to  $H_0$  or  $H_1$  ( $P(\theta \in \Theta_0 | \pi_I) \approx P(\theta \in \Theta_1 | \pi_I)$ ). There are many ways to formulate an inference prior with this

property. We propose use of a mixture prior constructed from the monitoring process as the inference prior:

$$\pi_I = \omega \cdot \pi_S + (1 - \omega) \cdot \pi_E$$

for  $\omega \in [0, 1]$ . Choosing  $\omega = 1/2$  for an equal mixture of  $\pi_S$  and  $\pi_E$  corresponds to an inference prior that is impartial to  $H_0$  and  $H_1$ , and is a practical choice of  $\pi_I$  is to be determined before the start of data collection. Define  $p(\mathbf{D}|\pi(\theta, \psi)) = \int p(\mathbf{D}|\theta)\pi(\theta, \psi)d(\theta, \psi)$  to be the marginal likelihood for the data given the prior  $\pi(\theta, \psi)$ . Choosing  $\omega$  based on posterior model probabilities of the null and alternative hypotheses yields  $\omega = p(\mathbf{D}|\pi_S)/(p(\mathbf{D}|\pi_S) + p(\mathbf{D}|\pi_E))$ .

The determination of a significant trial result is given by

$$P(\theta \in \Theta_1|\mathbf{D}, \pi_I) \geq \delta.$$

All relevant information about  $\theta$  can be derived from its marginal posterior distribution with an inference prior (e.g. posterior mean, credible intervals). For example, the posterior mean using the inference prior will be a two-part mixture of the posterior means using the skeptical and enthusiastic priors:

$$\begin{aligned} E(\theta|\mathbf{D}, \pi_I) &= \omega \cdot E(\theta|\mathbf{D}, \pi_S) + (1 - \omega) \cdot E(\theta|\mathbf{D}, \pi_E) \\ \int_{\Theta} \theta p(\theta|\mathbf{D}, \pi_I)d\theta &= \omega \cdot \int_{\Theta} \theta p(\theta|\mathbf{D}, \pi_S)d\theta + (1 - \omega) \cdot \int_{\Theta} \theta p(\theta|\mathbf{D}, \pi_E)d\theta \end{aligned}$$

As an alternative strategy to futility analysis, one can monitor the probability of success (POS) for the trial. The probability of getting a convincing result at the end of the trail can be computed using the interim data. Let  $p(\theta|\mathbf{D}, \pi_I)$  denote the posterior distribution for  $\theta$  based on the inference prior  $\pi_I$  and the current data  $\mathbf{D}$ . Let  $\xi$  denote the POS which

is given as follows:

$$\begin{aligned}\xi &= P[\mathbf{D}_1 \in \mathbb{R}^{dim(\mathbf{D}_1)} | P(\theta \in \Theta_1 | \mathbf{D}_1, \mathbf{D}, \pi_I) \geq \delta] \\ &= E[1\{P(\theta \in \Theta_1 | \mathbf{D}_1, \mathbf{D}, \pi_I) \geq \delta\}]\end{aligned}$$

where the expectation is taken with respect to the posterior predictive distribution  $p(\mathbf{D}_1)$  for future data  $\mathbf{D}_1$  (which includes subjects yet to enroll):

$$p(\mathbf{D}_1) = \int p(\mathbf{D}_1 | \theta) \cdot \pi(\theta | \mathbf{D}) d\theta.$$

One may stop the enrollment if  $\xi$  is sufficiently small (i.e.  $\xi < 0.05$ ).

### 3 Examples – (EVAN)

#### 3.1 Single-Arm Oncology Proof-of-Activity Trial w/ Binary Endpoint

Consider a single-arm oncology proof-of-activity trial with a binary endpoint. The data  $\mathbf{D}$  is assumed to be Binomially distributed. The response rate  $\theta$  is the parameter effect of interest, which is the only unknown quantity in this simple situation.

Consider testing the hypothesis  $H_0 : \theta \leq \theta_0$  versus  $H_1 : \theta > \theta_0$ . Using the general notation  $\Theta_0 = [0, \theta_0]$  and  $\Theta_1 = (\theta_0, 1]$ . Consider a highly clinically relevant treatment effect  $\theta_A > \theta_0$ . It is desirable that the trial have appropriate power (probability of proving  $H_1$  when  $\theta = \theta_A$ ).

Monitoring priors for this trial will be made using the concepts of a skeptical prior and an enthusiastic prior. Recall a skeptic is “all but convinced” that  $H_0$  is true a-priori,

therefore  $P(\theta \in \Theta_0 | \pi_S) \geq \delta$ . An optimist is “all but convinced” that  $H_1$  is true a-priori, therefore  $P(\theta \in \Theta_1 | \pi_E) \geq \delta$ .

Beta priors for  $\theta$  will be used to provide closed-form expressions of the posterior distributions via Beta-Binomial conjugacy (the posterior distribution  $p(\theta | \mathbf{D})$  will be Beta distributed). The Beta distribution has two shape parameters. These parameters can be determined uniquely by specifying the desired mean and variance of the distribution. It is intuitive to center the skeptical and enthusiastic priors around the quantities  $\theta_0$  and  $\theta_A$  respectively, so that  $E(\pi_S) = \theta_0$  and  $E(\pi_E) = \theta_A$ . The variance for the skeptical and enthusiastic priors is then uniquely determined through by the choice of threshold  $\delta$ . In particular, let  $\pi_S(\theta) \sim \mathcal{B}(\alpha, \beta)$  be Beta distributed with shape parameters  $(\alpha, \beta)$ . There is a single choice of  $(\alpha, \beta)$  such that:

$$\theta_0 = E(\pi_S) = \int_{\Theta} \pi_S(\theta) d\theta = \frac{\alpha}{\alpha + \beta} \text{ and } \delta = \int_{\Theta_0} \pi_S(\theta) d\theta = \int_0^{\theta_0} \frac{\theta^{\alpha-1}(1-\theta)^{\beta-1}}{B(\alpha, \beta)} d\theta$$

where  $B(\alpha, \beta)$  is the Beta function.

