

# A Strategy for Structured Use of Bayesian Sequential Monitoring in Clinical Trials

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## Abstract

Conclusions from Bayesian sequential monitoring are coherent when specification of prior distributions are intuitively related to the research objectives. A compelling level of evidence is required to terminate enrollment for either efficacy or futility. This paper defines monitoring priors using generalized normal distributions parameterized via three specified quantities (mode and two tail probabilities), which reflect prior belief defined using a consistent definition of compelling level of evidence. These concepts are demonstrated through simulations based on a single-arm proof-of-activity trial in pediatric ulcerative colitis and a parallel two-group design in pediatric lupis.

*Keywords:* Generalized normal distribution, monitoring priors, real world evidence

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# 1 Introduction

A goal of the 21st Century Cures Act (U.S. Congress 2016) is to expedite the approval process for new drugs and devices through the incorporation of real-world evidence into clinical trial data summaries. Similarly, an objective of the Prescription Drug User Fee Act VI is to enhance the capacity to review “complex adaptive, Bayesian, and other novel clinical trial designs.” (U.S. Food and Drug Administration n.d.) Bayesian designs are natural for incorporating external evidence through prior distributions. This is useful in areas where clinical trials would take a lot of time due to slow enrollment or long follow-up periods, and where relevant external data exists. For example, a treatment for a rare pediatric disease might have difficulties with enrollment, and there may be relevant data from adult trials which could augment the trial findings and lead to a conclusion of efficacy sooner. Group sequential designs also have the possible benefits of leading to conclusions earlier, saving time and resources, as well as reducing the exposure of patients to inferior treatments. Bayesian sequential designs which incorporate external evidence therefore have a much increased capacity to expedite the approval process for effective treatments, but they must be carefully planned. The effects of interim analyses and the informativeness of the priors must be well understood. 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.

The likelihood principle asserts that any data with the same likelihood function should lead to the same conclusion (Berger & Wolpert 1988). In the context of sequential analysis of clinical trials, the stopping rule that led to the termination of data collection is irrelevant to the conclusion (Barnard 1947, Anscombe 1963, Cornfield 1966*a,b*). It is most succinctly as “It is entirely appropriate to collect data until a point has been proven or disproven, or until the data collector runs out of time, money, or patience.” (Edwards et al. 1963). Bayesian conclusions are not affected by frequent or even continual monitoring of the data, and such interim analyses should be encouraged to terminate data collection if appropriate (Berry 1989, 1993, Spiegelhalter et al. 1994).

Interpretation of conclusions from the Bayesian perspective is natural when specification of prior distributions are intuitively related to the research objectives (e.g. skeptical and enthusiastic priors) (Freedman & Spiegelhalter 1989, 1992, Spiegelhalter et al. 1993, Fayers et al. 1997) which is necessary for regulatory agencies (Parmar & Machin 1993). Bayesian monitoring is further formalized by specifying the loss function via decision theory (Carlin et al. 1998).

This paper is organized as follows: Section 2 contains a brief review of Bayesian hypothesis testing using posterior probabilities, and describes the method for defining monitoring and inference priors. Examples are in Section 3, with Section 3.1 containing a one-arm study and Section 3.2 a two-arm study.

## 2 Methods

### 2.1 Preliminaries

#### 2.1.1 Bayesian hypothesis testing using posterior probabilities

Consider a one-arm trial with a single measured outcome per patient. The objective is to make inference on a single unknown quantity. Let  $\mathbf{D}$  be a random variable representing the data collected in the trial with density  $p(\mathbf{D}|\theta)$ , where  $\theta$  is the parameter of interest with sample space  $\theta \in \Theta$ . For example, in the context of a simple binary outcome (e.g., objective response to treatment) based on sample size  $n$ ,  $\mathbf{D} = (y_1, \dots, y_n)$  may correspond to the  $n$  indicators for whether or not subjects responded to a treatment and  $\theta \in [0, 1]$  may correspond to an assumed common probability of response.

Formal Bayesian hypothesis testing requires the specification of prior probabilities on the hypotheses (e.g.,  $p(H_i)$  for  $i = 0, 1$ ) and prior distributions for  $\theta$  for each hypothesis (e.g.,  $\pi(\theta|H_i)$  for  $i = 0, 1$ ). Consider the hypotheses  $H_0 : \theta \in \Theta_0$  versus  $H_1 : \theta \in \Theta_1$  where  $\Theta_0 \cup \Theta_1 = \Theta$  and  $\Theta_0 \cap \Theta_1 = \emptyset$ .

The posterior probability of hypothesis  $H_i$  is

$$p(H_i|\mathbf{D}) = \frac{p(\mathbf{D}|H_i) \cdot p(H_i)}{p(\mathbf{D}|H_0) \cdot p(H_0) + p(\mathbf{D}|H_1) \cdot p(H_1)} \quad (1)$$

$$= \frac{\int_{\Theta_i} p(\mathbf{D}|\theta, H_i) \pi(\theta|H_i) d\theta \cdot p(H_i)}{p(\mathbf{D}|H_0) \cdot p(H_0) + p(\mathbf{D}|H_1) \cdot p(H_1)}. \quad (2)$$

The posterior probability of the *event defining*  $H_i$  is

$$P(\theta \in \Theta_i|\mathbf{D}) = \int_{\Theta_i} p(\theta|\mathbf{D}) d\theta \quad (3)$$

$$= \frac{\int_{\Theta_i} p(\mathbf{D}|\theta) \pi(\theta) d\theta}{\int_{\Theta} p(\mathbf{D}|\theta) \pi(\theta) d\theta} \quad (4)$$

$$= \frac{\int_{\Theta_i} p(\mathbf{D}|\theta) \pi(\theta|\theta \in \Theta_i) d\theta \cdot P(\theta \in \Theta_i)}{\int_{\Theta} p(\mathbf{D}|\theta) \pi(\theta) d\theta}, \quad (5)$$

where  $P(\theta \in \Theta_i) = \int_{\Theta_i} \pi(\theta) d\theta$ .

When  $p(H_i) = P(\theta \in \Theta_i)$  and  $\pi(\theta|H_i) = \pi(\theta|\theta \in \Theta_i)$  for  $i = 0, 1$ , it follows that the posterior probability of the event defining the alternative hypothesis and the posterior probability of the alternative hypothesis are equivalent.

Consistent with the specifications of  $p(H_i)$  and  $\pi(\theta|H_i)$  as described above, in what follows we will refer to the quantity  $P(\theta \in \Theta_1|\mathbf{D})$  as the posterior probability of  $H_i$  for ease of exposition.

#### 2.1.2 Compelling level of evidence

Define  $\epsilon$  as the *residual uncertainty* of  $H_i$  being true relative to the competing hypothesis, and define  $1 - \epsilon \in (0, 1)$  as the threshold for a *compelling level of evidence* that some claim about  $\theta$  is true. We say

that an individual is *all but convinced* that  $H_i$  is true given the observed data if they believe that

$$P(\theta \in \Theta_i | \mathbf{D}) > 1 - \epsilon. \quad (6)$$

Furthermore,  $1 - \epsilon \in (0, 1)$  can be used as a threshold for *a compelling a priori belief* that some claim about  $\theta$  is true before the beginning of the trial. We say that an individual is *all but convinced* that  $H_i$  is true a priori if they believe that

$$P(\theta \in \Theta_i) > 1 - \epsilon. \quad (7)$$

### 2.1.3 Skeptical and Enthusiastic Monitoring Priors

Continuing the trial setup from Section 2.1, suppose every subject receives active treatment during the follow-up period from enrollment to study completion. The length of follow-up is the same for each subject. Subjects are enrolled progressively such that there is a time when there are both subjects with completed outcomes and subjects undergoing follow-up. In this paper we introduce two types of prior: monitoring and inference priors.

The purpose of monitoring priors is to help answer the question “Is the evidence compelling enough to end the trial early?” Monitoring priors are used for interim analyses on the data from subjects who completed follow-up while additional outcomes are pending. A promising interim result that shows clear efficacy of the treatment would justify stopping the enrollment of additional subjects, while enrolled subjects would continue receiving the presumed effective treatment during the follow-up period. A discouraging interim result that shows clear futility of the treatment would justify stopping the enrollment of additional subjects, and may call for enrolled patients undergoing follow-up to stop receiving the presumed ineffective treatment.

To have either efficacy or futility to be “clear” the evidence must be convincing to individuals with diverse opinions of  $\theta$ . The judgment of efficacy must be convincing even to an individual who was initially skeptical about the benefit of the treatment. Likewise, the judgment of futility must be convincing to an individual who was initially optimistic. For this reason monitoring priors generally represent relatively extreme (but still plausible) beliefs about  $\theta$ . If a skeptic has become confident that the treatment is efficacious, that implies essentially anyone with some degree of equipoise would also be convinced, hence individuals with diverse opinions have a consensus. Alternatively, if an enthusiast has become convinced that the treatment is ineffective, then essentially everyone will share that opinion.

Monitoring priors will be defined based on the concepts of compelling a priori belief defined in Section 2.1. Continuing the trial setup from Section 2.1, suppose that  $\theta$  corresponds to a probability of desired

response, and the null hypothesis is  $H_0 : \theta \leq \theta_0$  where  $\theta_0$  is the expected null response among untreated subjects. Let  $\theta_1 > \theta_0$  be a highly efficacious response probability.

We define an enthusiastic prior  $\pi_E(\theta)$  as a prior that is centered around  $\theta_1$  and reflects the belief of an individual that is *all but convinced* that  $H_i$  is true a priori, that is,

$$P(\theta > \theta_0 | \pi_E) > 1 - \epsilon. \quad (8)$$

Consider a similarly defined skeptical prior  $\pi_S(\theta)$  that is centered around  $\theta_0$  and reflects the belief of an individual that is *all but convinced* that  $H_0$  is true a priori, that is,  $P(\theta \leq \theta_0 | \pi_S) > 1 - \epsilon$ . Having this belief demonstrates such an extreme disbelief in the possibility of a positive effect that conducting the trial at all would be viewed as dubious. This is analogous to specifying a prior model probability on  $H_0$  that is  $1 - \epsilon$  and that is not consistent with their being clinical equipoise about the hypotheses; such extreme skepticism is not rational if a trial is to be conducted.

