

A Structured Framework for Bayesian Sequential Monitoring in Clinical Trials

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SUMMARY: This introduction is much too generic. The introduction needs to (1) briefly highlight the motivation (using one or two sentences; value of sequential monitoring and incorporating external information into the design prospectively), (2) fully describe *all* novel aspects of the paper (this is go a long way to getting the paper accepted or rejected), and (3) how the method is demonstrated in the paper. I have modified the final sentence which I think is good to keep but feel free to tweak.

Conclusions from Bayesian clinical trials are most useful when specification of prior distributions are intuitively related to the research objectives. This paper defines monitoring priors using generalized normal distributions which reflect prior belief defined using a standardized definition of compelling level of evidence. The generalized normal distribution adds a layer of flexibility to the foundational normal distribution to reflect prior belief, which has a tangible impact on the operating characteristics of a clinical trial design. The proposed method is demonstrated by designing a simple single-arm proof-of-activity trial in pediatric ulcerative colitis and a two-group randomized controlled trial in pediatric lupus with both designs incorporating information from adult trials to varying degrees.

KEY WORDS:

This paper has been submitted for consideration for publication in *Biometrics*

1. Introduction

In the clinical development of a therapeutic product, **often challenges** impede a clinical trial from reaching its **primary objectives** (e.g. difficulty in enrolling, limited patient populations, long latency in observing the outcome of interest, etc.). In settings where **pertinent existing data** are available, Bayesian designs offer a natural approach for incorporating that information into the design and analysis of future trials. An example where Bayesian methods could be valuable is in the area of pediatric clinical trials where enrollment is often difficult and where relevant data from adult trials are often available. Utilizing information from the adult trials may result in pediatric trials **that are more efficient** (e.g., increased power, fewer subjects required and/or shorter trial durations).

This above paragraph should briefly introduce sequential monitoring. As it is, the first paragraph seems to imply Bayesian methods are all about information borrowing but the sequential monitoring aspect is also very important. The total paragraph length should be no longer than twice the current one.

At this point in the introduction you need to discuss our methodological innovations. What is our method (at a high level) and how can it be helpful in practice. This revised abstract can pull heavily from this section. We cannot get more than a few paragraphs into the paper without telling the reader what we are doing that is novel. You will lose the reviewer! It is critical in this portion that we are attempting to develop a framework for sequential monitoring that can be applied broadly and consistently which may be appealing to regulators. That is a big point. In this section you can take some of what you have below to contrast the Bayesian approach and frequentist approaches but you don't want to dwell on that too much. Flip the order – focus on Bayes and explain how frequentist methods are different and make sure anything you say about frequentist methods is precisely correct. For

example, I do not think the statement about pre-specified interim analyses / alpha spending functions is correct and we will get slammed if we make false claims. Alpha spending functions were developed to make the rigidity of a fixed number of analyses and fixed timing go away were they not – read up on this before revising.

Add material... customize this... Conclusions from Bayesian inferences are not affected by the frequency with which the data are monitored, and such interim analyses should be encouraged to terminate data collection if appropriate (Berry, 1989, 1993; Spiegelhalter et al., 1994). The Bayesian perspective is based on the likelihood principle which asserts that any data with the same likelihood function should lead to the same conclusion (Berger and Wolpert, 1988). In the context of sequential analysis of clinical trials, the stopping rule that leads to the termination of data collection is irrelevant to the conclusion (Barnard, 1947; Anscombe, 1963; Cornfield, 1966a,b). In contrast ... add stuff Frequentist group sequential designs rely on pre-specified interim analyses and spending functions to maintain desired trial operating characteristics (Pocock, 1977; O'Brien and Fleming, 1979).

At this point point in the introduction you can be into the recent literature on sequential trials. Where have these methods been used post-2000? You don't need to describe methods in depth but do need to show you have knowledge of what has been done recently (relevant stuff). If there is little that is fine.

Much of the text in orange can be wove in above, referenced elsewhere in the paper or cut.