Alternatively, the variance could be determined by specifying a desired quantile of the prior distribution which would then be reflected in  $\delta$ . For example, suppose it is desirable that the skeptical prior places small probability  $\lambda > 0$  that the  $\theta \geq \theta_A$ , which is the highly clinically relevant treatment effect. Then there is a single choice of  $(\alpha, \beta)$  such that

$$\theta_0 = E(\pi_S) = \int_{\Theta} \pi_S(\theta) d\theta = \frac{\alpha}{\alpha + \beta} \text{ and } \lambda = \int_{\theta_A}^1 \pi_S(\theta) d\theta = \int_{\theta_A}^1 \frac{\theta^{\alpha-1}(1-\theta)^{\beta-1}}{B(\alpha, \beta)} d\theta,$$

in which case  $\delta = \int_{\Theta_0} \pi_S(\theta) d\theta$  is a deterministic quantity.

Motivated by a trial for Vemurafenib (Hyman et al. (2015)) let  $\theta_0 = 0.15$  and  $\theta_A = 0.45$ . Consider the hypotheses

$$H_0 : \theta \leq 0.15$$

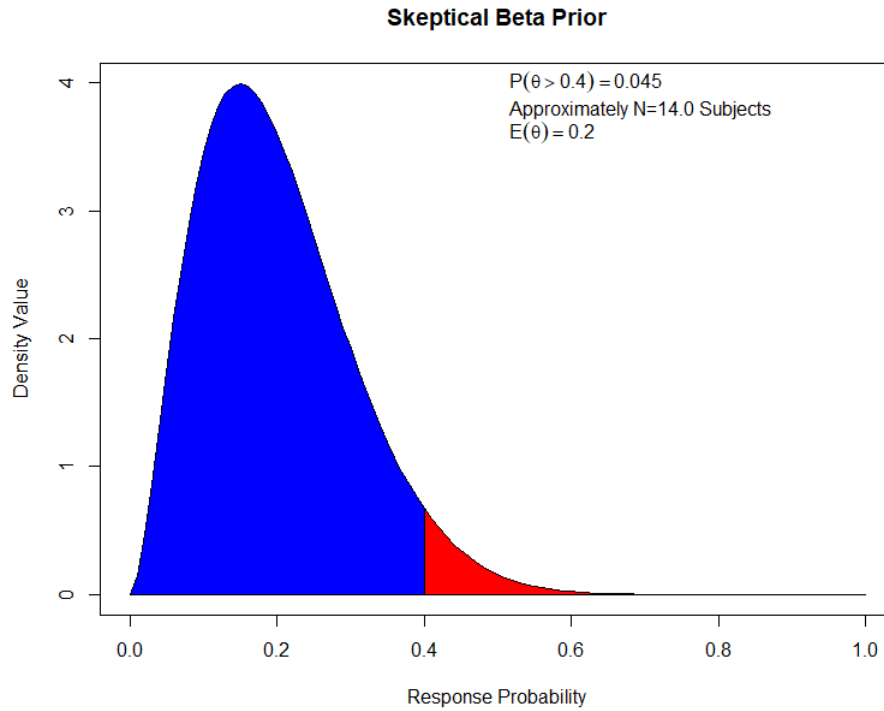
$$H_1 : \theta > 0.15$$



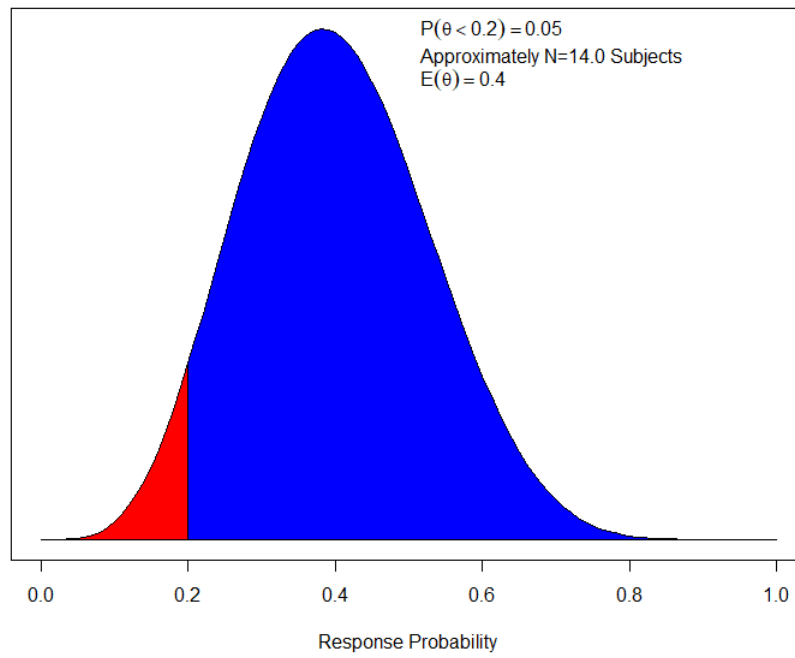
The skeptical prior will be Beta distributed, centered around  $\theta_0 = 0.15$ , and have 2.5% prior probability that  $\theta > \theta_A$ . Similarly, the enthusiastic prior will be centered around  $\theta_A = 0.45$  and have 2.5% prior probability that  $\theta < \theta_0$ . These priors are distributed as