Instead, we define the skeptical prior  $\pi_S(\theta)$  to be centered around  $\theta_0$  and reflects the belief of an individual that is *all but convinced* that a highly efficacious response probability is unlikely, that is,

$$P(\theta > \theta_1 | \pi_S) < \epsilon. \quad (9)$$

The enthusiastic and skeptical conditions defined in (8), (9) will be referred to as tail-probability constraints.

#### 2.1.4 Criteria for Early Stoppage

The use of monitoring based on changing the opinion of skeptical and enthusiastic 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 disillusioned by the data to stop further experimentation” (Spiegelhalter et al. (1994)). Early termination of enrollment is appropriate if diverse prior opinions about  $\theta$  would be in agreement given the interim data (e.g. the skeptical and enthusiastic person reach the same conclusion).

The skeptic, whose prior belief is reflected in (9), becomes convinced the treatment is effective if there is compelling evidence that  $\theta > \theta_0$  is true (6), that is,

$$P(\theta < \theta_1 | \pi_S) > 1 - \epsilon \Rightarrow P(\theta > \theta_0 | \mathbf{D}, \pi_S) > 1 - \epsilon. \quad (10)$$

Consider  $\theta < \frac{\theta_0 + \theta_1}{2}$  to be a response that is less than the highly efficacious response probability  $\theta_1$ . The enthusiast, whose prior belief is reflected in (8), becomes convinced the treatment is ineffective, or not as effective as anticipated, if there is compelling evidence that  $\theta < \frac{\theta_0 + \theta_1}{2}$ , that is,

$$P(\theta > \theta_0 | \pi_E) > 1 - \epsilon \Rightarrow P\left(\theta < \frac{\theta_0 + \theta_1}{2} \middle| \mathbf{D}, \pi_E\right) > 1 - \epsilon. \quad (11)$$

## 2.2 Monitoring Prior Specification

### 2.2.1 Normal Family of Distributions

The enthusiastic and skeptical priors defined in (8), (9) each have a required center (modal value) and tail-probability constraint, however, there are still many ways to parameterize such distributions. The specification of the mean and variance of a normal distribution completely specifies the modal value and tail-probability constraints, and is therefore sufficient for defining enthusiastic and skeptical priors.

Consider the normal distribution for a random variable  $\theta$

$$p(\theta; \mu, \sigma) = \frac{1}{\sigma\sqrt{2\pi}} \exp \left\{ -\frac{1}{2} \left( \frac{\theta - \mu}{\sigma} \right)^2 \right\} \quad (12)$$

with quantile function for  $p \in (0, 1)$

$$Q(p; \mu, \sigma) = \mu + \sigma\sqrt{2} \operatorname{erf}^{-1}(2p - 1) \quad (13)$$

where  $\operatorname{erf}^{-1}$  is the inverse of the error function.

Consider creating an enthusiastic prior that is centered around  $\theta_1$  and satisfies the tail-probability condition of (8), which is expressed as  $Q(\theta_0; \mu = \theta_1, \sigma) = \epsilon$ . This is the normal distribution

$$\pi_E(\theta) \sim N \left( \mu = \theta_1, \sigma = \frac{\theta_0 - \theta_1}{\sqrt{2} \operatorname{erf}^{-1}(2\epsilon - 1)} \right) \quad (14)$$

By symmetry, a skeptical prior that is centered around  $\theta_0$  and satisfies the tail-probability condition of (9), which is expressed as  $Q(\theta_1; \mu = \theta_0, \sigma) = 1 - \epsilon$ , is the normal distribution with  $\mu = \theta_0$  and the same variance as (14).

### 2.2.2 The Generalized Normal Family of Distributions

For additional flexibility, we will consider the generalized normal distribution for prior specification. Consider the generalized normal distribution for a random variable  $\theta$

$$p(\theta; \mu, \alpha, \beta) = \frac{\beta}{2\alpha\Gamma(1/\beta)} \exp \left\{ - \left( \frac{|\theta - \mu|}{\alpha} \right)^\beta \right\} \quad (15)$$

where  $\mu \in \mathbb{R}$  is a location parameter,  $\alpha > 0$  is a scale parameter, and  $\beta > 0$  is a shape parameter. Note that  $\beta = 2$  corresponds to the normal distribution.

The quantile function for  $p \in (0, 1)$  is

$$Q(p; \mu, \alpha, \beta) = \operatorname{sign}(p - 0.5) g \left( 2|p - 0.5|; \frac{1}{\beta} \left( \frac{1}{\alpha} \right)^\beta \right)^{1-\beta} + \mu, \quad (16)$$

where  $g\left(2|p - 0.5|; \frac{1}{\beta} \left(\frac{1}{\alpha}\right)^\beta\right)$  refers to the inverse CDF for a gamma distribution with shape  $\frac{1}{\beta}$  and rate  $(\frac{1}{\alpha})^\beta$  evaluated at  $2|p - 0.5|$ .

Consider creating an enthusiastic prior that is centered around  $\theta_1$  and satisfies the tail-probability condition of (8), which is expressed as

$$Q(\theta_0 : \mu = \theta_1, \alpha, \beta) = \epsilon \quad (17)$$

and that also satisfies a second tail-probability condition

$$Q\left(\frac{\theta_0 + \theta_1}{2}; \mu = \theta_1, \alpha, \beta\right) = \epsilon + \gamma \quad (18)$$

for  $\gamma > \epsilon$ . There is a unique combination of  $\alpha$  and  $\beta$  that satisfy (17) and (18).

The modification of  $\beta$  can be used to concentrate or flatten the distribution around the modal value. If  $\beta < 2$  then the distribution becomes more peaked relative to a normal distribution, and if  $\beta > 2$  then the distribution becomes flatter. Examples of skeptical and enthusiastic priors for a single parameter  $\theta$  based on the trial from Section 2.1 are displayed in Figure 1. The location and shape parameters are pre-specified, and the scale parameter is chosen to satisfy the tail-probability constraints (8), (9).

The normal and generalized normal family of distributions can be truncated to a restricted domain that reflects the research quantity of interest (e.g. a response probability on  $[0,1]$ ).

### 2.2.3 Application to higher dimensions

The generalized normal distribution can be used to parameterize skeptical and enthusiastic priors for trials with multiple unknown quantities of interest. Suppose the trial from Section 2.1 has added a control arm, and let  $\theta_0$  and  $\theta_1$  be the response proportions for a control and treatment group respectively. Suppose that the risk difference  $\theta_1 - \theta_0$  is of interest. Let  $\delta_0$  denote a null risk difference and  $\delta_1$  denote a highly efficacious risk difference.

Consider the following representation of the joint prior for  $\theta_1$  and  $\theta_0$ :

$$\pi(\theta_0, \theta_1) = \pi(\theta_0) \times \pi(\theta_1 | \theta_0). \quad (19)$$

Each of these components can be represented in the form of (15) by

$$\pi(\theta_0) \propto \exp \left\{ - \left( \frac{|\theta_0 - \mu_0|}{\alpha_0} \right)^{\beta_0} \right\} \quad (20)$$

$$\pi(\theta_1 | \theta_0) \propto \exp \left\{ - \left( \frac{|(\theta_1 - \theta_0) - \delta|}{\alpha_1} \right)^{\beta_1} \right\} f(\theta_0). \quad (21)$$

The component  $\pi(\theta_0)$  reflects prior opinion about the response rate in the placebo group, and the component  $\pi(\theta_1 | \theta_0)$  can be used to express pessimism or optimism in the difference in proportions  $\theta_1 - \theta_0$ .

