

A Structured Framework for Bayesian Sequential Monitoring in Clinical Trials

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SUMMARY:

The Bayesian paradigm is naturally suited for sequentially monitoring clinical trials and incorporating external data. We present a Bayesian framework for sequential monitoring that makes use of external data that can be consistently applied for a wide range of clinical trial applications. The basis for this framework is the idea that specification of priors used for sequential monitoring and the stopping criteria can be semi-algorithmic byproducts of the trial hypotheses and relevant external data, decreasing the degree of subjectivity in prior elicitation. Monitoring priors are defined using the family of generalized normal distributions which provide a flexible approach for prior specification, naturally allowing one to construct a prior that is more peaked or flat about the most plausible parameter values compared to a normal prior. External data are incorporated into the monitoring process through mixing an a priori skeptical prior with an enthusiastic one using a weight that can be fixed or adaptively estimated. The proposed method is applied in two examples (1) a simple single-arm proof-of-concept trial and (2) a two-group randomized controlled trial. Both examples are modeled after completed pediatric trials and the designs incorporate information from adult trials to varying degrees. Preposterior analysis of each trial design is performed to illustrate that the proposed Bayesian approaches proposed provide good frequentist operating characteristics without having that explicit focus.

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1. Introduction

Enrolling the number of patients needed to adequately address objectives of a clinical trial can be difficult. This challenge is especially apparent in cases where the disease for which the investigational product (IP) is an intended treatment is rare or where the focus is on pediatric disease. There is increased interest in innovative ways to perform trials in these settings to facilitate obtaining substantial evidence of treatment benefit as efficiently as possible given the challenge of enrolling patients in a timely fashion. Indeed, this is exemplified by in the draft guidance from the United States Food and Drug Administration (FDA) which outlines procedures for interacting with FDA on complex innovative trial designs (FDA, 2019), abbreviated CID, and the FDA CID Pilot Program which was initiated to fulfill a performance goal set forth under the PDUFA IV legislation. In the draft guidance (see Section II) it is noted that CID are defined as “trial designs that have rarely or never been used to date to provide substantial evidence of effectiveness in new drug applications or biologics license applications.” The potential use of Bayesian methods are discussed throughout the draft guidance and, in particular, the use of Bayesian methods to extrapolate information from adult patients to pediatric settings is given as one type of CID for which there is interest (see Section II, Part C).

In settings where patients are difficult to enroll, and therefore meaningful numbers of patients will complete follow up prior to the trial reaching full enrollment, the concept of frequently monitoring interim data to determine whether a trial (or enrollment) can be stopped becomes appealing. In the author’s opinion, the use of Bayesian sequential methods, rooted in the likelihood principle and thus completely consistent with frequent or even continual data monitoring (provided it is logistically feasible), provide an ideal basis from which to develop CIDs for these settings. Moreover, in settings where pertinent preexisting

data are available, Bayesian methods inarguably provide a natural approach for incorporating that information via a prior distribution into the design and analysis of a future trial.

In this paper, we propose a strategy for designing sequentially monitored clinical trials that entails eliciting priors used to monitor enrollment and/or data collection (i.e., monitoring priors) and stopping criteria that can be derived in semi-automatic fashion based on standard inputs for trial planning. These inputs include (1) the boundary null value for the treatment effect, (2) a plausible, clinically meaningful value for the treatment effect, and (3) a criteria for defining what constitutes substantial evidence of efficacy. In principle, the plausible, clinically meaningful value for the treatment effect should be informed from a relevant external data, when available.

Skeptical and enthusiastic priors are developed using the generalized normal family of distributions. This flexible family includes the normal distribution and provides the capacity to construct monitoring priors that reflect nuanced prior opinion about the treatment effect (Section 2.2.1). A conditional-marginal prior factorization is proposed for settings where there are one or more nuisance parameters (Section 2.2.4) and we illustrate how prior information can be use in both marginal distribution for the treatment effect and conditional distribution for the nuisance parameters, if desired.

We perform preposterior analysis to examine a variety of operating characteristics for the proposed design and to understand how key operating characteristics are influenced by the frequency of monitoring. Specifically, we estimate the probability of stopping early at an interim analysis due to their being substantial evidence of efficacy or for futility, the expected sample size and trial duration, the average posterior mean, and the coverage probabilities for 95% credible intervals for the treatment effect. In most cases, patients will be ongoing in the trial at the time interim data are obtained that lead to ending enrollment as a result of their being substantial evidence of efficacy. It is our assumption that in many cases these

patients will complete the study protocol and, accordingly, we also explore the degree that interim evidence attenuates on average, once final data are available.

Bayesian sequential designs are often restricted to have explicit frequentist properties (Ventz and Trippa, 2015; Zhu and Yu, 2015). Prior work has shown such restrictions can result in Bayesian and frequentist designs that have stopping rules which are nearly identical (Stallard et al., 2020; Kopp-Schneider et al., 2019; Zhu et al., 2019). While it is possible to calibrate a Bayesian design to have specific frequentist operating characteristics, we do not advocate for that strategy. Instead, we propose Bayesian framework that leverages what the authors argue is an intuitive criteria for stopping enrollment and/or data collection at any point (based on posterior inference using a consistent criteria for substantial evidence) without explicit focus on strict type I error control – something that is not achievable when prior information are incorporated into the analysis (Psioda and Ibrahim, 2019).

This paper is organized as follows: Section 2.1 reviews Bayesian hypothesis testing using posterior probabilities and the use of skeptical and enthusiastic priors for efficacy and futility monitoring. Section 2.2 presents a method for parameterizing monitoring priors using the generalized normal distribution and for incorporating prior information into the monitoring priors, as well as construction of inference priors and a method to specify priors for nuisance parameters. Examples are given in Section 3, with Section 3.1 presenting an example based on a single-arm trial and Section 3.2 presenting an example based on a parallel two-group randomized, control trial.

2. Methods

2.1 Preliminaries

2.1.1 Bayesian Hypothesis Testing. Consider a clinical trial application where the primary objective is to test a hypothesis about an unknown quantity of interest which we denote by θ

with possible values for θ falling in the parameter space Θ . For example, in a single-arm trial with binary response endpoint, $\theta \in (0, 1)$ may be the response probability associated with patients receiving the investigational treatment. In a two-arm trial with binary response endpoint, $\theta \in (-1, 1)$ may be the difference in response probabilities between patients receiving the investigational treatment and those receiving the control treatment (e.g., placebo).

Throughout the paper we will let \mathbf{D} represent the data collected in a trial at some point in time. For example, for the two-arm trial example above and assuming no covariates other than the treatment indicator, $\mathbf{D} = \{y_i, z_i : i = 1, \dots, n\}$ where y_i is an indicator of response for patient i and z_i is an indicator for whether patient i was assigned the investigational treatment. We use the generic representation $p(\mathbf{D}|\theta, \eta)$ to reflect the density or mass function for the collective data \mathbf{D} as a function of θ and potential nuisance parameters η which could be multi-dimensional. For the two-arm trial example, η might correspond to the response probability for patients receiving the control treatment or some transformation thereof. For ease of exposition, for the remainder of Section 2.1 we will focus on the case where θ is the only unknown parameter and ignore η .

Consider the hypothesis $H_0 : \theta \in \Theta_0$ versus $H_1 : \theta \in \Theta_1$. The posterior probability that $\theta \in \Theta_i$ is given by

$$P(\theta \in \Theta_i | \mathbf{D}) = \frac{\int_{\Theta_i} p(\mathbf{D}|\theta) \pi(\theta) d\theta}{\int_{\Theta} p(\mathbf{D}|\theta) \pi(\theta) d\theta} \quad (1)$$

where $p(\mathbf{D}|\theta)$ is also referred to as the likelihood and denoted by $\mathcal{L}(\theta|\mathbf{D})$. We will also refer to $P(\theta \in \Theta_i | \mathbf{D})$ as the posterior probability of hypothesis H_i . See Web Appendix A for a brief discussion of the appropriateness of referring to $P(\theta \in \Theta_i | \mathbf{D})$ as the posterior probability of hypothesis H_i .

2.1.2 Formalizing the Statistical Concept of Substantial Evidence. Consider the one-sided hypotheses $H_0 : \theta \leq \theta_0$ versus $H_1 : \theta > \theta_0$ for fixed θ_0 . Often in Bayesian hypothesis testing, one rejects the null hypothesis when $P(\theta > \theta_0 | \mathbf{D})$ exceeds a prespecified threshold. Let ϵ

represent the *residual uncertainty* regarding a claim and define $1 - \epsilon$ to be the threshold such that posterior probabilities in favor of a claim (e.g., that $\theta > \theta_0$) that exceed $1 - \epsilon$ are viewed as providing *substantial evidence* that the claim is true. Leveraging common practice, we will use $\epsilon = 0.025$ for the examples presented herein so that $1 - \epsilon = 0.975$ is the threshold that determines when evidence of a claim is substantial. Our purpose in this paper is not to debate the appropriateness of using 0.975 as a threshold for defining substantial evidence but rather to develop a strategy for prior elicitation that leverages an accepted threshold to make prior elicitation more structured for sequentially monitored trials in hopes that this added structure facilitates the use of sequential monitoring more broadly and consistently.