General advice... The last sentence in the orange text illustrates a style of writing you want to try and avoid when writing statistical papers. The entire paragraph describes an approach for doing something and then the last sentence says we use that approach. The

better strategy is to say exactly what we are doing and give credit through name or citation to ideas that first came from others

Interpretation of conclusions from the Bayesian perspective is natural when specification of prior distributions are intuitively related to the research objectives. Skeptical and enthusiastic monitoring priors are used to evaluate efficacy and futility at an interim analysis (Freedman and Spiegelhalter, 1989, 1992; Spiegelhalter et al., 1993; Fayers et al., 1997). The most common Bayesian metrics for assessing evidence at interim analyses are posterior probabilities and predictive probabilities, and the choice of metric depends on the research objective. Posterior probabilities assess the level of evidence in favor of the null or alternative hypothesis, and predictive probabilities determine the capacity for the trial to show convincing evidence in favor of the alternative hypothesis if more outcomes are ascertained. This paper uses posterior probabilities to highlight how the level of evidence at interim analyses is linked to monitoring prior specification.

As noted above, the below type of paragraph needs to cover very early in the paper and needs to be specific about what are are doing. This is very general and also not perfectly precise. For example, I'm not sure the framework addresses how to specify the trial hypotheses really.

This paper presents a structured framework to determine the major components of a Bayesian sequentially monitored clinical trial, including the trial hypothesis, monitoring priors, and stopping criteria. It is shown that the generalized normal distribution is an intuitive and flexible choice for monitoring prior specification.

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. 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 example, for the two-arm trial example above η would correspond to the response probability for patients receiving the control treatment.

Consider the hypotheses $H_0 : \theta \in \Theta_0$ versus $H_1 : \theta \in \Theta_1$ where $\Theta_0 \cup \Theta_1 = \Theta$ and $\Theta_0 \cap \Theta_1 = \emptyset$. 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 (θ, η) specified over the parameter space defined with respect to each of the hypotheses (e.g. $\pi(\theta, \eta|H_i)$ for

$i = 0, 1$). 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 .

The posterior probability of hypothesis H_i is given by

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

where $p(\mathbf{D}|H_i) = \int_{\Theta_i} p(\mathbf{D}|\theta)\pi(\theta|H_i)d\theta$ is the marginal likelihood associated with hypothesis H_i . In practice, most Bayesian methods for clinical trials perform hypothesis testing based on the posterior probability of the *event defining* H_i . For this approach, one simply needs to specify a prior $\pi(\theta)$ representing belief about θ overall and compute the posterior distribution. The posterior probability that $\theta \in \Theta_i$ is given by

$$P(\theta \in \Theta_i|\mathbf{D}) = \frac{\int_{\Theta_i} p(\mathbf{D}|\theta)\pi(\theta)d\theta}{\int_{\Theta} p(\mathbf{D}|\theta)\pi(\theta)d\theta} = \frac{\int_{\Theta_i} p(\mathbf{D}|\theta)\pi(\theta|\theta \in \Theta_i)d\theta \cdot P(\theta \in \Theta_i)}{\sum_{j=0,1} \int_{\Theta_j} p(\mathbf{D}|\theta)\pi(\theta|\theta \in \Theta_j)d\theta \cdot P(\theta \in \Theta_j)} \quad (2)$$

where $P(\theta \in \Theta_i) = \int_{\Theta_i} \pi(\theta)d\theta$. We can readily see that the $P(\theta \in \Theta_i|\mathbf{D})$ is equal to $p(H_i|\mathbf{D})$ if one takes $p(H_i) = P(\theta \in \Theta_i)$ and $\pi(\theta|H_i) = \pi(\theta|\theta \in \Theta_i)$ for $i = 0, 1$. If in fact $\pi(\theta)$ does represent belief about θ , these choices are perhaps the most intuitive and thus we should have no reservation referring to $P(\theta \in \Theta_i|\mathbf{D})$ as the probability that hypothesis H_i is true. For these reasons, in what follows we will refer to the quantity $P(\theta \in \Theta_i|\mathbf{D})$ as the posterior probability of H_i for ease of exposition.

2.1.2 Formalizing the Statistical Concept of Substantial Evidence. For testing one-sided hypotheses such as $H_0 : \theta \leq \theta_0$ versus $H_1 : \theta > \theta_0$ using posterior probabilities, the null hypothesis is rejected when $P(\theta > \theta_0|\mathbf{D})$ exceeds a predefined threshold. Leveraging this common practice, we define the posterior probability threshold $1 - \epsilon = 0.975$ to be the threshold for what constitutes *substantial evidence* in favor of a claim (e.g., that $\theta > \theta_0$) and, correspondingly, we refer to ϵ as the threshold for insignificant *residual uncertainty*. 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.

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

$$P_\pi(\theta \in \Theta_i) = 1 - \epsilon, \quad (3)$$

where the subscript π in (3) 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 (Fayers et al., 1997) on the premature termination of trials, 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 to be tested. 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 rationale for definitions of a priori skeptical and enthusiastic perspectives that can be used for early stopping decisions in favor of efficacy and futility, respectively.