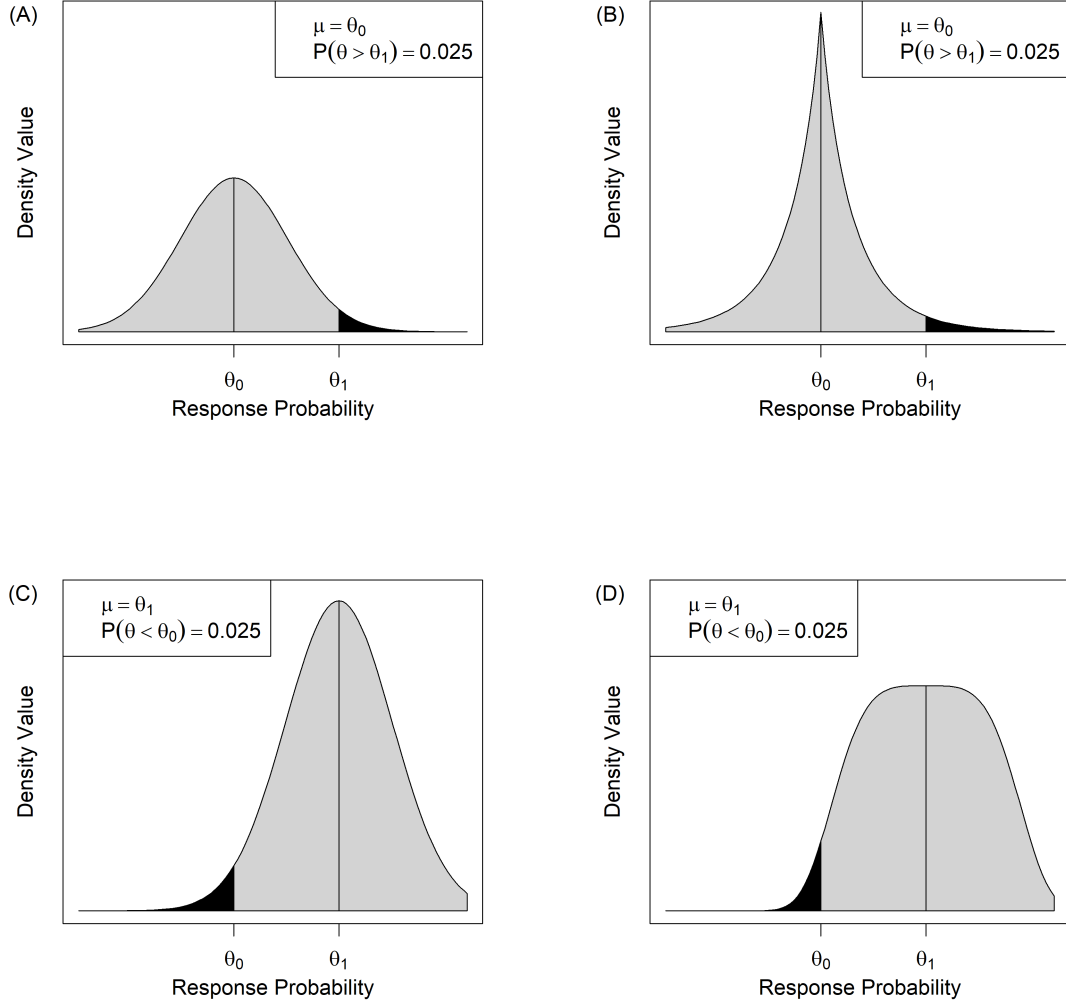


Figure 1: A, Skeptical prior, normal distribution. B, Skeptical prior, generalized normal distribution with added concentration around modal value. C, Enthusiastic prior, normal distribution. D, Enthusiastic prior, generalized normal distribution with added flattening around modal value.



The enthusiastic prior condition from (8) become

$$P(\theta_1 - \theta_0 > \delta_0) = 1 - \epsilon. \quad (22)$$

The skeptical prior condition from (9) become

$$P(\theta_1 - \theta_0 < \delta_1) = 1 - \epsilon. \quad (23)$$

Examples of skeptical and enthusiastic priors are displayed in Figure 2.

## 2.3 Mixture Inference Priors

### 2.3.1 Definition

The purpose of the inference prior is to synthesize the posterior inferences from the a priori diverse perspectives to facilitate interpretation of the data once it has been obtained. In this paper we propose using an inference prior that is a combination of the skeptical and enthusiastic priors that were used for monitoring.

The skeptical and enthusiastic monitoring priors defined in Section 2.1.3 represent extreme but plausible beliefs about  $\theta$ . While analysis with these priors provides a rational perspective from which one can determine whether interim data are sufficient to cease enrolling patients, the a priori belief of most stakeholders will likely fall somewhere in between. Thus, when it interpreting the final data once in hand, intermediate perspectives should be considered. To that end, we define an inference prior as a mixture prior constructed by mixing the monitoring priors. Formally, the inference prior associated with mixing weight  $\omega$  is given by

$$\pi_I(\theta) = \omega \cdot \pi_S(\theta) + (1 - \omega) \cdot \pi_E(\theta), \quad (24)$$

where  $\omega \in [0, 1]$ . The specification of  $\omega$  is done a priori, and the value  $\omega = 1/2$  will be referred to as an agnostic inference prior since it gives equal weight to the skeptical and enthusiastic prior.

The distribution of  $\theta$  using the inference prior,  $p(\theta|\mathbf{D}, \pi_I)$ , will be used to compute summaries of  $\theta$  such as the posterior mean and quantiles. The posterior distribution for  $\theta$  using (24) is

$$p(\theta|\mathbf{D}, \pi_I) = \hat{\omega} \cdot p(\theta|\mathbf{D}, \pi_S) + (1 - \hat{\omega}) \cdot p(\theta|\mathbf{D}, \pi_E) \quad (25)$$

where the updated mixing weight is

$$\hat{\omega} = \frac{\omega \cdot p(\mathbf{D}|\pi_S)}{\omega \cdot p(\mathbf{D}|\pi_S) + (1 - \omega) \cdot p(\mathbf{D}|\pi_E)} \quad (26)$$

where  $p(\mathbf{D}|\pi_S) = \int p(\mathbf{D}|\theta)\pi_S(\theta)d\theta$  and  $p(\mathbf{D}|\pi_E) = \int p(\mathbf{D}|\theta)\pi_E(\theta)d\theta$ .

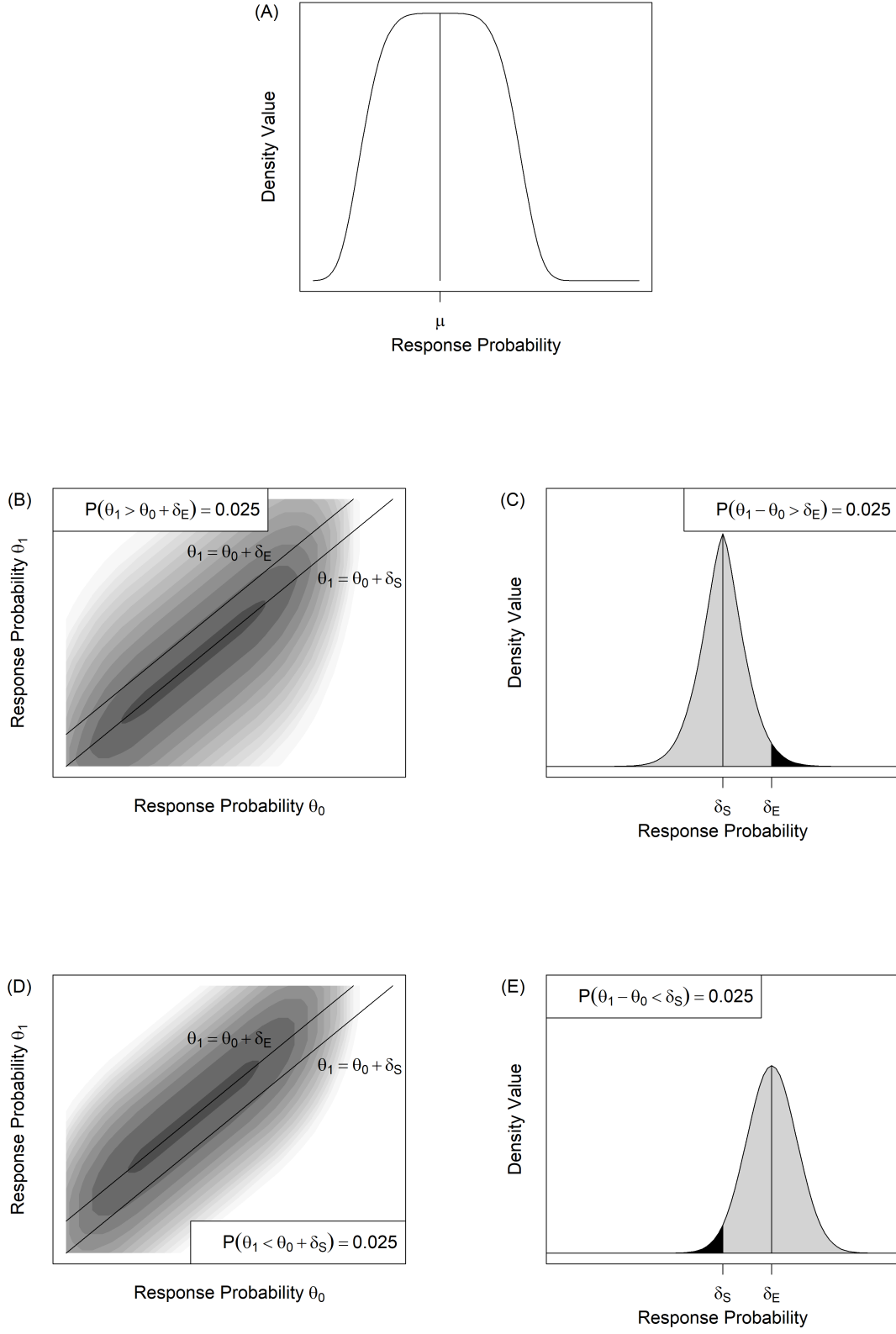


Figure 2: A, Univariate prior  $\pi(\theta_0)$ . B, Skeptical joint prior  $\pi_S(\theta_0, \theta_1)$ . C, Skeptical marginal prior  $\pi_S(\theta_1 - \theta_0)$ . D, Enthusiastic joint prior  $\pi_E(\theta_0, \theta_1)$ . E, Enthusiastic marginal prior  $\pi_E(\theta_1 - \theta_0)$ .

### 2.3.2 Incorporating Prior Information in the Monitoring Priors

The skeptical and enthusiastic monitoring priors can be viewed as a weighted combination such as in the inference prior (24) with weights  $\omega = 1$  and  $\omega = 0$  respectively. This weighted combination can be used as a replacement for the monitoring prior for any fixed weight  $\omega$ . For example, a “not-as-skeptical” prior can be defined as  $\tilde{\pi}_S(\theta) = 0.75 \cdot \pi_S(\theta) + 0.25 \cdot \pi_E(\theta)$ .

Alternatively,  $\omega$  can be informed by the data. Let  $\hat{\theta} = \operatorname{argmax}\{p(\mathbf{D}|\theta)\}$  be the maximum likelihood estimator of  $\theta$  given the data. Define

$$\omega = \frac{\pi_S(\hat{\theta})}{\pi_S(\hat{\theta}) + \pi_E(\hat{\theta})} \quad (27)$$

as a mixing weight that dynamically gives preference to the prior that has the higher density evaluated at  $\hat{\theta}$ .

## 3 Examples

### 3.1 Single-Arm Proof-of-Activity Trial with Binary Endpoint

#### 3.1.1 Motivating example

Consider the T72 pediatric trial “A Study of the Safety and Efficacy of Infliximab (REMICADE) in Pediatric Patients With Moderately to Severely Active Ulcerative Colitis” (NCT00336492) Hyams et al. (2012). Infliximab was given to all subjects at the 5mg/kg dose at weeks 0, 2, and 6, and the primary end point was response at week 8. Response was measured by improvement in disease severity scores.