Formally, we say that an individual whose belief is summarized by the distribution $\pi(\theta)$ is *all but convinced* that H_i is true if

$$P_\pi(\theta \in \Theta_i) = 1 - \epsilon, \quad (2)$$

where the subscript π in (2) is simply to indicate that the probability is calculated based on $\pi(\theta)$ which could be either a prior or posterior distribution.

2.1.3 Skeptical and Enthusiastic Monitoring Priors. Having formalized concepts for *substantial evidence* and being *all but convinced* of a claim, we can now develop a structured framework for constructing skeptical and enthusiastic monitoring priors which will be used to determine early stopping rules for efficacy and futility, respectively. The use of monitoring based on changing the opinion of skeptical and enthusiastic observers has been described as overcoming a handicap (Freedman and Spiegelhalter, 1989) and providing a brake on the premature termination of trials (Fayers et al., 1997), and as constructing “an adversary who will need to be disillusioned by the data to stop further experimentation” (Spiegelhalter et al., 1994). Skeptical and enthusiastic monitoring priors represent two extreme but plausible beliefs about the quantity of interest θ relative to the hypotheses considered. The purpose of

monitoring priors is to help answer the question “Is the evidence compelling enough to stop enrollment for the trial or possibly end it altogether?”

Monitoring priors are used for interim analyses of the data. A promising interim analysis that provides substantial evidence of efficacy may justify ending enrollment, while enrolled patients would continue to receive the treatment for the pre-planned period of exposure. A discouraging interim analysis that provides substantial evidence of futility may justify ending enrollment, and may call for enrolled patients who are ongoing in the trial to be transitioned off the investigational treatment (i.e., termination of investigation of the treatment). For the Bayesian, the question becomes “From what prior perspective must the evidence be substantial to justify one of the two actions described above?” A key contribution of this work is to give structured definitions for skeptical and enthusiastic perspectives that can be used to inform early stopping decisions in favor of efficacy and futility, respectively.

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 the prior $\pi_E(\theta)$ satisfying (i) $\arg\max_{\theta} \pi_E(\theta) = \theta_1$ and (ii) $P_E(\theta > \theta_0) = 1 - \epsilon$, where the subscript E indicates that the probability is based on $\pi_E(\theta)$. 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) $\arg\max_{\theta} \pi_S(\theta) = \theta_0$ 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.

Note that the proposed development of the skeptical prior does not generally reflect

skepticism regarding whether the alternative hypothesis is true. Indeed, assuming a symmetric skeptical prior is elicited (as we propose), the *induced* prior probabilities on the hypotheses satisfy $p(H_0) = p(H_1)$. Thus, the skeptical prior simply reflects skepticism regarding the possibility of large treatment effects but is otherwise consistent with clinical equipoise regarding the two hypotheses.

Unlike the frequentist approach, whether the totality of evidence in favor of a hypothesis is substantial is influenced by the prior distribution used for analysis. It is natural that one would stop a trial early in favor of efficacy or futility when the evidence in favor of the appropriate claim is compelling to an a priori skeptic or enthusiastic observer, respectively, as defined above. For example, if at any point data sufficiently convince an observer whose prior belief is in accordance with $\pi_S(\theta)$ that the alternative is true, then any less skeptical observer would also be convinced. Therefore, ceasing enrollment and possibly collection of additional data in order to assess whether the treatment is beneficial would be a reasonable action from most any rational perspective. Similarly, if at any point data sufficiently convince an observer whose prior belief is in accordance with $\pi_E(\theta)$ that the effect of interest is significantly less than what was originally believed, then any less enthusiastic observer would be similarly convinced. Therefore, ceasing the collection of data altogether would be a reasonable action from most any rational perspective.

2.1.4 Maximum Sample Size and Formal Stoppage Criteria. In this section we formalize stopping criteria for futility and efficacy and give general advice for specifying a maximum sample size for the trial. Although sequentially monitored trials in principle require no fixed sample size, in practice due to resource constraints it will almost always be the case that a maximum sample size exists. We recommend that (resources permitting) the maximum sample size, denoted by n_{\max} , should be chosen so that there is a high probability that the trial generates substantial evidence from the perspective of the skeptic when in fact

$\theta \approx \theta_1$ in a scenario where the data are only examined once when the full set of outcomes are ascertained. The rationale behind this strategy is that one would want to ensure the trial's sample size is sufficient so that there is high probability the data collected will provide substantial evidence of treatment benefit to observers having relatively extreme skepticism regarding the magnitude of treatment benefit a priori.

For a sequentially monitored trial, observed data are analyzed as often as is feasible in accordance with the cost and/or logistical challenges of assembling the necessary data. For example, if an outcome requires adjudication by a committee of clinical experts, it may not be possible to reanalyze the data after each new patient's outcome is obtained due to scheduling or other constraints on the adjudication panel. In other scenarios, a patient's outcome may be based on a laboratory parameter's change after a fixed period of time and the rate limiting factor for sequential monitoring will be how quickly samples can be shipped, processed, and entered into a database for analysis. The strategies presented herein for sequential monitoring are appropriate regardless of how frequently data can be monitored even if the motivation for sequential monitoring is scenarios where frequent monitoring is feasible.

Stopping criteria for efficacy are defined from the perspective of a skeptical observer. The skeptic becomes convinced that a treatment is effective if at some point the observed data suggest there is substantial evidence that the alternative hypothesis is true. Formally, the early stopping criteria are met based on data \mathbf{D} when $P_S(\theta > \theta_0 | \mathbf{D}) > 1 - \epsilon$. Note that the evidence must *exceed* the threshold for what defines it being substantial. When the evidence in favor of the alternative surpasses this threshold, it may no longer be necessary to enroll patients for the purpose of proving treatment efficacy.

Stopping criteria for futility monitoring are defined from the perspective of the enthusiastic observer. At first thought it may seem appealing to stop the trial when the enthusiast becomes convinced that the null hypothesis is true, that is, that $P_E(\theta \leq \theta_0 | \mathbf{D}) > 1 - \epsilon$.

However, notice that when $\theta = \theta_0$, $P_E(\theta \leq \theta_0 | \mathbf{D})$ approaches 0.5 for large sample sizes. Therefore this potential futility criteria would not be satisfiable unless the observed data were consistent with values of θ much less than θ_0 . For this reason, we consider a different approach. Recalling that θ_1 represents a plausible, clinically meaningful treatment effect, the early stopping criteria are met based on data \mathbf{D} when $P_E(\theta < \theta_1 | \mathbf{D}) > 1 - \epsilon$. In this case the trial may be stopped due to there being substantial evidence that the treatment effect is much less than hypothesized (i.e., θ_1).

2.2 Specifying Monitoring Priors

2.2.1 Generalized Normal Distribution. The skeptical and enthusiastic monitoring priors defined in Section 2.1.3 have mode value and tail-probability constraints. However, these constraints alone do not uniquely determine the priors. There are infinitely many distributions which satisfy these conditions. However, the mode and tail constraints do uniquely determine a pair of normal distributions which might serve as a default set of monitoring priors. The density for a normal distribution $\mathcal{N}(\mu, \sigma)$ is $f(\theta) = \frac{1}{\sqrt{2\pi}\sigma} \exp(-\frac{1}{2}(\frac{\theta-\mu}{\sigma})^2)$ where μ is a location parameter and $\sigma > 0$ is the standard deviation. A default enthusiastic monitoring prior satisfying (i) $\arg\max_{\theta} \pi_E(\theta) = \theta_1$ and (ii) $P_E(\theta > \theta_0) = 1 - \epsilon$ is the normal distribution with location θ_1 and standard deviation $\sigma = \frac{\theta_1 - \theta_0}{\Phi^{-1}(1 - \epsilon)}$, where Φ^{-1} denotes the quantile function of a standard normal. Note that the specification of μ and σ completely determine the density at all points, including the value of the density at the mode which is $f(\theta_1) = \frac{1}{\sqrt{2\pi}\sigma}$.

Using a normal distribution for the monitoring prior is motivated by the Bayesian Central Limit Theorem which states that, under general conditions, the posterior distribution for θ approaches normality as the sample size increases, regardless of the initial choice of prior. Therefore, a normally distributed monitoring prior is consistent with belief derived from a sufficiently large (hypothetical) dataset with maximum likelihood estimate equal to the mode value required by the prior. It may be desirable to construct a monitoring prior with a

different shape at the mode than what is possible when using the normal distribution. Note that these flattened and concentrated priors by construction have different density values at the mode than what would be expected from a large sample collection of data according to the Bayesian Central Limit Theorem. Choosing a flattened distribution is appropriate when one wishes to reflect more uncertainty regarding the likelihood that θ is near θ_1 (relative to what is permitted by the normal distribution), while maintaining the same residual uncertainty that $\theta < \theta_0$. Similarly, choosing a concentrated distribution is appropriate when one wishes to reflect a higher degree of certainty that θ is near θ_1 , while maintaining residual uncertainty that $\theta < \theta_0$.