$$\pi_S(\theta) \sim \mathcal{B}(1.187, 6.724)$$

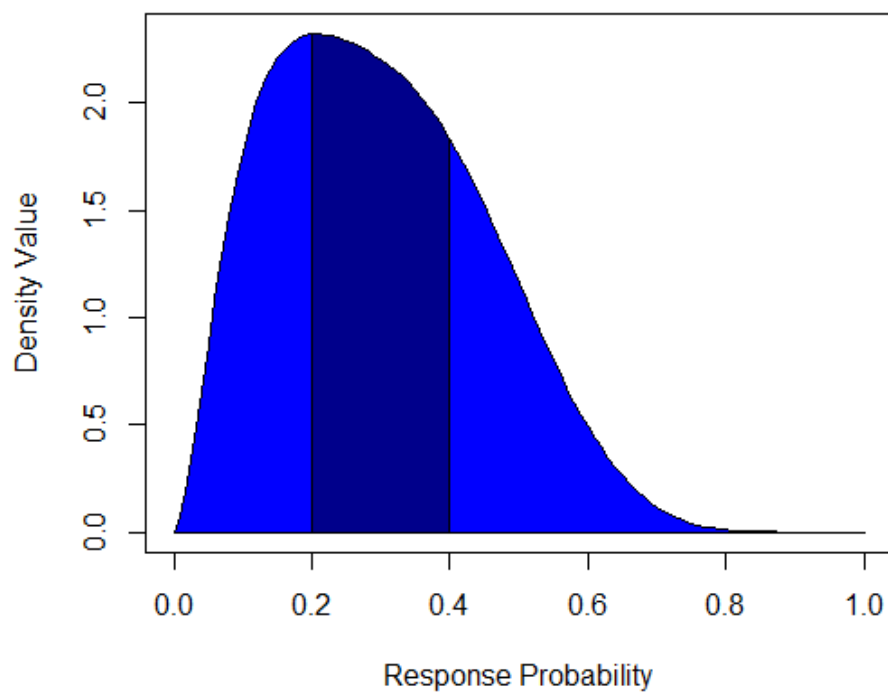
$$\pi_E(\theta) \sim \mathcal{B}(3.681, 4.499).$$



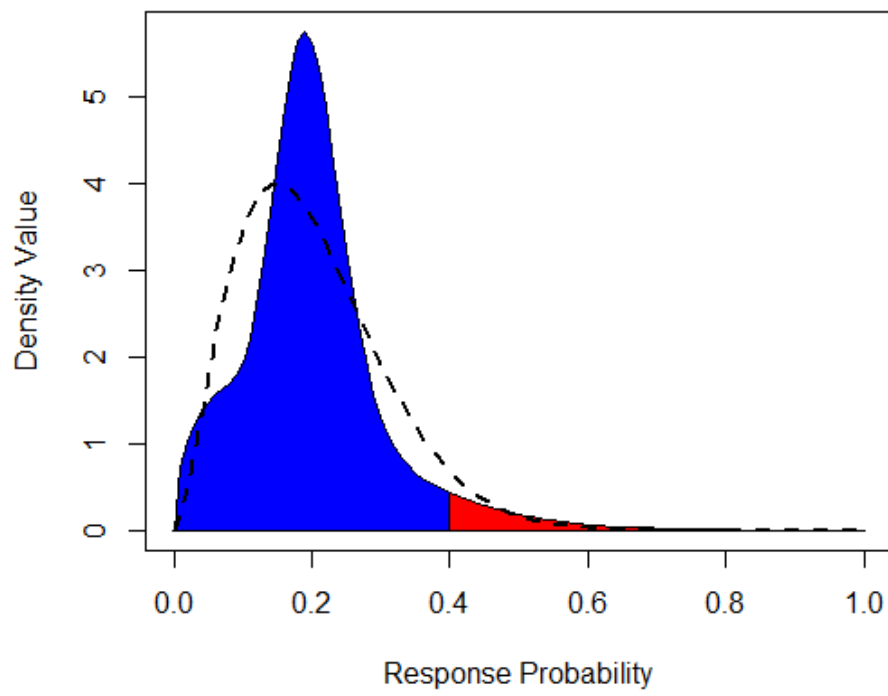
### Enthusiastic Beta Prior



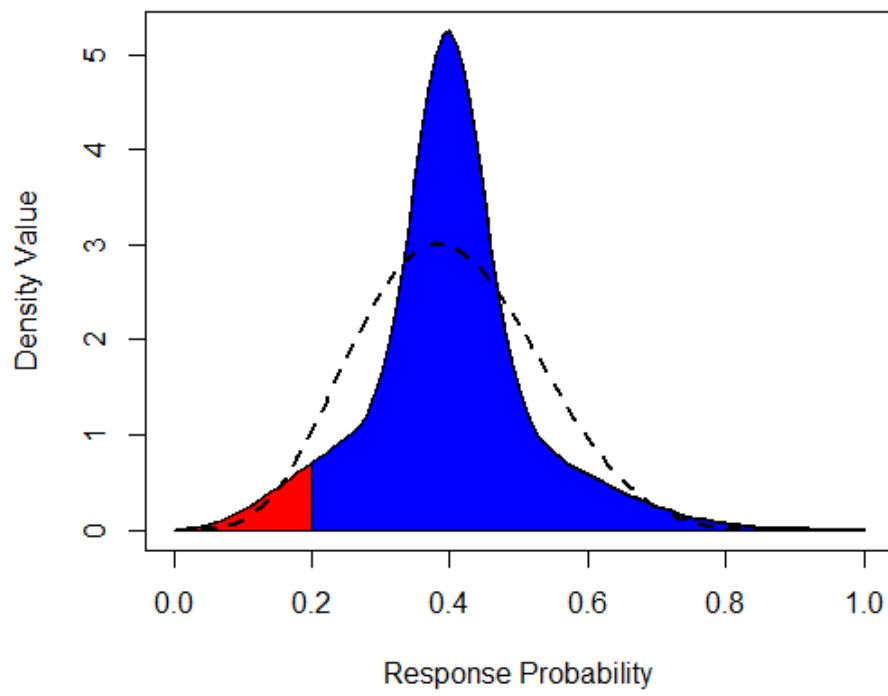
### 50/50 Mixture of Skeptical and Enthusiastic Priors