The initial enrollment occurred on August 25, 2006, and the last assessment was June 24, 2010. If the patient showed improvement at week 8 then they continued treatment and would have their last assessment at week 54. The response rate at 8 weeks was 73.3% ( $N = 60$ ), so it is likely that the last assessment was at week 54, and we can infer enrollment took place over approximately 33.5 months (approximately 1 enrollment per 17 days).

The sample size of 60 patients was chosen to ensure 12% precision in estimating the true response proportion with at 95% CI, assuming a response rate of 67% as was observed among adults from the ACT 1 and ACT 2 trials Rutgeerts et al. (2005) at the same 5mg/kg dose ( $N = 242$ ). A 95% confidence interval that excluded 0.40 was determined to be a clinically significant result.

### 3.1.2 Model formulation & prior elicitation

The data  $\mathbf{D}$  are assumed to be independent Bernoulli random variables with common response probability  $\theta$ . The null response value is  $\theta_0 = 0.40$  and a highly efficacious response probability is  $\theta_1 = 0.67$ . The hypothesis for this trial is  $H_0 : \theta \leq \theta_0$  vs  $H_1 : \theta > \theta_0$ .

The default skeptical and enthusiastic priors will be of the form (15) and are truncated to the unit interval.

$$\pi_S(\theta) \propto \exp \left\{ -\frac{|\theta - \theta_0|^{\beta_S}}{\alpha_S} \right\} I(\theta \in [0, 1]) \quad (28)$$

$$\pi_E(\theta) \propto \exp \left\{ -\frac{|\theta - \theta_1|^{\beta_E}}{\alpha_E} \right\} I(\theta \in [0, 1]) \quad (29)$$

The values  $\beta_S$  and  $\beta_E$  are pre-specified and  $\alpha_S$  and  $\alpha_E$  are chosen to satisfy the tail-probability conditions (8)-(9).

The skeptical prior is shown in Figure 1(B), which has added concentration around the null response value  $\theta_0$  by pre-specifying  $\beta_S > 2$ . The enthusiastic prior is shown in Figure 1(C) with a default choice of  $\beta_E = 2$ . The level of residual uncertainty is given by  $\epsilon = 0.025$ . The skeptical prior was chosen to have additional Type 1 error control. A comparison of the various combinations of the monitoring priors in Figure 1 is provided in Appendix 5.2.

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

$$\text{Efficacy criteria (EFF): } P(\theta > \theta_0 | \mathbf{D}, \pi_S) \geq 1 - \epsilon \quad (30)$$

$$\text{Futility criteria (FUT): } P\left(\theta \leq \frac{\theta_0 + \theta_1}{2} \middle| \mathbf{D}, \pi_E\right) \geq 1 - \epsilon \quad (31)$$

$$\text{Maximum sample size: } N = 112 \text{ patient outcomes obtained} \quad (32)$$

where the maximum sample size was chosen based on a frequentist design to have 80% power at a true response proportion of  $\frac{\theta_0 + \theta_1}{2} = 0.535$ .

If enrollment is terminated due to the efficacy or futility criteria being satisfied, those subjects who are still undergoing follow-up will still have their outcomes considered in the final analysis.

### 3.1.3 Example paths

Violin plots are used to show the results of a simulated trials with the initial prior specification (first panel), three interim analyses (middle panels), and a final analysis (last panel), where interim analyses are conducted after every 10 completed outcomes. The first panel shows the skeptical and enthusiastic prior distributions from (28), (29), which are the same as introduced in Figure 1(b) and (c). The other panels

show the posterior distributions using the skeptical and enthusiastic priors respectively. An inference prior is defined as the mixture (24) with  $\omega = 0.5$ , and its mean and 95% credible intervals are shown.

Figure 3(a) shows the results of a trial where at the third interim analysis the efficacy condition (30) is satisfied and enrollment is terminated. Note that in the final analysis the efficacy condition is no longer at the  $1 - \epsilon$  threshold. A discussion of this type of “evidence decrease” is given in Section 3.1.4.

Figure 3(b) shows the results of a trial where at the third interim analysis the futility condition (31) is satisfied and enrollment is terminated.

### 3.1.4 Preposterior Analysis of Operating Characteristics

An interim analysis will be completed after every 2 subjects complete follow-up. The inference prior is defined as the mixture (24) with  $\omega = 0.5$  is used in evaluating the posterior mean and coverage probability.

Figure 4 shows the operating characters of this particular trial design. Stopping early for efficacy refers to satisfying (30), stopping early for futility refers to satisfying (31), and inconclusive findings refers to (32).

When the true response probability is  $\theta = \theta_0$ , there is a 3.9% probability of stopping the trial early for efficacy. The posterior mean shows a slight bias towards the alternative hypothesis.

Figure 4 addresses the particular situation of when the efficacy criteria (30) is satisfied at an interim analysis triggering termination of enrollment of additional subjects, but once the outcomes of subjects undergoing follow-up are ascertained the criteria is no longer satisfied. The distribution of the efficacy criteria given the final data for these cases are shown. The probability of these cases occurring is reflected by the percent agreement between interim and final results, and it is shown that as  $\theta$  increases there is a higher probability of agreement and therefore a lower probability of evidence decrease.

The median efficacy criteria is very close to  $1 - \epsilon$  and in the vast majority of cases (greater than 10th percentile) the efficacy criteria is still very high. Therefore, for this trial design, the interim and final results are not highly discrepant with respect to the efficacy criteria in these cases.

### 3.1.5 Type 1 error rate by the frequency of data monitoring

Figure 5 shows the probability of the efficacy criteria (30) being satisfied at an interim or final analysis when  $\theta = \theta_0$ . The monitoring frequency is 1 when an interim analysis is made after every completed outcome (i.e. fully sequential), and is 112 (the maximum sample size) if the only analysis is done at the maximum sample size.

The probability of the efficacy criteria being (errantly) satisfied is the highest for a fully sequential design, and decreases as the monitoring frequency decreases. However, the probability of the efficacy

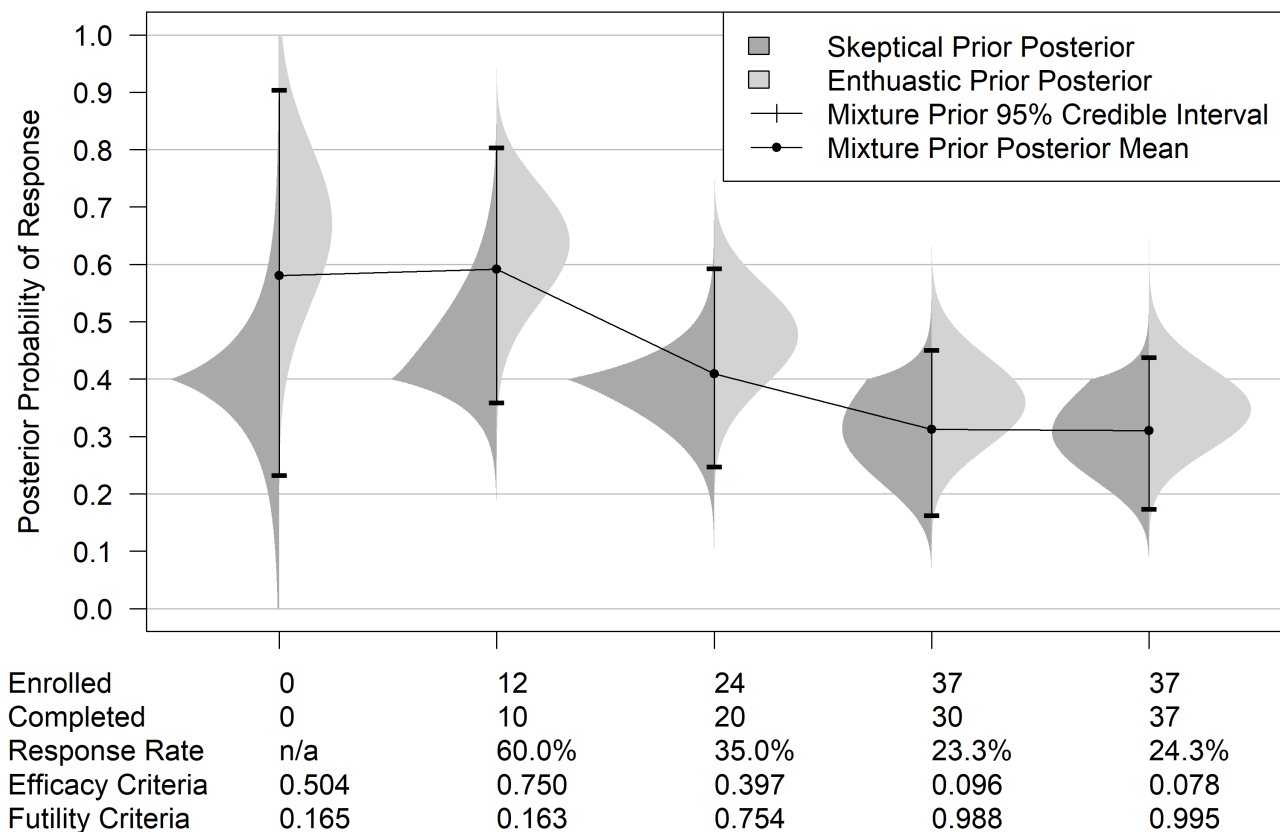
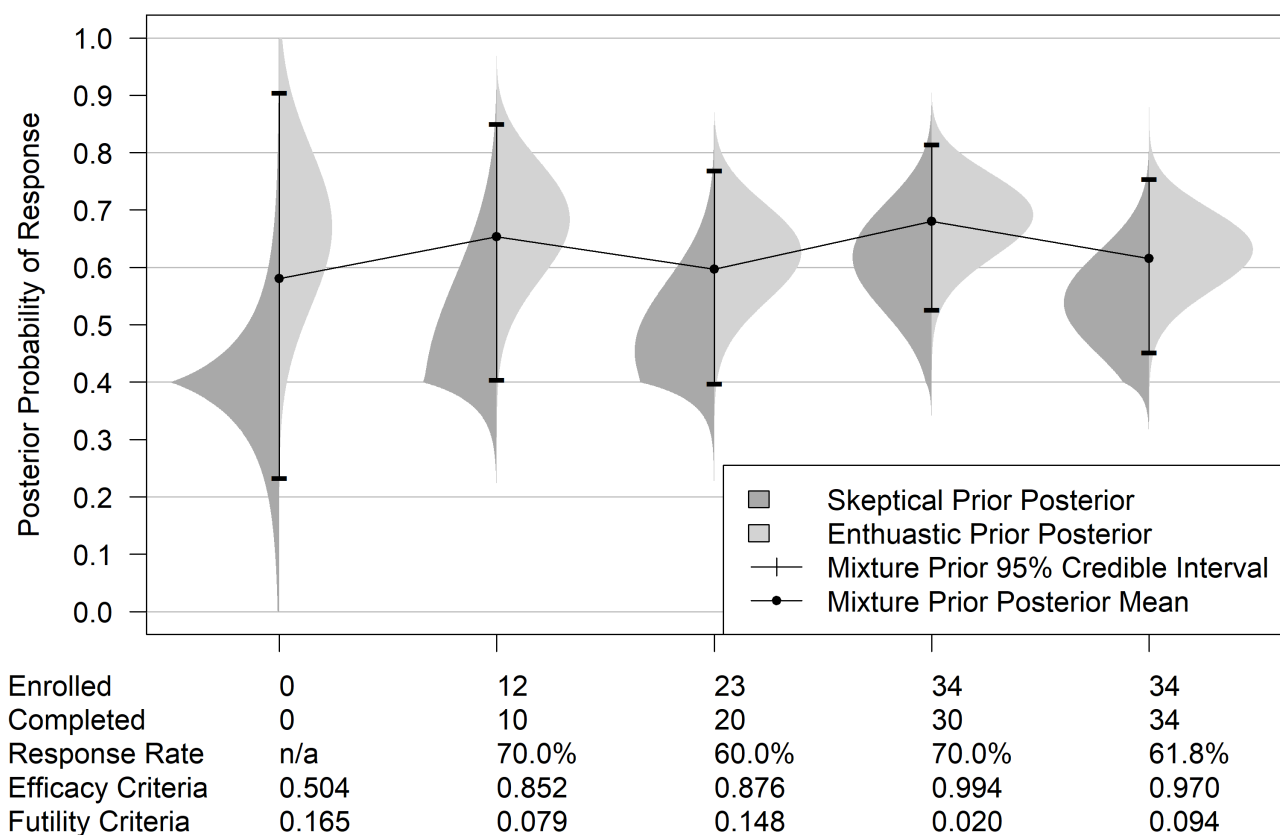