The family of generalized normal distributions, which contains the normal distribution as a special case, is able to accommodate changes in the density value at the mode while still satisfying the mode value and tail probability constraints. 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 (Nadarajah, 2005). Fixing the location parameter to be the mode value and changing the shape and scale parameters in conjunction can maintain the tail probability constraint while also changing the density value at the mode. Recall the density at the mode for a default enthusiastic prior is $f(\theta_1) = \frac{1}{\sqrt{2\pi}\sigma}$. An enthusiastic 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 flattened distribution and $k > 1$ indicating a peaked distribution at the mode, relative to the default normal distribution. Web Appendix B details a procedure for parameterizing flattened and concentrated monitoring priors using the generalized normal distribution.

The flattened and concentrated distributions for different choices of k are shown in Figure 1.

[Figure 1 about here.]

Panel B of Figure 1 presents a concentrated enthusiastic prior that satisfies the mode value and tail probability constraints given in Section 2.1.3, and that has $k = 1.5$ times the density value at the mode as compared to the default normal distribution. Increasing the density value at the mode translates to a more peaked distribution about the mode as compared to the default normal distribution (shown in Panel A). Panel C of Figure 1 presents a flattened enthusiastic prior that satisfies the mode value and tail probability constraints given in Section 2.1.3, and that has $k = 0.67$ times the density value at the mode as compared to the default normal distribution. This translates to a distribution that is significantly more flat about the mode value than the default normal distribution. Although we have focused on an enthusiastic prior in our discussion here, the same ideas apply to skeptical priors as well.

The approach we have proposed results in a unique flattened or concentrated prior. While there is no *correct* choice for the scale factor k for either an enthusiastic or skeptical prior, the author's choices of 1.5 and 0.67 are reasonable perturbations from that afforded by the normal distribution and will be used henceforth to demonstrate the methodology proposed. Lastly, we note that the default normal, flattened, and concentrated priors can all be truncated while maintaining the mode and tail probability constraints. This will be necessary when the parameter of interest has bounded support (e.g., θ is a response probability).

We define a *locally non-informative prior* as a prior that satisfies $\pi_{NI}(\theta_0) = \pi_{NI}(\theta_1)$, and where $\pi_{NI}(\theta)$ is approximately equal for all $\theta \in [\theta_0, \theta_1]$. The locally non-informative prior is shown in panel D of Figure 1, and the technical definition is in Web Appendix B.

2.2.2 Incorporating Prior Information in the Monitoring Priors. The monitoring priors are constructed based on the quantities θ_0 and θ_1 , as well as the definition of sufficient level of evidence. As described previously, prior information may be directly used in the construction of the enthusiastic prior (e.g., choice of θ_1). It may also be desirable to incorporate prior

information into the monitoring process when making a determination of when to stop enrollment early for efficacy. To facilitate this, we introduce a procedure for modifying the skeptical prior such that, if the enthusiastic prior is congruent with observed data, the degree of skepticism can be adaptively lessened. We propose incorporating prior information into the monitoring process for efficacy through constructing a mixture prior from the skeptical and enthusiastic priors using a mixing weight that is constructed from measures of compatibility between the observed data and the skeptical and enthusiastic priors. We define the *adaptive skeptical monitoring prior* as the mixture distribution

$$\pi_{AS}(\theta) = \omega \cdot \pi_S(\theta) + (1 - \omega) \cdot \pi_E(\theta), \quad (3)$$

where $\omega \in [0, 1]$ is an adaptively determined mixing weight.

The mixing weight ω is determined by an assessment of prior-data conflict, proposed by Box (Box, 1980), derived using the prior predictive distribution of the data which is defined (in our case) using the skeptical and enthusiastic monitoring priors. 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

$$p(\mathbf{D}) = \int \mathcal{L}(\theta|\mathbf{D})\pi(\theta)d\theta. \quad (4)$$

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

$$\psi(\mathbf{D}_{\text{obs}}) = \int p(\mathbf{D})1[p(\mathbf{D}) \leq p(\mathbf{D}_{\text{obs}})]d(\mathbf{D}) \quad (5)$$

which in the case of discrete data is equal to $\psi(\mathbf{D}_{\text{obs}}) = \sum_{\mathbf{D}} p(\mathbf{D})1[p(\mathbf{D}) \leq p(\mathbf{D}_{\text{obs}})]$. Box's p-value can be interpreted as the probability of observing data as or more extreme than \mathbf{D}_{obs} , given the predictive distribution. Small values of $\psi(\mathbf{D}_{\text{obs}})$ indicate a lack of compatibility between the prior and the data. We propose using the skeptical and enthusiastic priors $\pi_S(\theta)$ and $\pi_E(\theta)$ to compute the quantities in (4) and (5) to create compatibility measurements $\psi^{(S)}(\mathbf{D}_{\text{obs}})$ and $\psi^{(E)}(\mathbf{D}_{\text{obs}})$ which are used to determine the mixing weight

in (3). If $\psi^{(E)}(\mathbf{D}_{\text{obs}}) > \psi^{(S)}(\mathbf{D}_{\text{obs}})$, then the observed data are more consistent with the enthusiastic prior, which should be given a greater weight in the mixture. Similarly, if $\psi^{(S)}(\mathbf{D}_{\text{obs}}) > \psi^{(E)}(\mathbf{D}_{\text{obs}})$ then the skeptical prior should be given a greater mixing weight.

We propose a conservative choice of mixing weight which gives full weight to the skeptical prior (i.e. $\omega = 1$) whenever $\psi^{(S)}(\mathbf{D}_{\text{obs}}) \geq \psi^{(E)}(\mathbf{D}_{\text{obs}})$ is

$$\omega = \begin{cases} 1 & \text{if } \psi^{(S)}(\mathbf{D}_{\text{obs}}) \geq \psi^{(E)}(\mathbf{D}_{\text{obs}}) \\ 1 - [\psi^{(E)}(\mathbf{D}_{\text{obs}}) - \psi^{(S)}(\mathbf{D}_{\text{obs}})] & \text{if } \psi^{(S)}(\mathbf{D}_{\text{obs}}) < \psi^{(E)}(\mathbf{D}_{\text{obs}}) \end{cases} \quad (6)$$

As can be seen, for the proposed approach the weight given to the enthusiastic component is the *excess compatibility* in favor of the enthusiastic prior.

2.2.3 Inference Priors. 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. The skeptical and enthusiastic monitoring priors defined in Section 2.1.3 represent extreme but plausible beliefs about θ . While analysis with these priors provides a rational perspective from which one can determine whether interim data are sufficient to cease enrolling patients, the belief of most stakeholders will likely fall somewhere between the two perspectives. Thus, when interpreting the final data once in hand, intermediate perspectives should be considered. To that end, we define an inference prior through mixing the two monitoring priors along with (potentially) a locally non-informative prior to provide added robustness, if desired.

Define the inference prior as

$$\pi(\theta) = \omega_S \cdot \pi_S(\theta) + \omega_E \cdot \pi_E(\theta) + \omega_{NI} \cdot \pi_{NI}(\theta) \quad (7)$$

where $\omega_S + \omega_E + \omega_{NI} = 1$ and each weight is non-negative. One may take $\omega_{NI} = 0$ and fixed value of $\omega_S = \omega_E = 1/2$ to obtain a static, *agnostic* inference prior since it gives equal weight to the skeptical and enthusiastic prior. This type of inference prior is used in Section 3.1.