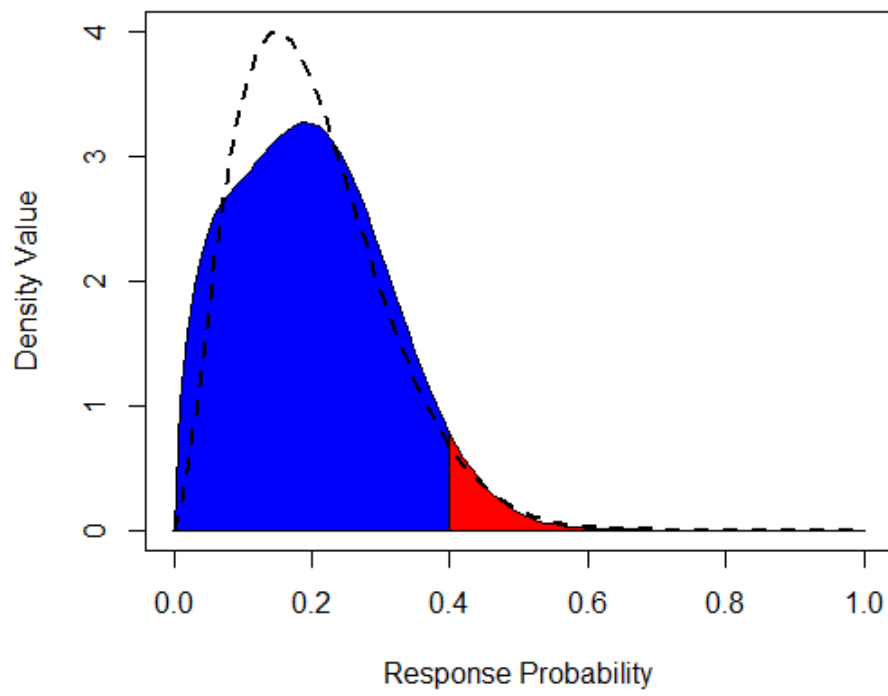
### Spike-Slab Skeptical Beta Prior



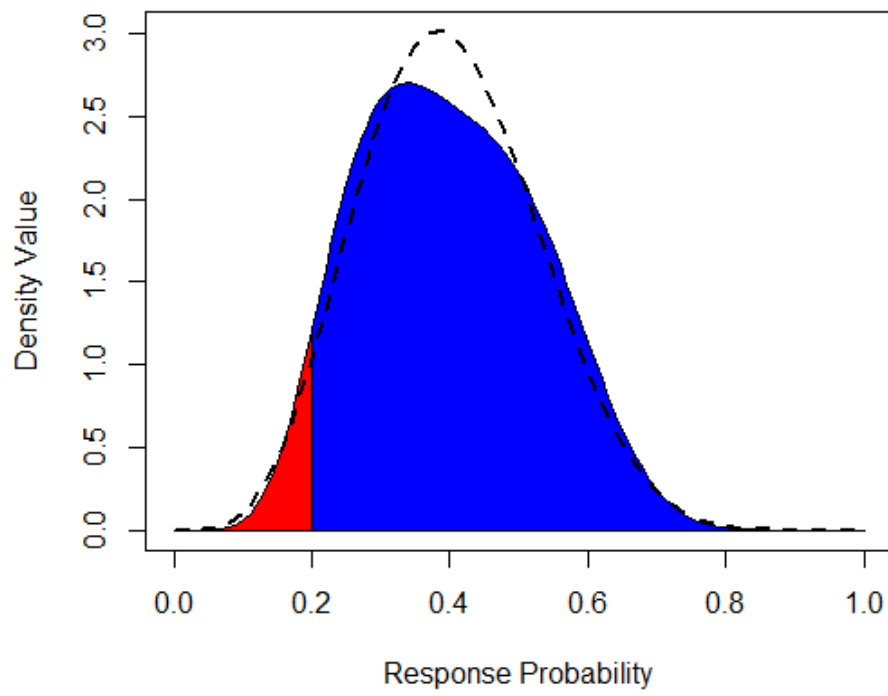
### Spike-Slab Enthusiastic Beta Prior



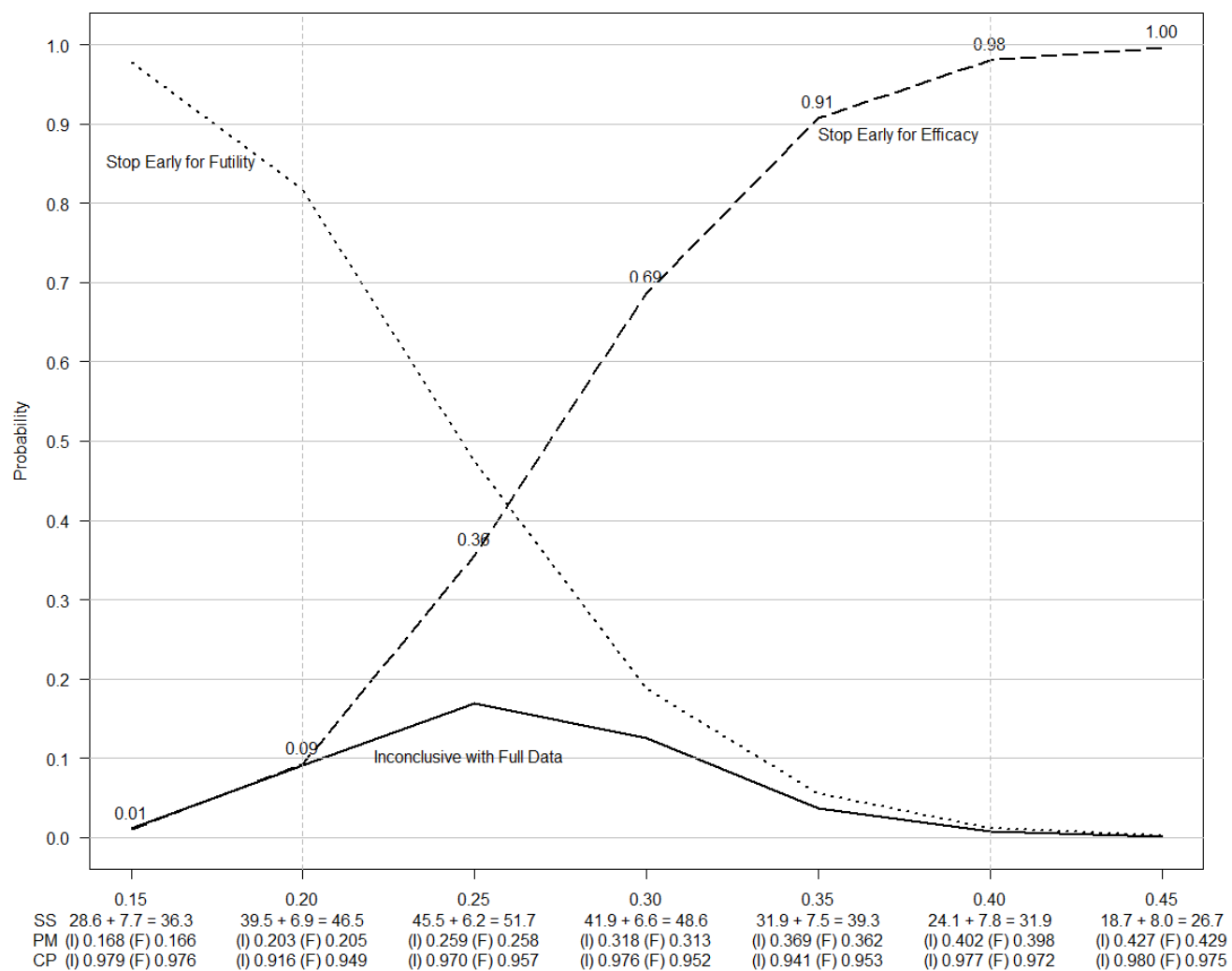
### Dampened Skeptical Beta Prior



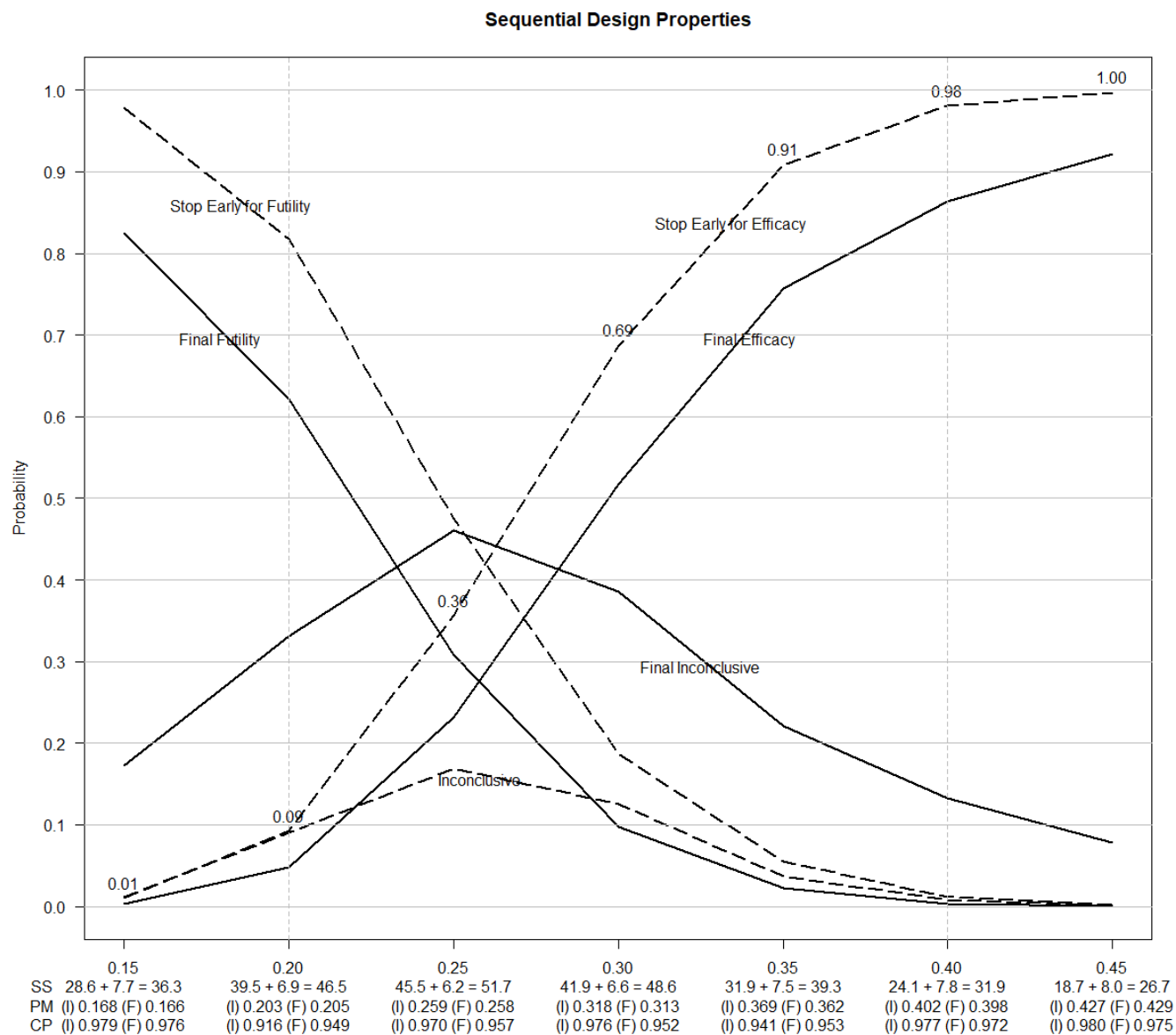
### Dampened Enthusiastic Beta Prior



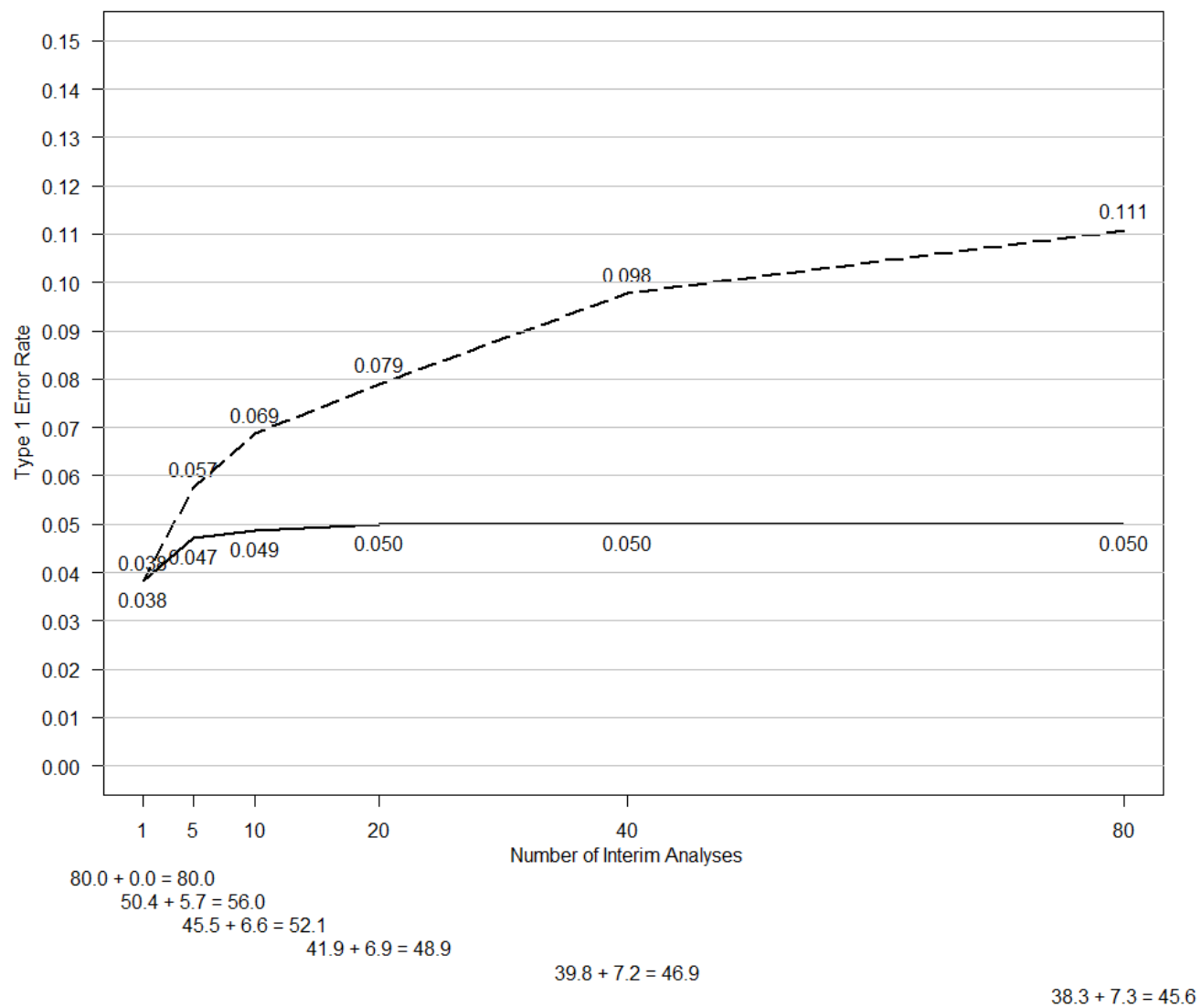
# Sequential Design Properties

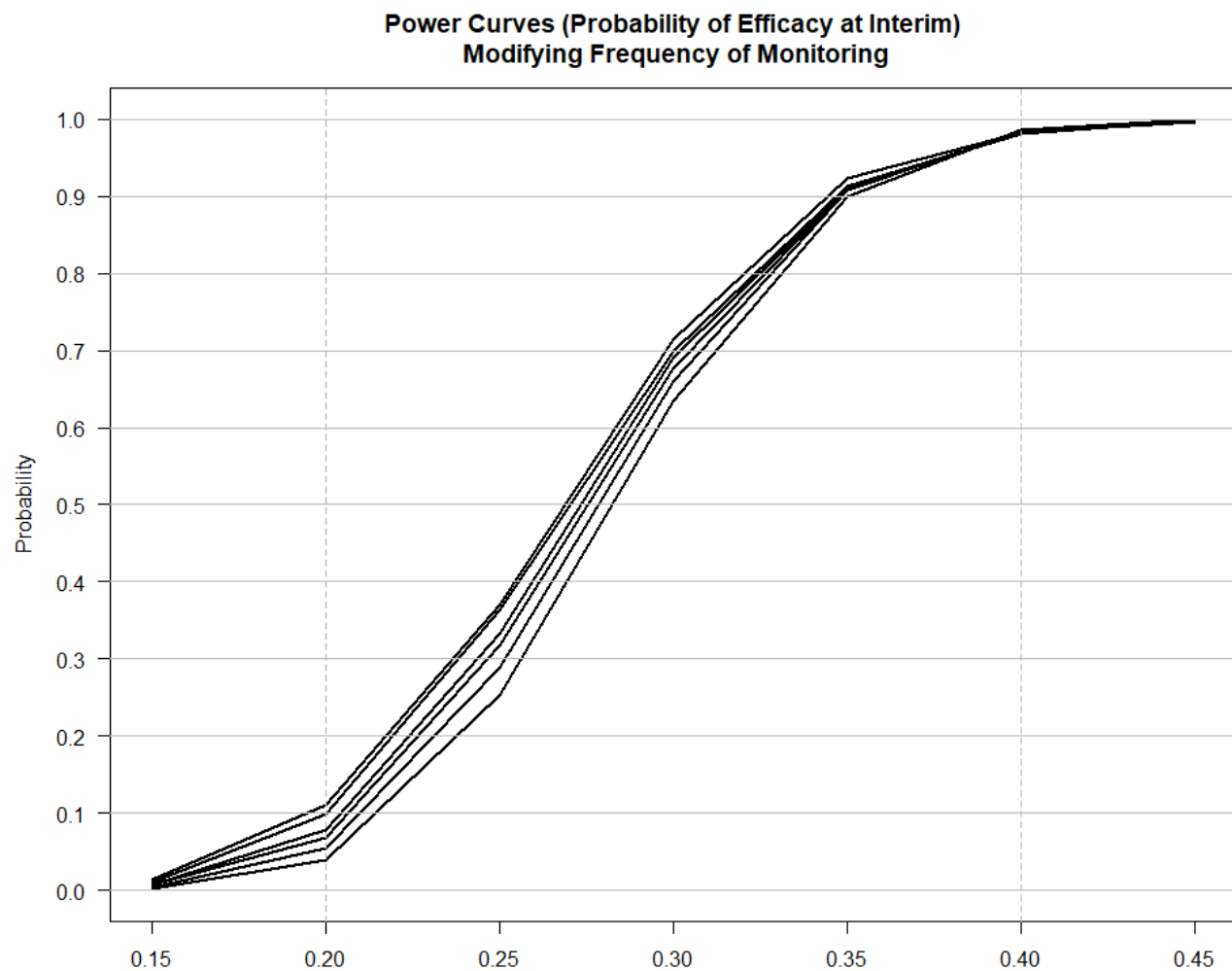