Figure 3: A, Early stoppage for efficacy. B, early stoppage for futility.

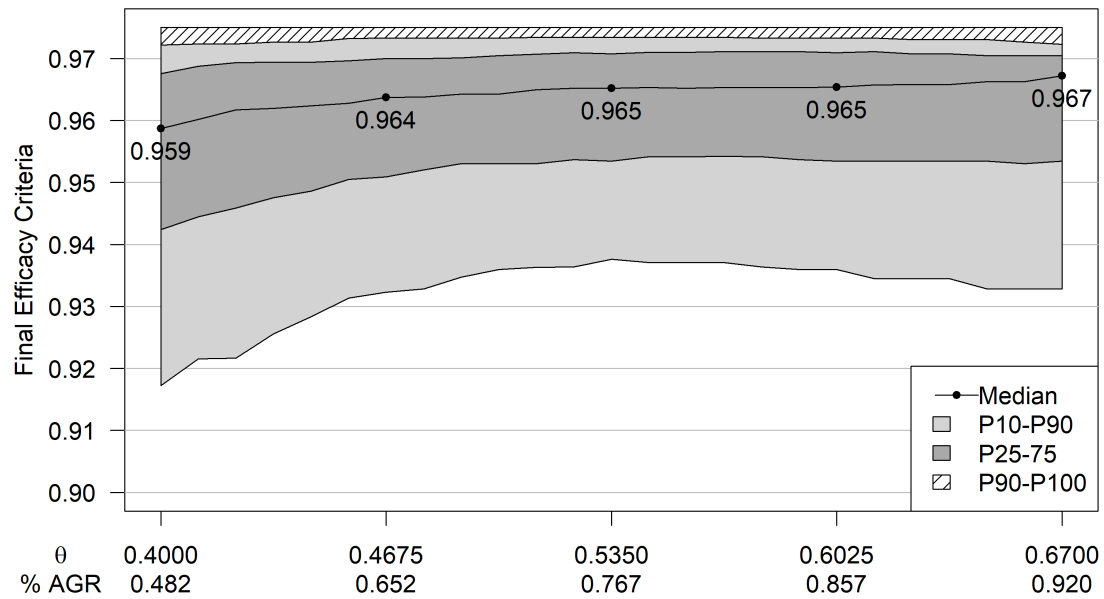
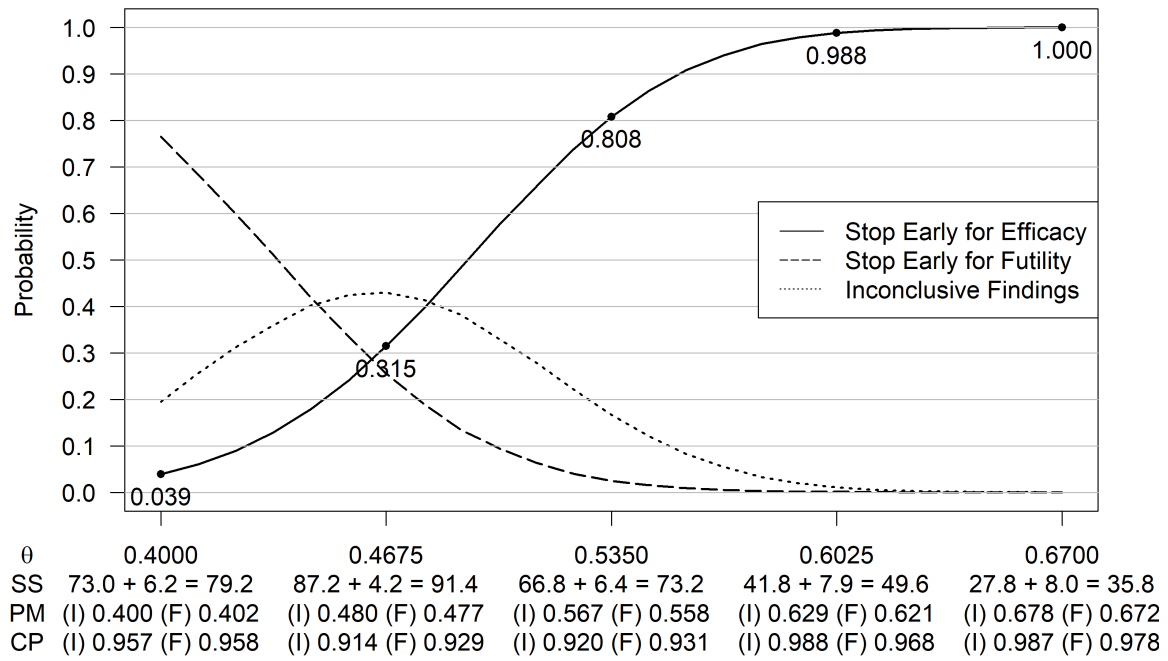


Figure 4: A, Sequential design properties. (SS; sample size, PM; posterior mean, CP; coverage probability, (I); interim analysis, (F); final analysis) B, Distribution of final posterior probability given interim stoppage and evidence decrease (% AGR; Percent of agreement between final and interim posterior probabilities relative to  $1 - \epsilon$  threshold)

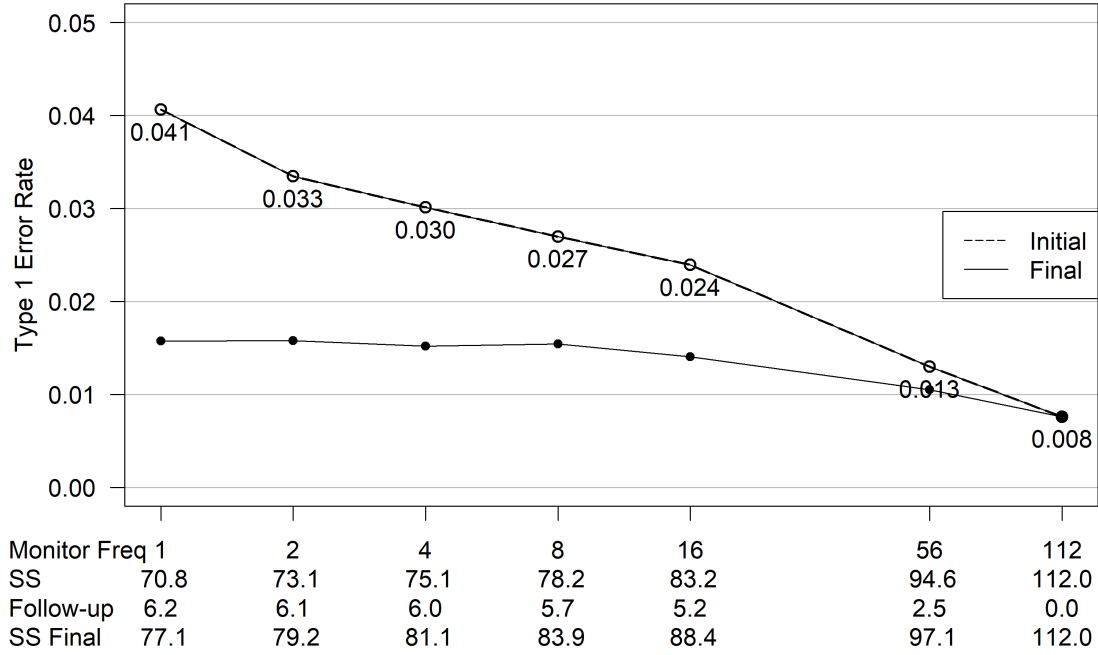


Figure 5: Probability of efficacy criteria being satisfied when  $\theta = \theta_0$ . SS; sample size. Monitor Freq; monitoring frequency.

criteria being satisfied with the final data is very low for any type of sequential monitoring (under 0.02 in all cases).