For ease of exposition, consider the hypotheses $H_0 : \theta \leq \theta_0$ versus $H_1 : \theta > \theta_0$ where θ represents a treatment effect of interest and let $\theta_1 > \theta_0$ represent a plausible, clinically meaningful effect.

Define an enthusiastic prior $\pi_E(\theta)$ as a prior that suggests θ_1 is the most likely value of θ 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 satisfying

$$P_E(\theta > \theta_0) = 1 - \epsilon, \quad (4)$$

where the subscript E indicates that the probability is based on $\pi_E(\theta)$.

Define a skeptical prior $\pi_S(\theta)$ as a prior that suggests θ_0 is 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 satisfying

$$P_S(\theta < \theta_1) = 1 - \epsilon. \quad (5)$$

In what follows we refer to (4) and (5) as *tail-probability constraints*.

Note that the development of the skeptical prior does not generally reflect skepticism that the alternative hypothesis is true. Indeed, in most cases the *induced* prior model probabilities based on (1) will be such that $p(H_0) \approx p(H_1)$. The skeptical prior simply reflects that $\theta \geq \theta_1$ is exceedingly unlikely and is therefore consistent with their being clinical equipoise about the two hypotheses.

Unlike the frequentist approach, the degree to which evidence in favor of a hypothesis is substantial is influenced by the prior distribution on the quantity of interest. It is natural that one would stop a trial early in favor of efficacy or futility when the evidence in favor

of that 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 in fact the alternative is true, then most any rational observer would also be convinced and therefore ceasing the collection of data to prove that claim would be reasonable. Similarly, if at any point data sufficiently convince an observer whose prior belief is in accordance with $\pi_E(\theta)$ that in fact the effect of interest is less than what was originally believed, then most any rational observer would also be convinced and therefore ceasing the collection of data altogether would be reasonable.

2.1.4 Maximum Sample Size and Formal Stoppage Criteria. In this section we formalize a 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. 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 compelling 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 analyze the data after each patient's outcome data are available 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 is based on the skeptical viewpoint. 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.

Define the efficacy criteria for data \mathbf{D} as

$$\text{eff}(\mathbf{D}) = P_S(\theta > \theta_0 | \mathbf{D}), \quad (6)$$

and the threshold for substantial evidence to be

$$\text{eff}(\mathbf{D}) > 1 - \epsilon \quad (7)$$

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.

For futility monitoring, at first thought it may seem appealing to stop the trial when the enthusiast becomes convinced that the null hypothesis is true. However, for this to be the case the observed data must suggest $\theta \ll \theta_0$ since when $\theta = \theta_0$, $P_E(\theta \leq \theta_0 | \mathbf{D}) \rightarrow 0.5$ for large samples sizes. For this reason, we consider a different approach. Recalling that θ_1 represents a plausible, clinically meaningful treatment effect, we define $\theta_m = c \cdot \theta_0 + (1-c) \cdot \theta_1$ for $c \in [0, 1]$ to be a less than desirable treatment effect such that if it is the case that $P_E(\theta < \theta_m | \mathbf{D}) > 1 - \epsilon$, the trial may be stopped due to having a low probability of reaching a meaningful treatment effect. For example applications in this paper, we consider $c = 0.5$, so that $\theta_m = (\theta_0 + \theta_1)/2$.

Define the futility criteria for data \mathbf{D} as

$$\text{fut}(\mathbf{D}) = P_E(\theta \leq \theta_m | \mathbf{D}) \quad (8)$$

and the threshold for substantial evidence to be

$$\text{fut}(\mathbf{D}) > 1 - \epsilon \quad (9)$$

2.1.5 Mixture Inference Prior. 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 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 a priori belief of most stakeholders will likely fall somewhere in 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 as a mixture prior constructed by mixing the monitoring priors.