Alternatively, an adaptive inference prior is obtained as follows. One first computes the

quantities $\psi^{(S)}(\mathbf{D}_{\text{obs}})$, $\psi^{(E)}(\mathbf{D}_{\text{obs}})$, and $\psi^{(NI)}(\mathbf{D}_{\text{obs}})$ using the priors $\pi_S(\theta)$, $\pi_E(\theta)$, and $\pi_{NI}(\theta)$, respectively, based on Box's p-value as given in (5). Each of $\psi^{(S)}(\mathbf{D}_{\text{obs}})$, $\psi^{(E)}(\mathbf{D}_{\text{obs}})$, and $\psi^{(NI)}$ characterizes compatibility of the data with the respective prior. Our goal is to create a mixture prior which gives more weight to the skeptical (or enthusiastic) prior in situations where the data are highly compatible with that prior and that favors the locally non-informative prior if data exhibit low compatibility with both the skeptical and enthusiastic priors. To that end, we propose transforming $\psi^{(NI)}(\mathbf{D}_{\text{obs}})$ to obtain $\tilde{\psi}^{(NI)}(\mathbf{D}_{\text{obs}})$ which is defined as

$$\tilde{\psi}^{(NI)}(\mathbf{D}_{\text{obs}}) = \begin{cases} \psi^{(NI)}(\mathbf{D}_{\text{obs}}) - \max(\psi^{(S)}(\mathbf{D}_{\text{obs}}), \psi^{(E)}(\mathbf{D}_{\text{obs}})) & \text{if} \\ \psi^{(NI)}(\mathbf{D}_{\text{obs}}) > \max(\psi^{(S)}(\mathbf{D}_{\text{obs}}), \psi^{(E)}(\mathbf{D}_{\text{obs}})) \\ 0 & \text{if} \\ \psi^{(NI)}(\mathbf{D}_{\text{obs}}) \leq \max(\psi^{(S)}(\mathbf{D}_{\text{obs}}), \psi^{(E)}(\mathbf{D}_{\text{obs}})) \end{cases} . \quad (8)$$

We then let the mixing weights $\omega^{(E)}$, $\omega^{(S)}$, and $\omega^{(NI)}$ be the normalized values of $\psi^{(E)}(\mathbf{D}_{\text{obs}})$, $\psi^{(S)}(\mathbf{D}_{\text{obs}})$, and $\tilde{\psi}^{(NI)}(\mathbf{D}_{\text{obs}})$ so that their sum is unity (e.g. $\omega^{(E)} = \psi^{(E)}(\mathbf{D}_{\text{obs}}) / (\psi^{(E)}(\mathbf{D}_{\text{obs}}) + \psi^{(S)}(\mathbf{D}_{\text{obs}}) + \tilde{\psi}^{(NI)}(\mathbf{D}_{\text{obs}}))$). This type of inference prior is used in Section 3.2.

2.2.4 Prior Specification for Nuisance Parameters. Often there are additional parameters besides the treatment effect θ that are not of primary interest (i.e. nuisance parameters). It is necessary to elicit a prior distribution $\pi(\theta, \eta)$ for both unknown quantities. The marginal-conditional factorization of the joint prior $\pi(\theta, \eta) = \pi(\theta) \times \pi(\eta|\theta)$ allows direct parameterization of the marginal prior on the treatment effect and the ability to reflect prior opinion on the conditional distribution of the nuisance parameter. The prior for $\pi(\theta)$ will be a generalized normal distribution that satisfies the usual mode value and tail probability constraints. Our proposed method is to define $\pi(\eta|\theta)$ as a generalized normal distribution, with parameters chosen based on shape of the conditional distribution evaluated at the most likely value of $\pi(\theta)$. For example, if $\pi_S(\theta)$ is a skeptical prior, then the location, shape, and scale parameters

for a generalized normal distribution for $\pi(\eta|\theta)$ will be chosen based on $\pi(\eta|\theta = \theta_0)$. The location parameter will be the most likely value of η when $\theta = \theta_0$ (e.g. $\text{mode}(\eta|\theta = \theta_0) = \eta_0$), and shape and scale parameters will be chosen to reflect a reasonable amount of dispersion in η .

If the parameters θ and η assumed to be independent, then the joint prior can be factored as $\pi(\theta, \eta) = \pi(\theta) \times \pi(\eta)$ and the priors $\pi(\theta)$ and $\pi(\eta)$ can be elicited separately. Generally, there is the possibility for dependence in θ and η which must be taken into consideration when parameterizing $\pi(\eta|\theta)$. For example, suppose that θ is the risk difference between response probabilities of a treatment group and the control group, and denote the response probability in the control group by η . In this case θ and η are linked through constrained support (e.g. $0 \leq \theta + \eta \leq 1$). This prior specification is demonstrated in Figure 2, and Section 3.2.2 uses this representation of the joint prior. Panel A shows the marginal distribution $\pi(\theta)$, panel B shows the conditional distribution $\pi(\eta|\theta = \theta_0)$, and panel C shows the joint prior $\pi(\theta, \eta)$. In this example, the conditional distribution $\pi(\eta|\theta)$ will look very similar to the marginal distribution of $\pi(\eta)$ except at the boundaries of the parameter space.

[Figure 2 about here.]

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) which was conducted between August 2006 and June 2010. The population was patients ages 6 through 17 with ulcerative colitis measured by a baseline Mayo score of 6 or above on a scale of 0-12, where higher scores indicate more severe disease activity. A 5mg/kg dose of infliximab was given to

patients at weeks 0, 2, and 6. The primary endpoint was a dichotomous variable reflecting a 3-point or greater decrease in Mayo score from baseline to week 8. Patients were enrolled over approximately 33.5 months (approximately 1 patient enrolled per 17 days). The sample size of 60 patients was chosen so that a 95% two-sided confidence interval for the response probability would have 12% precision in estimating the true response proportion if the observed response rate was 0.67 (i.e. confidence interval half-width of 0.12). The rate of 0.67 was the observed response rate among adults in the ACT 1 and ACT 2 trials (Rutgeerts et al., 2005) at the same 5mg/kg dose ($N = 242$). Obtaining a 95% confidence interval that excluded 0.40 was used as the criterion for classifying the results as clinically significant. Clinical response was observed in 44 of 60 (73.3%) patients.

3.1.2 Model Formulation & Prior Elicitation. We use this trial as a motivating example to demonstrate the proposed framework for sequential monitoring. The data \mathbf{D} are assumed to be comprised of independent Bernoulli random variables having common response probability θ . As mentioned above, the primary hypotheses evaluated in the trial were $H_0 : \theta \leq 0.4$ and $H_1 : \theta > 0.4$. For purposes of monitoring, we took $\theta_1 = 0.67$ consistent with the ACT 1 and ACT 2 trial data. The example presented in this section make use of a concentrated skeptical prior and a default enthusiastic prior for monitoring. A comparison of design properties based on various combinations of the monitoring priors is given in Web Appendix D. In this example, we consider an inference prior defined as the mixture (3) using the fixed value $\omega = 0.5$ (i.e., a non-adaptive inference prior), which will be used determine the posterior mean and 95% credible intervals. For sequential monitoring, we consider analyzing the accumulating data after every 2 patients complete follow-up.

The early stopping criteria, as well as any quantity involving the posterior distribution of θ requires evaluating integrals of the dimension of θ (or the dimension of (θ, η) in the case of nuisance parameters). These quantities are 1- and 2-dimensional integrals which are

evaluated using numerical integration in R (R Core Team, 2017) using the *pracma* package (Borchers, 2019).

3.1.3 Example Paths. Violin plots are used to illustrate the results of two particular simulations of this trial. For each trial, the monitoring priors (first set of distributions), the posterior distributions at three selected interim analyses (middle sets), and from the final analysis (last set) are shown.

Figure 3(A) shows the results of a trial with early stopping for efficacy once 30 outcomes are ascertained, and enrollment is henceforth terminated. Note that the final data in this example no longer meet the criteria for substantial evidence of efficacy. Figure 3(B) shows the results of a trial with early stopping for futility once 30 outcomes are ascertained, and enrollment is henceforth terminated.

[Figure 3 about here.]

3.1.4 Preposterior Analysis of Operating Characteristics. The estimated operating characteristics presented in this section are based on 100,000 simulated trials per value of θ using the trial design as described in Section 3.1.2. Figure 4(A) shows key operating characteristics for this particular trial design. When the true response probability is $\theta_0 = 0.4$, the probability of stopping the trial early for efficacy is equal to 0.026, and at $\theta_1 = 0.67$ it is 0.953. The expected sample size is less than 60 for each value of θ considered. Furthermore, interim stoppage for either efficacy or futility occurred in each simulation. The expected sample sizes are the lowest when the true response probabilities are θ_0 or θ_1 . This is because the trial is more likely to be stopped for futility or efficacy when the data are consistent with the skeptical or enthusiastic priors respectively, which have modes at θ_0 and θ_1 . At $\theta_0 = 0.4$, the posterior mean estimates using the mixture prior are slightly greater than the true underlying value. This is because the mixture prior is a weighted combination of priors that have θ_0 and θ_1 as

the most likely values, and the enthusiastic component with mode θ_1 contributes bias towards greater values. In a similar way, at $\theta_1 = 0.67$, the posterior estimates using the mixture prior are slightly less than the true underlying value because the skeptical component with mode θ_0 contributes bias towards smaller values. The 95% credible intervals are shown to have coverage greater than 95% for all values of θ considered.

Given that the early stopping criteria was satisfied as an interim analysis, it is of interest to compare the posterior probability of efficacy once subjects in follow-up have completed outcomes using the same skeptical prior. It is of particular interest when the threshold for substantial evidence is satisfied for an interim analysis but is no longer satisfied once outcomes from patients in progress are ascertained, as was the case in Figure 3(A). The probability of such an occurrence and the difference between the posterior probabilities evaluated at the different time points is shown in Figure 4(B). The probability of these cases occurring is reflected by the percent agreement between interim and final results. Recall that when the generating value of theta is $\theta_0 = 0.4$, the trial is stopped early for efficacy with probability 0.026. Among these cases, the posterior probability is still greater than $1 - \epsilon$ with probability 0.433. This means that the completed outcomes from patients in progress at time enrollment was terminated are likely to add sufficient evidence to contradict the conclusion of efficacy. When the generating value of theta is $\theta_1 = 0.67$, the trial is stopped early for efficacy with probability 0.952, and among those cases the posterior probability is greater than $1 - \epsilon$ with probability 0.887.