## 3.2 Parallel Two-Group Design with Binary Endpoint

### 3.2.1 Motivating example

Consider the trial “The Pediatric Lupus Trial of Belimumab Plus Background Standard Therapy (PLUTO)” (NCT01649765). Subjects were randomized to Belimumab 10mg/kg or placebo, and the primary endpoint was response at week 52. Response was measured by improvement in disease severity scores. The goal was to test for superiority of Belimumab to placebo.

The study start date was September 7, 2012, and the primary completion date was January 24, 2018. Since the follow-up period is 52 weeks the last enrollment is estimated to be a year prior to the primary completion date yielding an average enrollment rate of one enrollment per 17.2 days.

The study design included enrollment of 100 subjects, the first 24 subjects randomized in a 5:1 ratio (Belimumab:placebo) and the remaining 76 subjects would be randomized in a 1:1 allocation ratio. Therefore, 58 subjects would be randomized to Belimumab and 42 to placebo. The sample size was based on



feasibility constraints rather than a power calculation, and the study was terminated after 93 subjects enrolled.

### 3.2.2 Model formulation & prior elicitation

The data  $\mathbf{D}$  are assumed to be independent Bernoulli random variables with response probability  $\theta_0$  for the placebo group and  $\theta_1$  for the treatment (IP for investigational product) group. The null response value for the difference  $\delta = \theta_1 - \theta_0 = 0$  is and a highly efficacious response probability is  $\delta = \theta_1 - \theta_0 = 0.12$ . Consider the hypothesis testing of IP superiority to control  $H_0 : \theta_1 - \theta_0 \leq 0$  vs.  $H_1 : \theta_1 - \theta_0 > 0$ . An estimate for the treatment probability from adult trials is  $\theta_1 = 0.51$ .

The priors will be chosen based on the generalized normal distribution (15) based on the joint specification in (19) and truncated to the unit square

The skeptical and enthusiastic priors will have the same component for

$$\pi(\theta_0) \propto \exp \left\{ - \left( \frac{|\theta_0 - \mu|}{\alpha} \right)^\beta \right\} \times I(\theta_0 \in [0, 1]) \quad (33)$$

The location parameter is chosen to be  $\mu = \theta_1 - \delta_E = 0.39$ . The shape and scale parameters  $\alpha$  and  $\beta$  are chosen so that the prior is flat in the region  $\mu \pm 0.10$  and is shown in Figure 2(E).

The skeptical and enthusiastic priors are differentiated by their parameterizations for

$$\pi_S(\theta_1|\theta_0) \propto \exp \left\{ - \left( \frac{|\theta_1 - \theta_0 - \delta_0|}{\alpha_S} \right)^{\beta_S} \right\} \times f_S(\theta_0) \times I((\theta_0, \theta_1) \in [0, 1] \times [0, 1]) \quad (34)$$

$$\pi_E(\theta_1|\theta_0) \propto \exp \left\{ - \left( \frac{|\theta_1 - \theta_0 - \delta_1|}{\alpha_E} \right)^{\beta_E} \right\} \times f_E(\theta_0) \times I((\theta_0, \theta_1) \in [0, 1] \times [0, 1]) \quad (35)$$

The values  $\beta_S$  and  $\beta_E$  are pre-specified and  $\alpha_S$  and  $\alpha_E$  are chosen to satisfy the tail-probability conditions (22)-(23).

The complete skeptical and enthusiastic priors are then given by

$$\pi_S(\theta_0, \theta_1) \propto \exp \left\{ - \left( \frac{|\theta_0 - \mu|}{\alpha} \right)^\beta \right\} \times \exp \left\{ - \left( \frac{|\theta_1 - \theta_0 - \delta_0|}{\alpha_S} \right)^{\beta_S} \right\} \times I((\theta_0, \theta_1) \in [0, 1] \times [0, 1]) \quad (36)$$

$$\pi_E(\theta_0, \theta_1) \propto \exp \left\{ - \left( \frac{|\theta_0 - \mu|}{\alpha} \right)^\beta \right\} \times \exp \left\{ - \left( \frac{|\theta_1 - \theta_0 - \delta_1|}{\alpha_E} \right)^{\beta_E} \right\} \times I((\theta_0, \theta_1) \in [0, 1] \times [0, 1]). \quad (37)$$

The joint priors  $\pi_S(\theta_0, \theta_1)$   $\pi_E(\theta_0, \theta_1)$  as well as the marginal priors  $\pi_S(\theta_1 - \theta_0)$ ,  $\pi_E(\theta_1 - \theta_0)$  are shown in Figure 2.

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

$$\text{Efficacy criteria (EFF): } P(\theta_1 - \theta_0 > \delta_0 | \mathbf{D}, \pi_S) \geq 1 - \epsilon \quad (38)$$

$$\text{Futility criteria (FUT): } P\left(\theta_1 - \theta_0 \leq \frac{\delta_0 + \delta_1}{2} \middle| \mathbf{D}, \pi_E\right) \geq 1 - \epsilon \quad (39)$$

$$\text{Maximum sample size: } N = 100 \text{ patient outcomes} \quad (40)$$

An interim analysis is completed after every 2 subjects have completed outcomes.

### 3.2.3 Preposterior Analysis of Operating Characteristics

A mixture prior  $\pi_I$  of the form (24) is used for efficiency monitoring where the choice of  $\omega$  is chosen at the outset to be in the set  $\{0.25, 0.5, 0.75, 1\}$ . Note that  $\omega = 1$  corresponds to the traditional skeptical prior and  $\omega = 0.5$  gives equal weight to the skeptical and enthusiastic components. When  $\omega = 0.25$  most of the weight to the enthusiastic component.

Figure ?? shows the probability of stopping early for efficacy (satisfying (38)) based on the choice of  $\omega$  used in the mixture prior for efficiency monitoring, and the associated sample sizes. Note that only in the case of  $\omega = 0.25$  is the probability of stopping the trial early for efficacy near 50% when  $\delta = \delta_1$ . Also, only in the case of  $\omega = 0.25$  is the expected sample size less than 90. Therefore, for this design, the monitoring prior for efficacy has to be mostly enthusiastic in order for reasonable efficacy conditions.

## 4 Discussion

## 5 Supplementary material

### 5.1 Type 1 error rate depending on enrollment schemes

Recall Figure 5 from Section 3.1 which showed Type 1 error properties for the single-arm design. Figure 7 shows results from a design that has a longer follow-up period. The interim sample sizes are the same for each monitoring frequency, however, the final sample sizes under the longer follow-up designs are much larger (over 20 subjects in follow-up for monitoring frequencies of 8 or fewer, compared to approximately 6 subjects in the shorter follow-up designs). The final probability of efficacy criteria being satisfied is generally slightly lower in the longer follow-up design, which is what we would expect since the larger final sample size contains more data consistent with a null result.