Define the inference prior associated with mixing weight ω as

$$\pi_I(\theta) = \omega \cdot \pi_S(\theta) + (1 - \omega) \cdot \pi_E(\theta), \quad (10)$$

where $\omega \in [0, 1]$. The specification of ω 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 θ using the inference prior, $p(\theta | \mathbf{D}, \pi_I)$, will be used to compute summaries of θ such as the posterior mean and quantiles. The posterior distribution for θ using (10) is

$$p(\theta | \mathbf{D}, \pi_I) = \hat{\omega} \cdot p(\theta | \mathbf{D}, \pi_S) + (1 - \hat{\omega}) \cdot p(\theta | \mathbf{D}, \pi_E) \quad (11)$$

where the updated mixing weight is

$$\hat{\omega} = \frac{\omega \cdot p(\mathbf{D}|\pi_S)}{\omega \cdot p(\mathbf{D}|\pi_S) + (1 - \omega) \cdot p(\mathbf{D}|\pi_E)} \quad (12)$$

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

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

$$\omega = \omega_{min} + (1 - \omega_{min}) \frac{\pi_S(\hat{\theta})}{\pi_S(\hat{\theta}) + \pi_E(\hat{\theta})} \quad (13)$$

as a mixing weight that dynamically gives preference to the prior that has the higher density evaluated at $\hat{\theta}$ with a minimum weight ω_{min} given to the skeptical component with $\omega_{min} \in [0, 1]$.

2.1.7 Operating Characteristics. Suppose that the trial has interim analyses based on the number of completed outcomes. Let $n_{initial}$ be the first instance where either the efficacy criteria or futility criteria are satisfied, or n_{max} if the efficacy criteria or futility criteria are not satisfied at any point. Let n_{final} be the final sample size which includes patients whose outcomes were in progress at the time of enrollment termination. Let $\mathbf{D}(n)$ denote the data after n completed outcomes are ascertained. Type 1 error and power are computed based on $\operatorname{eff}(\mathbf{D}(n_{initial}))$ and $\operatorname{eff}(\mathbf{D}(n_{final}))$, respectively. The posterior mean and credible intervals for θ are also evaluated for both $\mathbf{D}(n_{initial})$ and $\mathbf{D}(n_{final})$.

There is the possibility for disagreement between $\operatorname{eff}(\mathbf{D}(n_{initial}))$ and $\operatorname{eff}(\mathbf{D}(n_{final}))$. Of particular interest are cases when $\operatorname{eff}(\mathbf{D}(n_{initial})) > 1 - \epsilon$ and $\operatorname{eff}(\mathbf{D}(n_{final})) \leq 1 - \epsilon$, that

is, the threshold for substantial evidence is satisfied for an interim analysis but is no longer satisfied once outcomes from patients in progress are ascertained.

2.1.8 Computation. The efficacy criteria (6) and futility criteria (8), 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). In the examples in Section 3, these quantities are 1- and 2-dimensional integrals which are evaluated using numerical integration in R (R Core Team, 2017), in particular using the *pracma* package (Borchers, 2019). MCMC would likely be necessary if the dimension of (θ, η) is greater than 2.

2.2 Monitoring Prior Parameterization

Skeptical and enthusiastic monitoring priors defined in Section 2.1.3 have a required 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 skeptical and enthusiastic priors.

2.2.1 Normal Distribution $\mathcal{N}_p(\tilde{\mu}, q)$. Define $\theta \sim \mathcal{N}_p(\tilde{\mu}, q)$ as the normal distribution $\mathcal{N}(\mu, \sigma)$ that satisfies $\text{mode}(\theta) = \tilde{\mu}$ and $P(\theta \leq q) = p$. The values for the mean and standard deviation are $\mu = \tilde{\mu}$ and $\sigma = \frac{q-\mu}{\Phi^{-1}(p)}$, where Φ denotes the cumulative distribution function for a standard normal distribution, and Φ^{-1} denotes its quantile function. The distribution $\mathcal{N}_p(\tilde{\mu}, q)$ is well-defined for values (μ, q, p) that satisfy $\frac{q-\mu}{p-0.5} > 0$.

Since the normal distribution is completely specified by (μ, σ) , quantities such as $P(\theta \leq \tilde{q})$ are also specified for any \tilde{q} . In particular, if $\theta \sim \mathcal{N}_p(\tilde{\mu}, q)$ then $P(\theta \leq \frac{q+\mu}{2}) = \Phi(\frac{\Phi^{-1}(p)}{2})$. Furthermore, $P(\theta \in (\mu, \frac{q+\mu}{2})) = |p - \Phi(\frac{\Phi^{-1}(p)}{2})|$.