The distribution of the posterior probability given the final data for these cases are shown that even in the cases where there is evidence decrease, the final posterior probability is still similar to the $1 - \epsilon = 0.975$ threshold. For example, when the generating value of $\theta_1 = 0.67$, and in the 11.3% of situations where there is evidence decrease, 90% of these cases have a final posterior probability of approximately 0.93 or greater. These analyses

show that even if the skeptical prior was used for the final determination of efficacy rather than an inference prior, the final posterior probability of treatment efficacy would be similar to the posterior probability of efficacy that triggered stoppage of enrollment, and the level of similarity increases as the underlying response rate θ increases.

[Figure 4 about here.]

3.1.5 Type 1 Error Rate by the Frequency of Data Monitoring. Figure 5 shows the probability of stopping early for efficacy and the posterior probability that the alternative hypothesis is true at the final analysis when the true response probability is $\theta_0 = 0.4$. The monitoring frequency is one when an interim analysis is made after every completed outcome (i.e. fully sequential), and is 60 (the maximum sample size) if the only analysis is done at the maximum sample size. When there is only a single analysis completed at the maximum sample size, the probability of determining efficacy with the skeptical monitoring prior is 1.3%. For more frequent data monitoring, the probability of concluding efficacy at an interim analysis increases. This is to be expected; there are more opportunities for a conclusion of efficacy to be made with more frequent interim analyses and it is important that this probability is examined and viewed as an acceptable trade-off for advantages such as the corresponding decrease in expected sample sizes.

[Figure 5 about here.]

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) which was conducted between September 2012 and January 2018. The population was patients ages 5 through 17 with active systemic lupus erythematosus (SLE) measured by 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. The study design included enrollment of 100 patients, the first 24 patients randomized in a 5:1 allocation ratio (belimumab:placebo) and the remaining 76 patients in a 1:1 ratio, resulting in 58 patients randomized to belimumab and 42 to placebo. The sample size was based on feasibility constraints rather than a power calculation. Data from two studies of the use of belimumab in adults showed a placebo response rate of 0.39, and a 10mg/kg response rate of 0.51. Using these values for the null and anticipated response rates, a frequentist two-sided hypothesis test with confidence level 95% and power 70% would require 210 total patients assuming equal allocation, and with 80% power 266 patients would be required. Enrollment was terminated at 93 patients who 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.

A post-hoc Bayesian hierarchical analysis was conducted which used data from two studies of the use of belimumab in adults. Subjects in the pediatric trial had 1.5 times the odds of clinical response with 95% CI (0.6, 3.5), and a meta-analysis of the two adult studies showed an odds ratio of 1.6 with 95% CI (1.3, 2.1). The analysis used a mixture prior which was a weighted sum of a skeptical prior centered at null effect with effective sample size equal to 2 pediatric patients and an informative prior resulting from the meta-analysis. When the weight of the informative component was 0.55 and above, efficacy was concluded based on a 95% credible interval excluding one. The 0.55 weight of the informative component, interpreted as a 55% weight on the relevance of the adult information to the pediatric population, was determined to be a reasonable by the clinical team. Our method contrasts such a post-hoc

analysis with the prospective use of a monitoring prior for efficacy which gives weight to the adult data at interim analyses.

3.2.2 Model Formulation & Prior Elicitation. We use this trial as a template to demonstrate our framework, in particular the performance of our response-adaptive monitoring prior from Section 2.2.2. The adaptive prior is useful in this setting because the trial is underpowered and the prospective use of an informative monitoring prior for efficacy provides a different perspective than a post-hoc analysis with an informative prior. The data \mathbf{D} are assumed to be independent Bernoulli random variables with response probability η_0 for the placebo group and η_1 for the treatment group. This trial has a superiority hypothesis of treatment to control with null risk difference value denoted by $\theta_0 = 0$. An estimate for the pediatric response rate is denoted by $\eta_0 = 0.39$ (the placebo response rate from adult studies), and for purposes of monitoring, a highly efficacious difference probability is $\theta_1 = 0.12$ (i.e. anticipating the adult studies treatment response rate of 0.51) (Travis et al., 2019).

The skeptical monitoring prior is $\pi_S(\theta, \eta_0) = \pi_S(\theta) \times \pi(\eta_0|\theta)$, where $\pi_S(\theta)$ is a concentrated skeptical prior. The enthusiastic monitoring prior is $\pi_E(\theta, \eta_0) = \pi_E(\theta) \times \pi(\eta_0|\theta)$, where $\pi_E(\theta)$ is a default enthusiastic prior. The probability of concluding efficacy at an interim analysis is made using a mixture prior with dynamic weight of the form (6) as described in Section 2.2.2. A 3-part mixture inference prior of the form (7) as described in Section 2.2.3 will be used to estimate the posterior mean and coverage probabilities for θ .

A maximum sample size of $n_{\max} = 100$ was chosen based on the trial protocol. A minimum sample size of $n_{\min} = 70$ was chosen to provide an adequate number of placebo controls to be enrolled given the initial 5:1 allocation to the treatment group. An interim analysis is competed after every 2 patients have completed outcomes beginning at n_{\min} .

3.2.3 Preposterior Analysis of Operating Characteristics. Figure 6(A) shows the operating characteristics of this design using the adaptive weight monitoring prior and the 3-part

mixture inference prior. The generating response probability in the placebo group is 0.39, and the generating response probability in the treatment group is based on risk differences θ in $\{0, 0.06, 0.12, 0.18, 0.24\}$. When $\theta = 0$, there is probability 0.008 of concluding efficacy at an interim analysis. This probability increases to 0.193 at $\theta_1 = 0.12$. At the effect size 0.24 the probability of concluding efficacy increases to 0.711, and the expected final sample size is 90.3 patients.

Figure 6(B) shows the probability of stopping early for efficacy using a fixed weight mixture prior of the form (3) for efficacy monitoring with a fixed choice of ω chosen at the outset to be in the set $\{0.25, 0.5, 0.75, 1\}$, and the associated sample sizes. Note that $\omega = 1$ corresponds to the traditional skeptical prior, $\omega = 0.5$ gives equal weight to the skeptical and enthusiastic components, and $\omega = 0.25$ most of the weight is applied to the enthusiastic component. The adaptive weight mixture behaves similar to using a fixed weight prior that equally weighs the skeptical and enthusiastic prior.

[Figure 6 about here.]

Figure 7(A) shows the prior-data compatibility assessments $\psi^{(S)}$, $\psi^{(E)}$, $\psi^{(NI)}$ by observed risk difference. As expected, the skeptical and enthusiastic priors show highest compatibility when the observed risk difference matches the corresponding prior mode, and the non-informative prior shows high compatibility for a wide range of θ . Figure 7(B) shows the 3-part mixture inference prior weights ω_S , ω_E , ω_{NI} by observed risk difference. Recall our goal is to create a mixture prior which favors the skeptical or enthusiastic components in areas where high compatibility is demonstrated for those components, and favors the locally non-informative prior if both the skeptical and enthusiastic components show low compatibility. To this end, the skeptical and enthusiastic components have the highest weight when the observed data is aligned with the prior mode, and the locally non-informative prior has highest weight towards extreme values of the observed response difference.

[Figure 7 about here.]

4. Discussion

Bayesian methods are well suited for sequentially monitored clinical trials because of their natural interpretations and ability to incorporate external evidence through prior distributions. Monitoring priors used for efficacy and futility stopping fundamentally determine the operating characteristics of the trial, in addition to factors such as the frequency of data monitoring and number of patients in progress at enrollment termination.

This paper presents a structured framework for designing a Bayesian sequentially monitored clinical trial. The generalized normal distribution gives a flexible and intuitive way to create monitoring priors. It is required that the practitioner specify the mode value, a quantile condition, and an additional parameter which can concentrate or flatten the distribution around the mode value (with the normal distribution as the default case). This paper demonstrates how the operating characteristics are affected by the choice of monitoring priors.

Presentation of these concepts was simplified by generic choices for design parameters. The same quantity $1 - \epsilon$ was used as the threshold for substantial evidence in efficacy and futility monitoring. In practice, the value of ϵ could be different for these two purposes. Other distributions than the generalized normal could be used to create monitoring priors with the desired mode value and tail probability constraint (Section 2.2.1), and different assessments of prior-data conflict could be used to create a dynamic prior (Section 2.2.2). Each of these quantities could be modified to better suit the needs of the practitioner. This paper presents standardized recommendations for these quantities which can be used as the starting point for a design.

Although the examples provided are superiority trials with binary data and response probabilities as the parameter of interest, the framework applies to any type of data likelihood

and parameter of interest on an interval domain. Future work will involve demonstrating the framework in Bayesian clinical trials with survival outcomes.