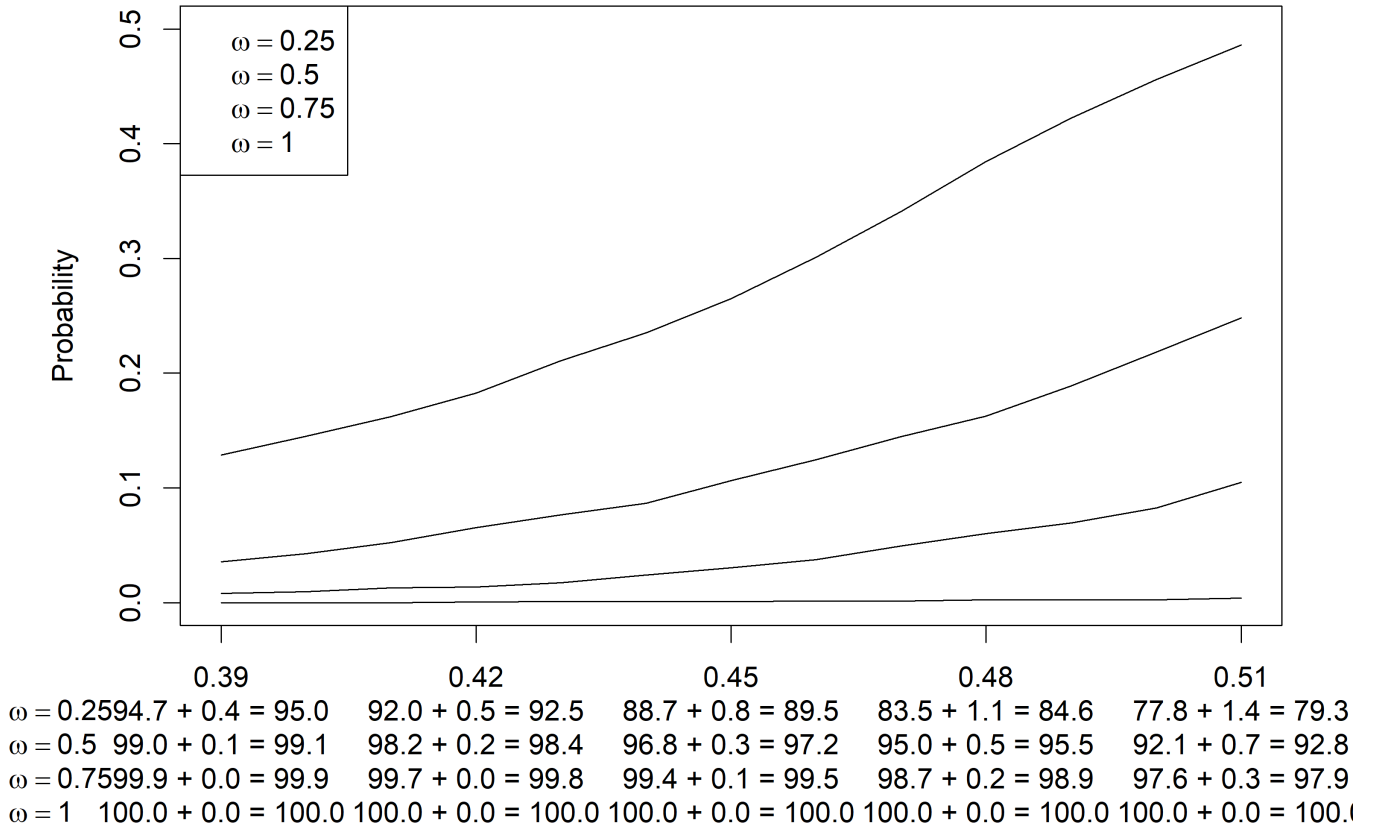


Figure 6: Probability of stopping for efficacy and associated sample sizes by choice of  $\omega$  used in a mixture inference prior for efficacy monitoring.

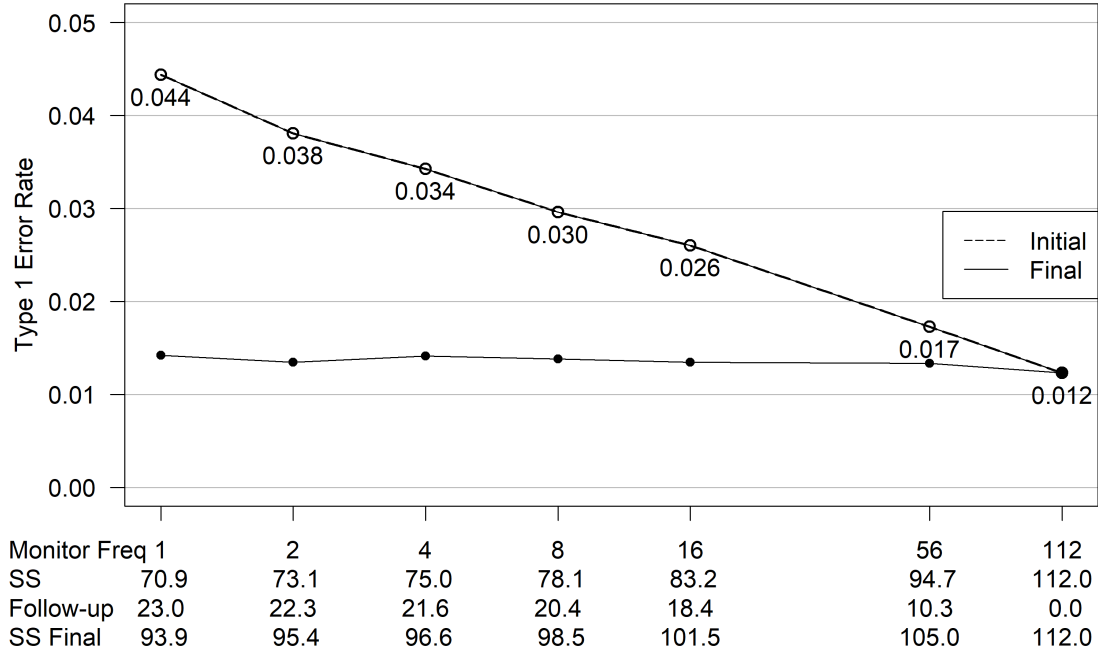


Figure 7: Single arm design from Example 3.1 with a longer follow-up period. Probability of efficacy criteria being satisfied when  $\theta = \theta_0$ . SS; sample size. Monitor Freq; monitoring frequency.

## 5.2 Robustness of parameterizations of monitoring priors

The analyses done in Section 3.1 used a concentrate skeptical prior and default enthusiastic prior. In this section we show the four possible designs using the combinations of skeptical and enthusiastic prior given in Figure 1.

Figures 8-9 shows what happens when the enthusiastic prior shifts from default to flattened, with the skeptical prior remaining fixed. Note that in the region between  $\theta_0$  and  $\frac{\theta_0 + \theta_1}{2}$  as the enthusiastic prior shifts from default to flattened, (a) the probability of stopping early for futility increases (b) the probability of inconclusive findings decreases and (c) the intermediate and final sample sizes decrease. This is because the enthusiastic prior gives more mass in for this region of  $\theta$ . The flattened enthusiastic prior was used in Section 3.1 to enhance the ability of futility monitoring to reduce the sample size.

Contrasting 8 and 9, we see that the probability of stopping early for efficacy is much higher at  $\theta_0$  when the default skeptical prior is used rather than the concentrated skeptical prior. This is because the default skeptical prior has less mass around  $\theta = \theta_0$ , therefore it is easier to convince the skeptic that  $\theta > \theta_0$  under the null result  $\theta = \theta_0$ . The concentrated skeptical prior was used in Section 3.1 to limit this probability and provide better Type 1 error control.

The choice of skeptical and enthusiastic prior affects the analysis, and their specification (e.g. default,

skeptical, enthusiastic) should be made with these properties in mind.

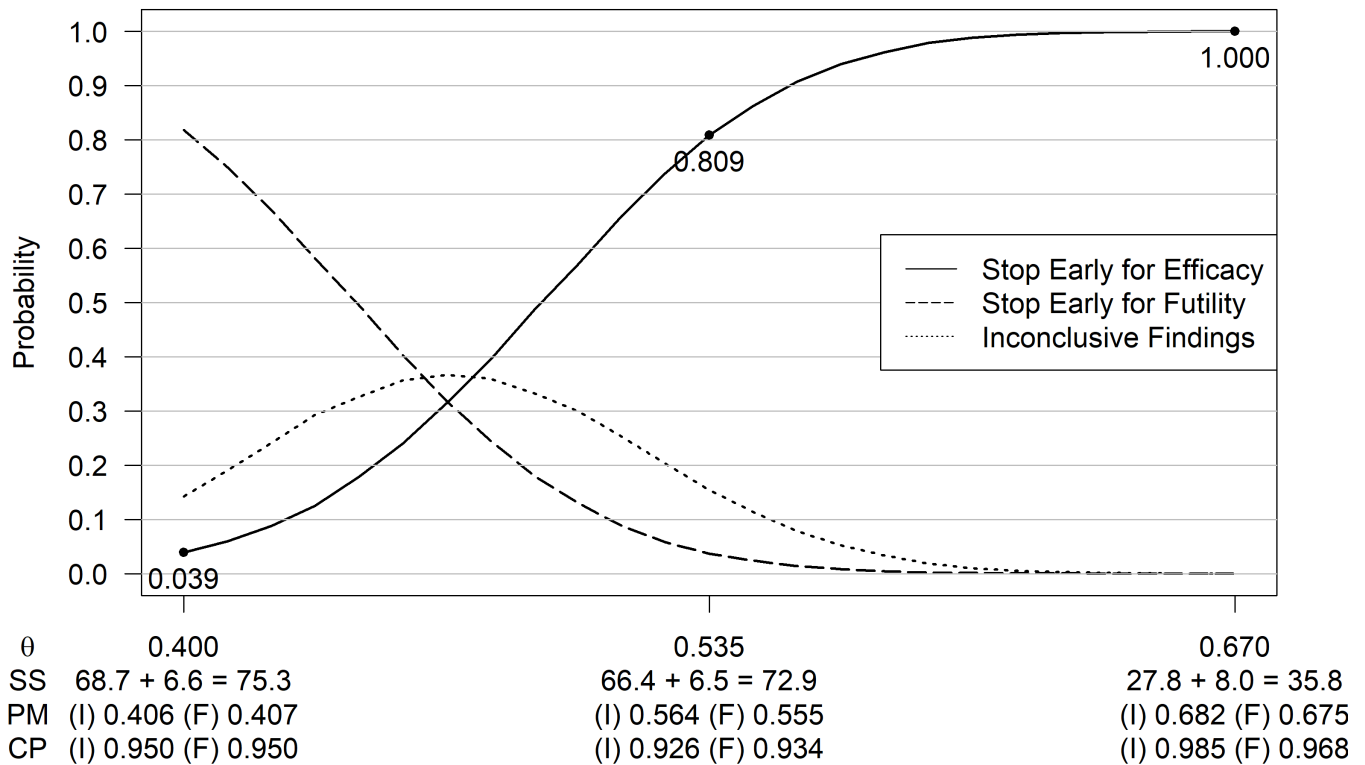
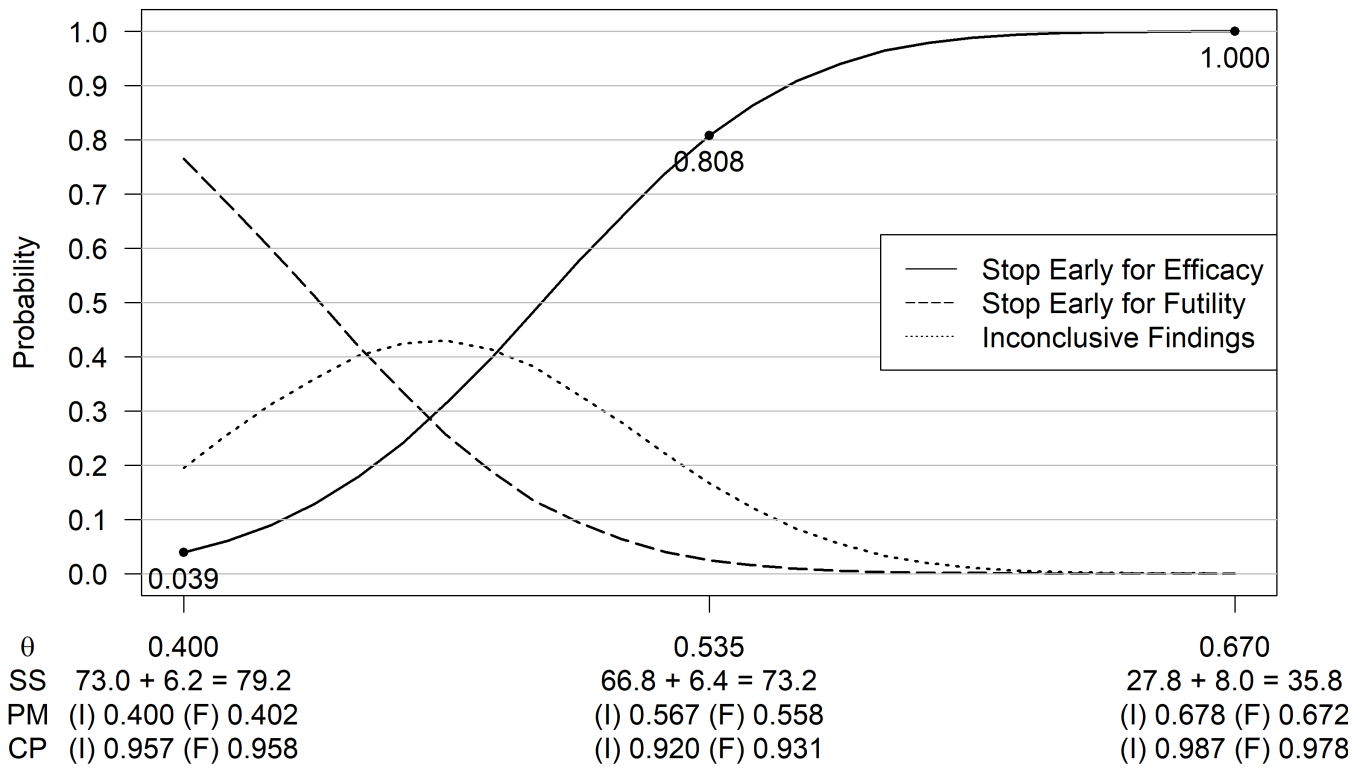