2.2.2 Generalized Normal Distributions $\mathcal{GN}_p(\tilde{\mu}, q, \gamma)$. The density for a generalized normal distribution $\mathcal{GN}(\mu, \alpha, \beta)$ is $f(\theta) = \frac{\beta}{2\alpha\Gamma(1/\beta)} \exp\{-(\frac{|\theta-\mu|}{\alpha})^\beta\}$ where μ is a location param-

eter, $\alpha > 0$ is a scale parameter, and $\beta > 0$ is a shape parameter (Nadarajah, 2005). Let $F_{\mu,\alpha,\beta}$ denote the cumulative distribution function of $\mathcal{GN}(\mu, \alpha, \beta)$. An expression for $F_{\mu,\alpha,\beta}$ is provided in the appendix, and computations involving $F_{\mu,\alpha,\beta}$ are done using the `gnorm` package (Griffin, 2018).

Define $\theta \sim \mathcal{GN}_p(\tilde{\mu}, q, \gamma)$ as the generalized normal distribution $\mathcal{GN}(\mu, \alpha, \beta)$ that satisfies $\text{mode}(\theta) = \tilde{\mu}$, $P(\theta \leq q) = p$, and $P(\theta \in (q, \frac{q+\mu}{2})) = \gamma \cdot |p - \Phi(\frac{\Phi^{-1}(p)}{2})|$. The mode is equal to $\mu = \tilde{\mu}$, and α and β are determined to minimize the function $(F_{\mu,\alpha,\beta}(q) - p)^2 + (F_{\mu,\alpha,\beta}(\frac{q+\mu}{2}) - \gamma \cdot |p - \Phi(\frac{\Phi^{-1}(p)}{2})|)^2$ with box-constrained optimization (Byrd et al., 1995). The restrictions on well-defined choices of $(p, \tilde{\mu}, q, \gamma)$ for the $\theta \sim \mathcal{GN}_p(\tilde{\mu}, q, \gamma)$ distribution are described in the appendix.

The flexibility to modify γ can change the distribution to be flatter or more concentrated around the modal value. Choosing $\gamma = 1$ corresponds to the normal distribution which is viewed as a default choice. If $\gamma > 1$ then the probability that $\theta \in (q, \frac{q+\mu}{2})$ increases and the concentration of θ around the modal value μ accordingly decreases, resulting in a flatter distribution around the modal value. If $\gamma < 1$ then the probability that $\theta \in (q, \frac{q+\mu}{2})$ decreases and the concentration of θ around the modal value μ accordingly increases, resulting in a more concentrated distribution around the modal value. Note that the tail probability $P(\theta \leq q) = p$ is maintained regardless of the choice of γ .

Flattening or concentrating the distribution around the modal value is useful for specifying monitoring priors that reflect varying opinions about the dispersion of θ . An example of parameterizing an enthusiastic prior with a $\mathcal{GN}_p(\tilde{\mu}, q, \gamma)$ distribution is demonstrated in Figure 1. Choosing a concentrated distribution is appropriate when prior belief reflects a higher degree of certainty that θ is in a narrow range around θ_1 , while maintaining residual uncertainty that $\theta < \theta_0$. This decreases the variance of the distribution, and can be seen to reflect a conservative opinion about the values of θ . Choosing a flattened distribution is

appropriate when θ is more likely to be in a wide range of values around θ_1 , while maintaining the same residual uncertainty that $\theta < \theta_0$. This increases the variance of the distribution, and can be seen to reflect a liberal opinion about the values of θ . The specification of $\gamma = 0.75$ will be used henceforth as a pre-determined value for creating a concentrated distribution, and $\gamma = 1.5$ will be used for creating a flattened distribution. These values of γ are chosen based on the intuitive graphical properties of the distribution (e.g. noticeably peaked around θ_1 , relatively flat around θ_1). Alternatively, the choice of γ could be specified to identify an additional probability constraint exactly (e.g. $P(\theta \in (\theta_0, \frac{\theta_0 + \theta_1}{2})) = 0.1$). The impact of flattening or concentrating the distribution of a monitoring prior on the operating characteristics of a trial is shown in Section 3.

2.2.3 Truncated Generalized Normal Distribution $\mathcal{GN}_{p,\Theta}(\tilde{\mu}, q, \gamma)$. The density for a generalized normal distribution truncated to the interval domain $\Theta = (\theta_{min}, \theta_{max})$, denoted by $\mathcal{GN}_{\Theta}(\mu, \alpha, \beta)$, is $f(\theta) = c \cdot \exp\left\{-\frac{|\theta - \mu|^\beta}{\alpha}\right\} I(\theta \in \Theta)$ where $c = \frac{\beta}{2\alpha\Gamma(1/\beta)} (F_{\mu,\alpha,\beta}(\theta_{max}) - F_{\mu,\alpha,\beta}(\theta_{min}))^{-1}$.