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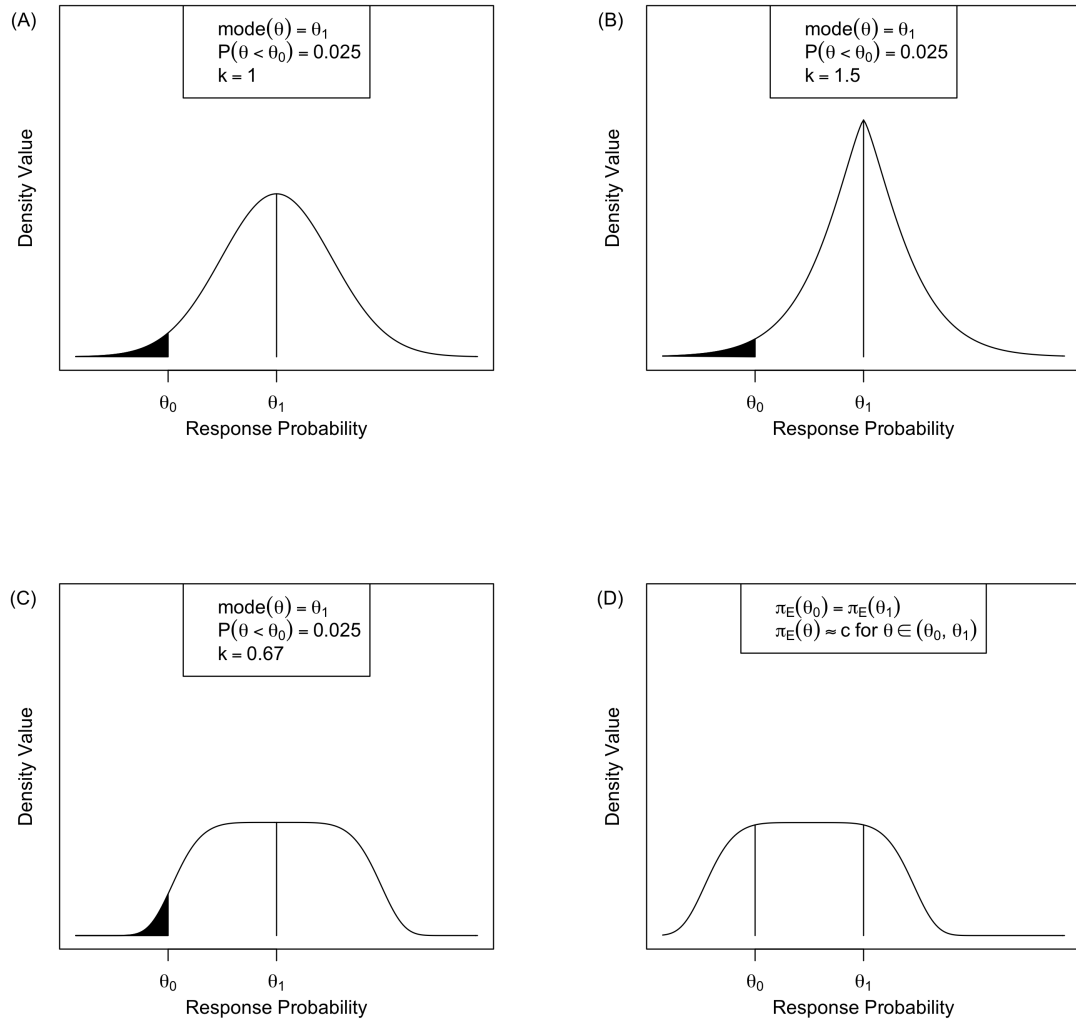


Figure 1. A, Default enthusiastic prior. B, Concentrated enthusiastic prior. C, Flattened enthusiastic prior. D, Locally non-informative prior

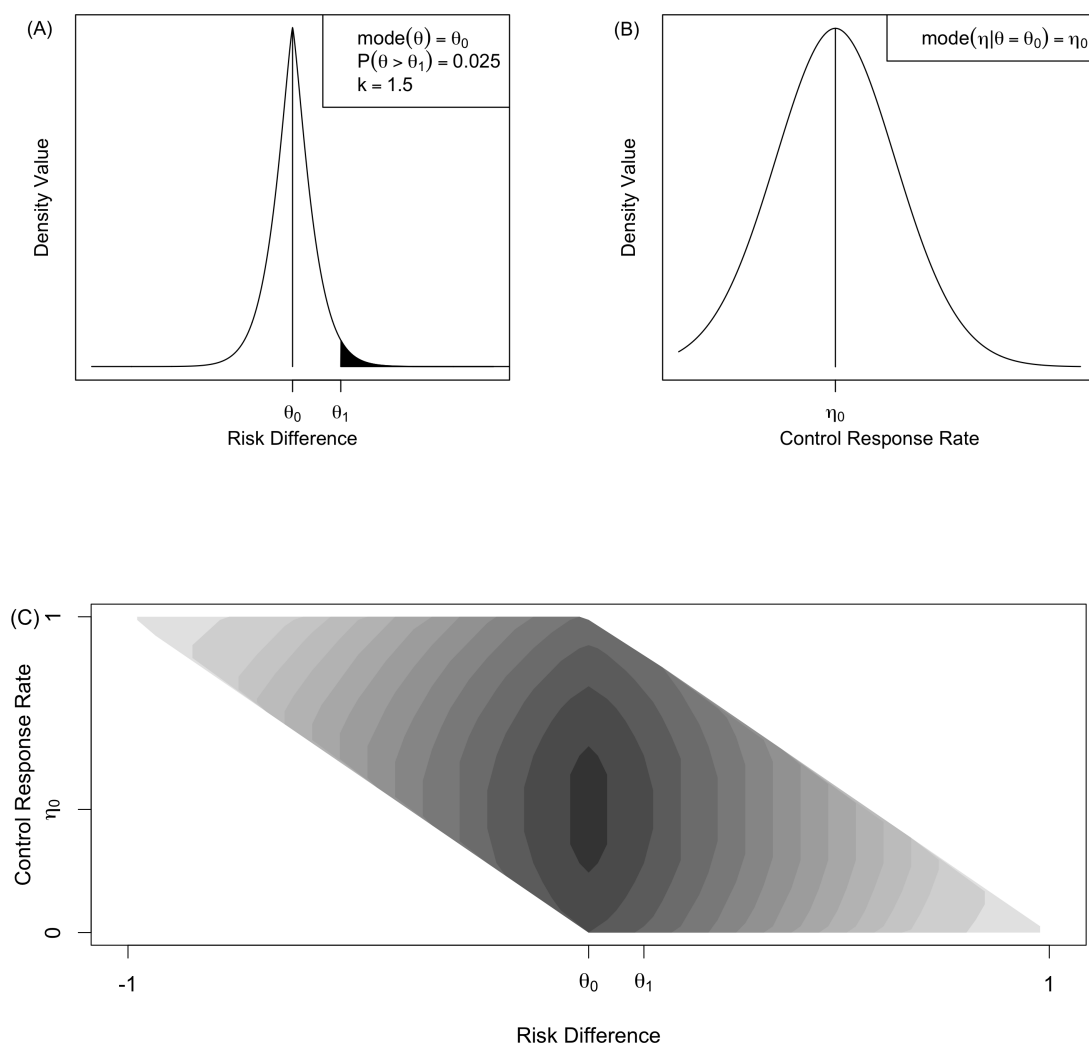


Figure 2. A, concentrated skeptical prior $\pi_S(\theta)$ truncated to $[-1, 1]$. B, conditional prior $\pi(\eta|\theta = \theta_0)$. C, joint prior $\pi(\theta, \eta) = \pi(\theta) \times \pi(\eta|\theta)$ truncated based on the conditions $-1 < \theta < 1$ and $0 < \theta + \eta < 1$.