# 4 month follow-up, 2 enrollments per month





The trial will proceed until one of the following three conditions are satisfied:

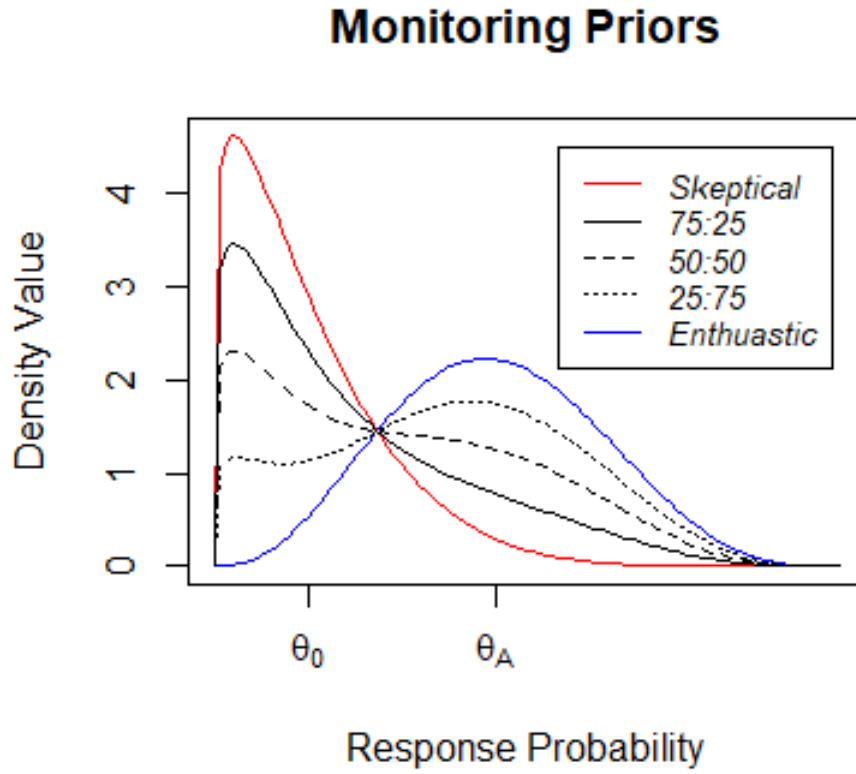
Efficacy criteria:  $P(\theta > 0.15|\mathbf{D}, \pi_S) \geq 0.95$

Futility criteria:  $P(\theta \leq 0.45|\mathbf{D}, \pi_E) \geq 0.95$

Exhausted resources:  $N = 14$  patient outcomes obtained,

where the maximum sample size is that of a frequentist trial design with a Type 1 error rate of 0.05 and 80% power.

The inference priors will be of the form  $\pi_I = \omega \cdot \pi_S + (1-\omega) \cdot \pi_E$  with  $\omega \in \{0, 1/4, 1/2, 3/4, 1\}$ .



- Show formulas for posterior model probabilities using inference prior
- Show formula that determines a significant trial result

Let  $y_1$  be the number of successes and  $y_0$  be the number of failures.

$$\text{Skeptical prior: } \pi_S(\theta) \sim \mathcal{B}(\alpha_S, \beta_S)$$

$$\text{Skeptical posterior: } p(\theta|\mathbf{D}, \pi_S) \sim \mathcal{B}(\alpha_S + y_1, \beta_S + y_0)$$

$$\text{Efficacy stopping: } P(\theta \in \Theta_1|\mathbf{D}, \pi_S) \geq \delta) \iff \int_{\theta_1}^1 p(\theta|\mathbf{D}, \pi_S)d\theta \geq \delta$$