Define $\theta \sim \mathcal{GN}_{p,\Theta}(\tilde{\mu}, q, \gamma)$ as the truncated generalized normal distribution $\mathcal{GN}_{\Theta}(\mu, \alpha, \beta)$ that satisfies $\text{mode}(\theta) = \tilde{\mu}$, $P(\theta \leq q) = p$, and $P(\theta \in (q, \frac{q + \mu}{2})) = \gamma|p - \Phi(\frac{\Phi^{-1}(p)}{2})|$. For example, consider creating skeptical and enthusiastic priors for a response probability on domain $[0, 1]$, as $\pi_S(\theta) = \mathcal{GN}_{p=1-\epsilon, \Theta=[0,1]}(\tilde{\mu} = \theta_0, q = \theta_1, \gamma = 1)$ and $\pi_E(\theta) = \mathcal{GN}_{p=\epsilon, \Theta=[0,1]}(\tilde{\mu} = \theta_1, q = \theta_0, \gamma = 1)$ respectively.

[Figure 1 about here.]

The generalized normal distribution can be used to parameterize skeptical and enthusiastic priors for trials with multiple unknown quantities of interest. Let θ be the parameter of interest and η be the nuisance parameters. Consider the following representation of the joint prior for θ and η : $\pi(\theta, \eta) = \pi(\theta) \times \pi(\eta|\theta)$. For example, suppose that θ is the risk difference between response probabilities of the treatment group and the placebo group η . The distribution for the risk difference is $\pi(\theta) \sim \mathcal{GN}_{p,\Theta=[-1,1]}()$. The domain of η is $[0, 1 - \theta]$ if

$\theta \geq 0$ and $(-\theta, 1)$ if $\theta < 0$. Define the prior for η to be $\pi(\eta|\theta) \sim \mathcal{GN}_{p,H=[\max(-\theta,0),\min(1,1+\theta)]}()$. This prior specification is demonstrated in Figure 2, and Section 3.2.2 uses this representation of the joint prior.

[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). Infliximab was given to all patients at the 5mg/kg dose at weeks 0, 2, and 6, and the primary endpoint was response at week 8. Response was measured by improvement in disease severity scores.

The trial was conducted between August 2006 and June 2010. Patients were enrolled over approximately 33.5 months (1 patient enrolled per 17 days)

The sample size of 60 patients was chosen to ensure 12% precision in estimating the true response proportion with 95% confidence interval, assuming a response rate of 0.67 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. At week 8, clinical response was observed in 44 out of 60 (73.3%) patients.

3.1.2 Model Formulation & Prior Elicitation. The data \mathbf{D} are assumed to be independent Bernoulli random variables with common response probability θ . The null response value is $\theta_0 = 0.4$, 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 intermediate response value is $\theta_m = 0.535$. The skeptical prior is $\pi_S(\theta) \sim \mathcal{GN}_{p=0.975,\Theta=[0,1]}(\tilde{\mu} = \theta_0, q = \theta_1, \gamma = 0.75)$. The scaling factor $\gamma < 1$ was

chosen to concentrate the distribution around the modal value to provide additional Type 1 error control. The enthusiastic prior is $\pi_E(\theta) \sim \mathcal{GN}_{p=0.025, \Theta=[0,1]}(\tilde{\mu} = \theta_1, q = \theta_0, \gamma = 1)$. The scaling factor $\gamma = 1$ was chosen as a default value corresponding to the truncated normal distribution. A comparison of the various combinations of the monitoring priors is provided in Appendix 4. An inference prior is defined as the mixture (10) with $\omega = 0.5$. The maximum sample size was increased from 60 to increase the probability of stopping the trial early due to efficacy at response proportion values between the null $\theta_0 = 0.4$ and the adult data $\theta_1 = 0.67$. The sample size of $n_{max} = 112$ based on a frequentist design to have 80% power to conclude efficacy with the skeptical monitoring prior at a true response proportion of $\theta_m = 0.535$. This increased power provides a better setting to demonstrate how the flattening or concentration of the skeptical monitoring prior impacts the operating characteristics.

3.1.3 Example Paths. Violin plots are used to show the results of simulated trials with the initial prior specification (first set of distributions), three interim analyses (middle sets), and a final analysis (last set), where interim analyses are conducted after every 10 completed outcomes.

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

[Figure 3 about here.]