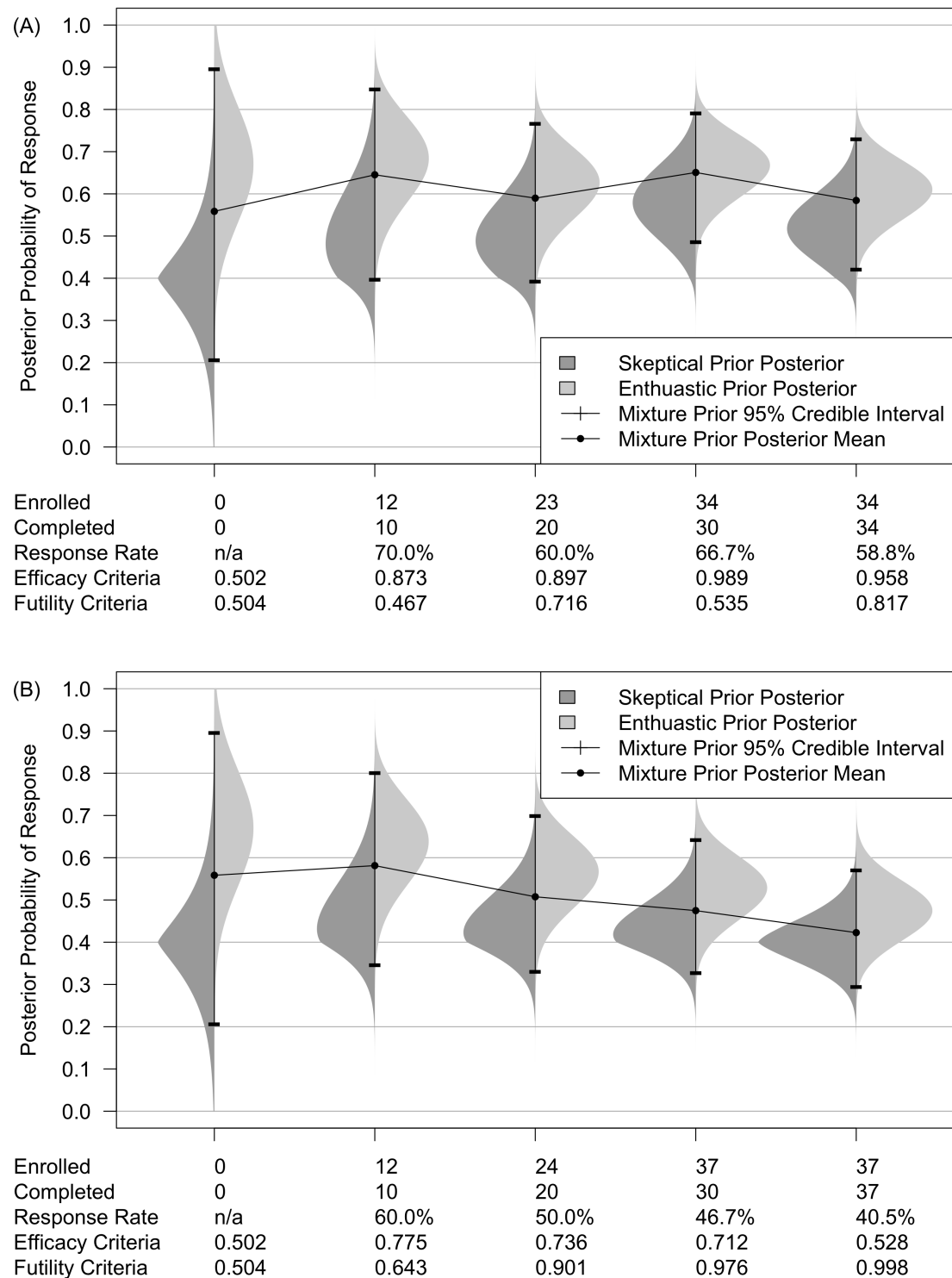


Figure 3. Example paths for the trial described in Section 3.1.2. A, Early stoppage for efficacy. B, early stoppage for futility.

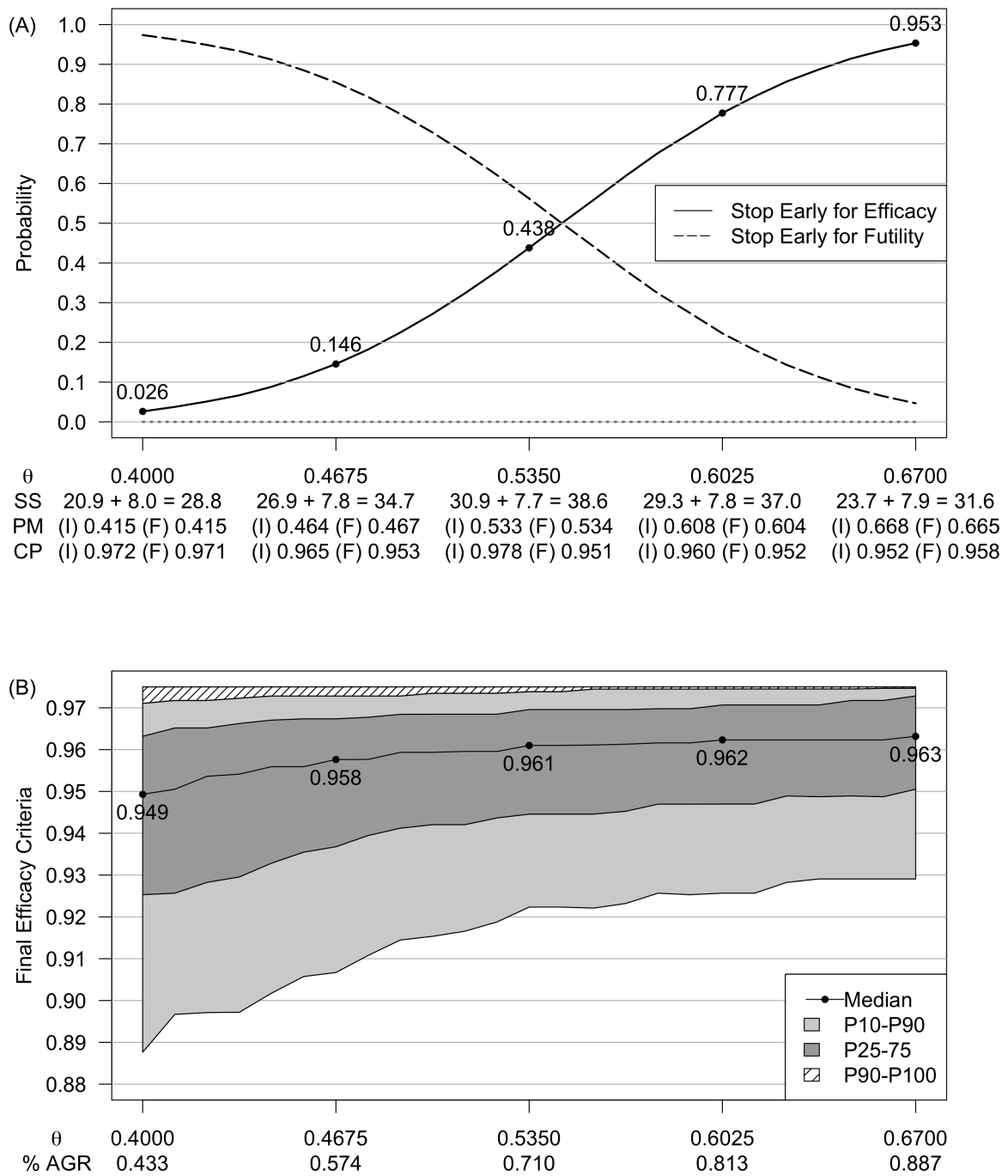


Figure 4. A, Sequential design properties. (SS; sample size, PM; posterior mean, CP; coverage probability, (I); interim analysis, (F); final analysis). B, Distribution of final posterior probability given interim stoppage and evidence decrease (% AGR; Percent of agreement between final and interim posterior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

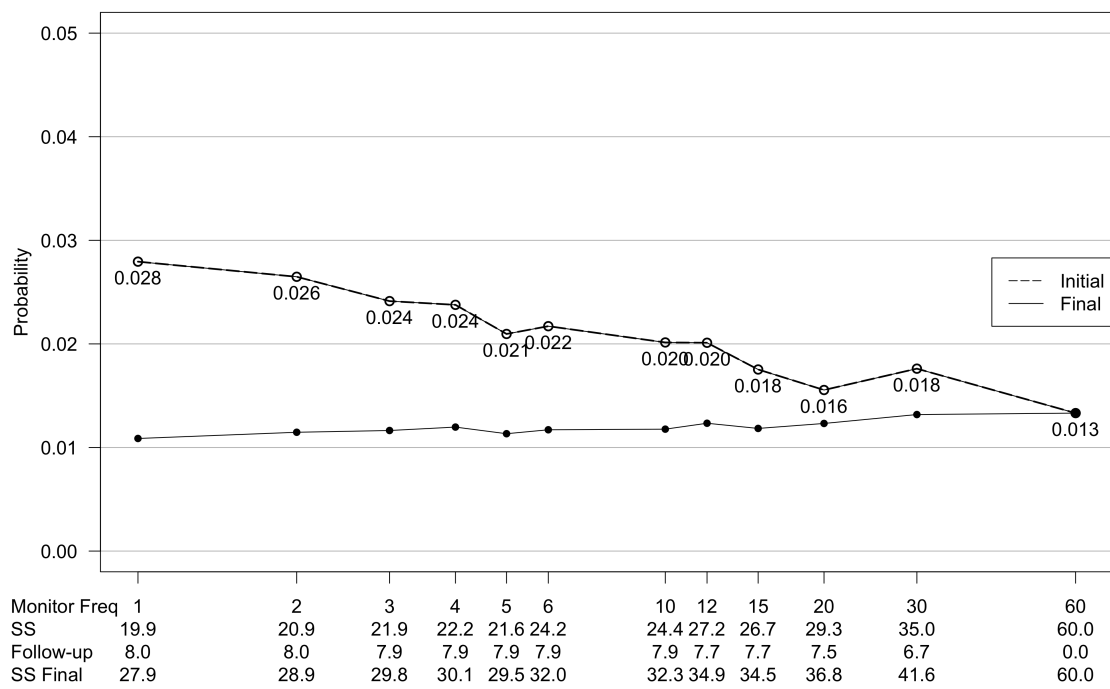


Figure 5. Probability of stopping early for efficacy and the posterior probability that the alternative hypothesis is true at the final analysis when $\theta = \theta_0$. SS; sample size. Monitor Freq; monitoring frequency.