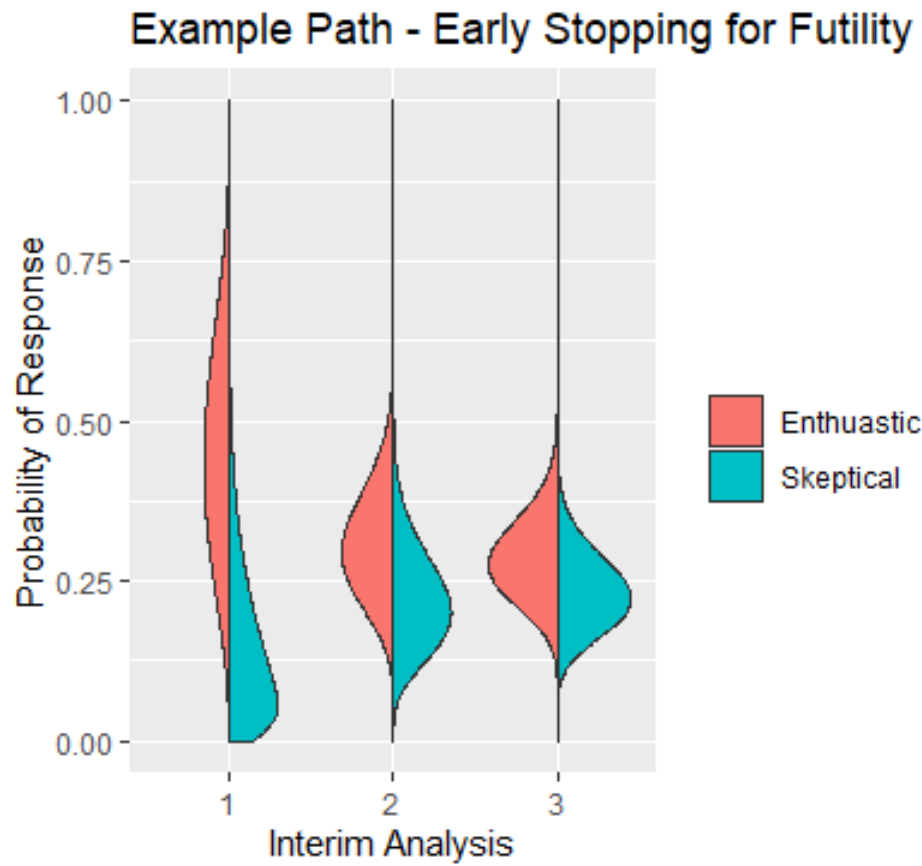
$$\text{Enthusiastic prior: } \pi_E(\theta) \sim \mathcal{B}(\alpha_E, \beta_E)$$

$$\text{Enthusiastic posterior: } p(\theta|\mathbf{D}, \pi_E) \sim \mathcal{B}(\alpha_E + y_1, \beta_E + y_0)$$

$$\text{Futility stopping: } P(\theta \in \Theta_0|\mathbf{D}, \pi_E) \geq \delta) \iff \int_0^{\theta_0} p(\theta|\mathbf{D}, \pi_E)d\theta \geq \delta$$

Figures needed:

1. An example path - early stoppage for efficacy (violin plots)
2. An example path - early stoppage for futility (violin plots)
3. Sequential design properties - slow vs. fast accrual (average sample size, posterior mean, coverage probabilities, distribution of final posterior probability).



Include plot of the Type 1 error rate by the frequency of data monitoring.

Look at varying the types of priors while keeping the tail areas the same. More spiked are OBF, less spiked are Pocock. Vary decay rate will affect bias not Type I/II error. Not dissimilar to Frequentist: flatter-Pocock, mass at null-OBF.

*Include details for how Bayesian monitoring has good frequentist properties even with frequent interim analyses.*

### 3.2 Parallel Two-Group Superiority Trial /w Continuous Binary Endpoint

Interesting because prior is on risk difference  $[-1,1]$  while also being non-informative on control group. Will need numerical integration to evaluate posteriors.

### 3.3 Three-Arm, Placebo Controlled Non-Inferiority Trial w/ Continuous Endpoint

$$P \rightarrow \beta_0 \text{ (placebo)}$$

$$C \rightarrow \beta_0 + \beta_1 \text{ (control)}$$

$$A \rightarrow \beta_0 + \beta_1 + \beta_2 \text{ (active)}$$

$$H_0 : \beta_2 - \delta\beta_1 \leq 0$$

Parameters of interest  $(\beta_1, \beta_2)$ , nuisance parameters  $(\beta_0, \sigma^2)$ .

Need priors  $\pi(\beta_0), \pi(\beta_1), \pi(\beta_2|\beta_1)$ .

Will use MCMC to evaluate posteriors.

## 4 Discussion – (MATT/EVAN)

Q: Why not reverse engineer priors to have exact Type 1 error properties?

A: This would basically be a frequentist method, in that the design would have to be adhered to exactly (including number and timing of data monitoring). Philosophically, designing a Bayesian study that requires rigid monitoring rules loses the advantages of Bayes from the likelihood principle.

## Meeting Notes 7/19/19

- For slides 22/23, it should say nmis not ymis.
- Violin plots are particular examples.
- Run replicates of trial to get frequentist properties.
- Poisson process enrollment,  $\lambda$ =rate parameter,  $1/\lambda$ =monthly enrollment. Consider the outcome ascertainment length in months.
- Interim/final results are consistent if quick/high enrollment relative to outcome ascertainment (think of the extreme example of instant ascertainment). Interim/final results could be inconsistent if slow/low enrollment relative to outcome ascertainment.
- The efficacy criteria (proving the null is not true (showing skeptical prior based centered  $H_0$  is now convinced)) is usually not changed in simulations.
- The futility criteria takes two forms: use futility prior based on intermediate value (between  $H_0$  and  $H_1$ ) if the intermediate value has clinical significance, otherwise use probability of success (POS). Pick one method to show in the paper, and show the other way is equivalent in the supplement.
- *Major point: Regardless of the frequency of monitoring there are good type 1 error rates.*
- Recall the best case for sequential monitoring is slow enrollment relative to outcome ascertainment (outcome ascertainment is quick to provide consistency with interim



and final results, enrollment is slow so there is substantial pragmatic benefit to ending trial early if possible).

- Create panel graph, with Slow, Medium, and High enrollment. Slow=1 subject per month, instantaneous outcome ascertainment. Medium=2 subjects per month, 1 month for outcome ascertainment. High=2 subjects per month, 2 months for outcome ascertainment. Show interim and final probability of rejecting  $H_0$ . Show how the type 1 error changes in each scenario. There is no gap in Slow case, and gap is highest in High case.
- Main ideas
  1. Show how the Bayesian monitoring can be done with examples based on violin plot idea. These examples will have variable enrollment rates to show agreement of interim/final.
  2. Show frequentist properties of sequential monitoring Bayesian trial when enrollment is slow relative to outcome ascertainment.
  3. Show how the frequentist Type 1 error rate inflates as a function of the # of times the data are monitored.
  4. Explore alternative distributions for skeptical and enthusiastic priors and discuss relationships to OBF and Pocock  $\alpha$ -spending. The alternative distributions could be mixtures of Betas.

## SUPPLEMENTARY MATERIAL

### 5 BibTeX

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