Figure 8: Modification of enthusiastic prior parameterization in Example 3.1. A, default enthusiastic prior (Figure 1(c)). B, flattened enthusiastic prior (Figure 1(d)). Both designs use concentrated skeptical prior (Figure 1(b)).

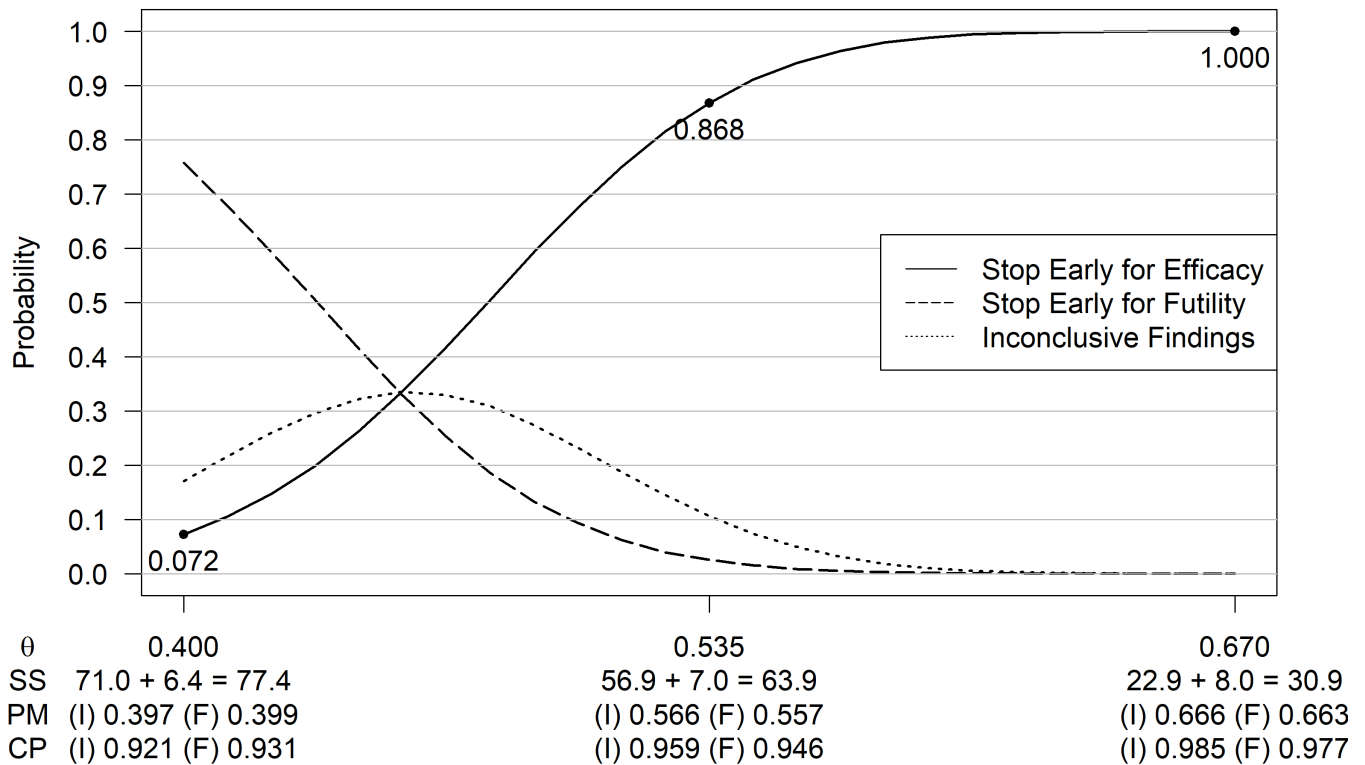
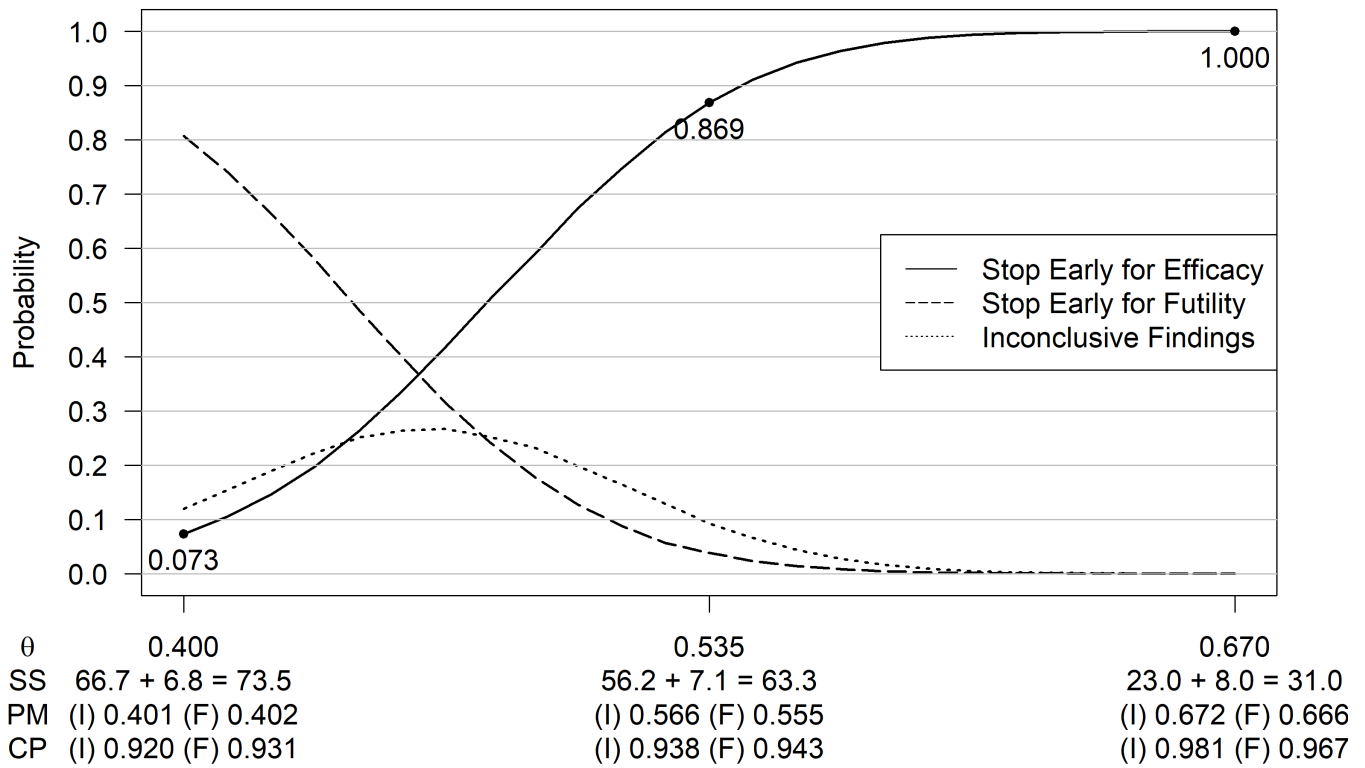


Figure 9: Modification of enthusiastic prior parameterization in Example 3.1. A, default enthusiastic prior (Figure 1(c)). B, flattened enthusiastic prior (Figure 1(d)). Both designs use default skeptical prior (Figure 1(a)).

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