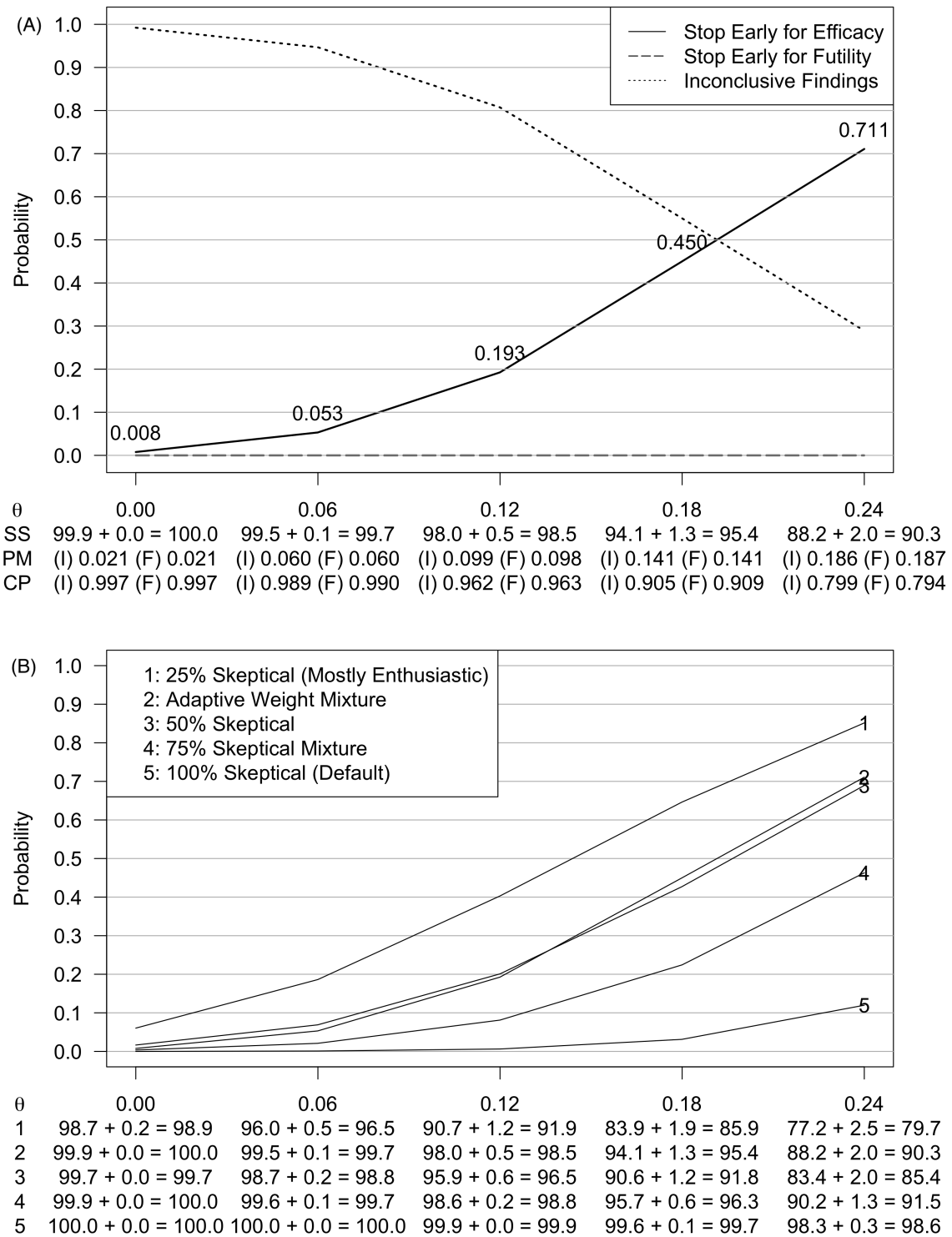


Figure 6. A, Sequential design properties using adaptive weight monitoring prior. (SS; sample size, PM; posterior mean, CP; coverage probability, (I); interim analysis, (F); final analysis). B, Probability of stopping for efficacy and associated sample sizes by true IP response rate θ with different choices of efficacy monitoring prior.

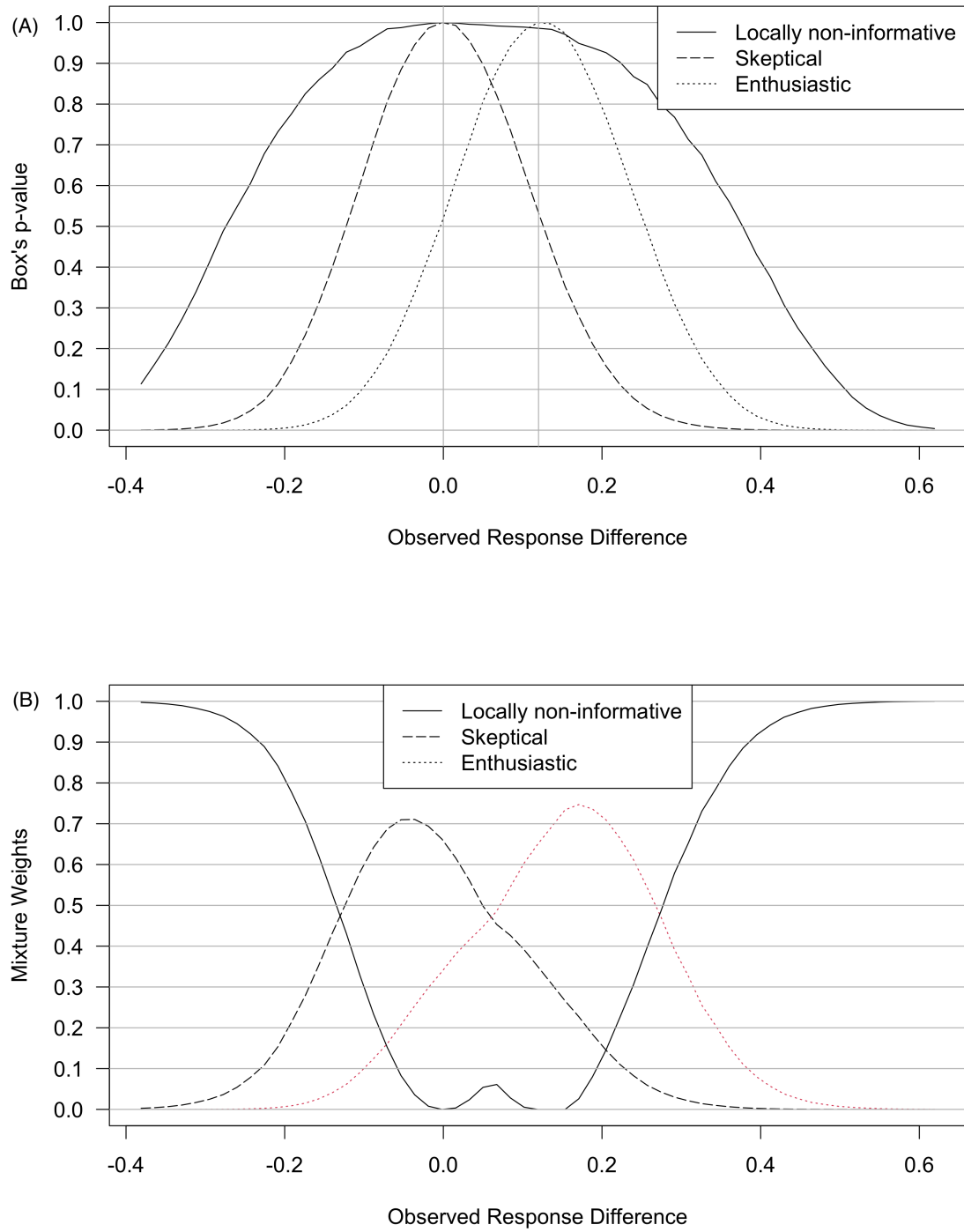


Figure 7. A; Prior-data compatibility assessments $\psi^{(S)}$, $\psi^{(E)}$, $\psi^{(NI)}$ by observed risk difference. B; 3-part mixture inference prior weights ω_S , ω_E , ω_{NI} by observed risk difference.