3.1.4 Preposterior Analysis of Operating Characteristics. Consider more frequent monitoring with an interim analysis occurring after every 2 patients complete follow-up. The following are generated from 10,000 simulations for the trial described in Section 3.1.2.

Figure 4(a) shows the operating characters of this particular trial design. Inconclusive findings refers to situations where the efficacy and futility criteria are not satisfied for any interim analysis. 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 bias towards the alternative hypothesis.

Figure 4(b) addresses the particular situation when the efficacy criteria is satisfied at an interim analysis triggering termination of enrollment of additional patients, but once the outcomes of patients 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 θ 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 the case of evidence decrease.

[Figure 4 about here.]

3.1.5 Type 1 Error Rate by the Frequency of Data Monitoring. Figure 5 shows the probability of the efficacy criteria being satisfied at an interim and final analysis when $\theta = \theta_0$. The initial sample size is the sample size when the efficacy criteria is satisfied and enrollment is henceforth terminated. The final sample size includes outcomes from those patients in progress at time of trial termination. If the efficacy criteria is not satisfied at any of the interim analyses, then the initial and final sample sizes are equal to the maximum sample size.

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

[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). Patients 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 patients, the first 24 patients randomized in a 5:1 ratio (belimumab:placebo) and the remaining 76 patients would be randomized in a 1:1 allocation ratio. Therefore, 58 patients 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 patients enrolled.

The results of this trial were inconclusive with the 93 patients. A post-hoc Bayesian analysis that gave 55% weight to adult data with response rate 0.51 was sufficient to provide evidence of positive treatment effect (Travis et al., 2019). 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.

3.2.2 Model Formulation & Prior Elicitation. 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 (IP for investigational product) group. The null response value for the difference $\theta_0 = 0$ and a highly efficacious difference is $\theta_1 = 0.12$. The hypothesis testing of IP superiority to control $H_0 : \theta \leq \theta_0$ v.s. $H_1 : \theta > \theta_0$. The intermediate response value is $\theta_m = 0.06$. An estimate for the pediatric response rate is $\eta_0 = 0.39$, which is 0.12 less than the adult data response rate.

The skeptical monitoring prior is $\pi_S(\theta, \eta_0) = \pi_S(\theta) \times \pi(\eta_0|\theta)$, where $\pi_S(\theta) \sim \mathcal{GN}_{p=0.975, \Theta=[-1,1]}(\tilde{\mu} = \theta_0, q = \theta_1, \gamma = 0.75)$. The value $\gamma = 0.75$ reflects a concentrated distribution which was chosen to reflect a conservative opinion for added Type 1 error control. The enthusiastic monitoring prior is $\pi_E(\theta, \eta_0) = \pi_E(\theta) \times \pi(\eta_0|\theta)$, where $\pi_E(\theta) \sim \mathcal{GN}_{p=0.025, \Theta=[-1,1]}(\tilde{\mu} = \theta_1, q = \theta_0, \gamma = 1)$. The value $\gamma = 1$ was chosen as the default value. For both the skeptical and enthusiastic monitoring prior, $\pi(\eta_0|\theta) \sim \mathcal{GN}_{p=0.975, H=[\max(-\theta, 0), \min(1, 1+\theta)]}(\tilde{\mu} = 0.39, q = 0.59, \gamma = 1.5)$. The value $\gamma = 1.5$ was chosen to reflect a liberal opinion about the distribution of η_0 . In general, it is recommended to use flattened priors for nuisance parameters.

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 completed after every 2 patients have completed outcomes beginning at n_{min} .

3.2.3 Preposterior Analysis of Operating Characteristics. A mixture prior of the form (10) is used for efficacy monitoring where the choice of ω 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 is applied to the enthusiastic component. Additionally, a mixture prior with dynamic weight of the form (13) is used with $\omega_{min} = 0.25$.

Figure 6 shows the probability of stopping early for efficacy based on the choice of ω 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 $\theta = \theta_1$. 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.

[Figure 6 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. While it is possible to calibrate a Bayesian design to have exact pre-specified frequentist properties (Kopp-Schneider et al., 2019), this re-introduces inflexibility (e.g. interim analyses must be pre-specified) that is unnecessary using a fully Bayesian method. Therefore, the objective is to present operating characteristics generally that are “well-calibrated” (Grieve, 2016) but not motivated by strict adherence to pre-specified thresholds.

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 modal value, a quantile condition, and an additional parameter which can concentrate or flatten the

distribution around the modal value (with the normal distribution as the default case). This paper demonstrates how the operating characteristics are affected by the choice of monitoring priors.

Examples included binomially distributed data with response probabilities as the parameter of interest. The generalized normal distribution with optional truncation can be used for any parameter of interest on an interval domain. Future work includes using the generalized normal distribution for priors in Bayesian clinical trials with survival outcomes.

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REFERENCES

- Anscombe, F. J. (1963). Sequential medical trials. *Journal of the American Statistical Association* **58**, 365–383.
- Barnard, G. A. (1947). A review of sequential analysis by abraham wald. *Journal of the American Statistical Association* pages 658–669.
- Berger, J. O. and Wolpert, R. L. (1988). *The likelihood principle (2nd ed.)*. Hayward (CA): Institute of Mathematical Statistics.
- Berry, D. A. (1989). Monitoring accumulating data in a clinical trial. *Biometrics* **45**, 1197.
- Berry, D. A. (1993). A case for bayesianism in clinical trials. *Statistics in Medicine* **12**, 1377–1404.
- Borchers, H. W. (2019). *pracma: Practical numerical math functions*.
- Byrd, R. H., Lu, P., Nocedal, J., and Zhu, C. (1995). A limited memory algorithm for bound constrained optimization. *SIAM Journal on Scientific Computing* **16**, 1190–1208.
- Cornfield, J. (1966a). A bayesian test of some classical hypotheses, with applications to sequential clinical trials. *Journal of the American Statistical Association* **61**, 577.
- Cornfield, J. (1966b). Sequential trials, sequential analysis and the likelihood principle. *The American Statistician* **20**, 18–23.

- Fayers, P. M., Ashby, D., and Parmar, M. K. B. (1997). Tutorial in biostatistics: Bayesian data monitoring in clinical trials. *Statistics in Medicine* **16**, 1413–1430.
- Freedman, L. S. and Spiegelhalter, D. J. (1989). Comparison of bayesian with group sequential methods for monitoring clinical trials. *Controlled Clinical Trials* **10**, 357–367.
- Freedman, L. S. and Spiegelhalter, D. J. (1992). Application of bayesian statistics to decision making during a clinical trial. *Statistics in Medicine* **11**, 23–35.
- Grieve, A. P. (2016). Idle thoughts of a ‘well-calibrated’ bayesian in clinical drug development. *Pharmaceutical Statistics* **15**, 96–108.
- Griffin, M. (2018). Working with the exponential power distribution using gnrm.
- Hyams, J., Damaraju, L., Blank, M., Johanss, J., Guzzo, C., Winter, H. S., Kugathasan, S., Cohen, S., Markowitz, J., Escher, J. C., Veereman–Wauters, G., Crandall, W., Baldassano, R., and Griffiths, A. (2012). Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. *Clinical Gastroenterology and Hepatology* **10**, 391 – 399.e1.
- Kopp-Schneider, A., Wiesenfarth, M., Witt, R., Edelmann, D., Witt, O., and Abel, U. (2019). Monitoring futility and efficacy in phase ii trials with bayesian posterior distributions—a calibration approach. *Biometrical Journal* **61**, 488–502.
- Nadarajah, S. (2005). A generalized normal distribution. *Journal of Applied Statistics* **32**, 685–694.
- O’Brien, P. C. and Fleming, T. R. (1979). A multiple testing procedure for clinical trials. *Biometrics* **35**, 549–556.
- Pocock, S. J. (1977). Group sequential methods in the design and analysis of clinical trials. *Biometrika* **64**, 191–199.
- R Core Team (2017). R: A language and environment for statistical computing.

- Rutgeerts, P., Sandborn, W. J., Feagan, B. G., Reinisch, W., Olson, A., Johannis, J., Travers, S., Rachmilewitz, D., Hanauer, S. B., Lichtenstein, G. R., de Villiers, W. J., Present, D., Sands, B. E., and Colombel, J. F. (2005). Infliximab for induction and maintenance therapy for ulcerative colitis. *New England Journal of Medicine* **353**, 2462–2476.
- Spiegelhalter, D. J., Freedman, L. S., and Parmar, M. K. B. (1993). Applying bayesian ideas in drug development and clinical trials. *Statistics in Medicine* **12**, 1501–1511.
- Spiegelhalter, D. J., Freedman, L. S., and Parmar, M. K. B. (1994). Bayesian approaches to randomized trials. *Journal of the Royal Statistical Society. Series A (Statistics in Society)* **157**, 357–416.
- Travis, J., Neuner, R., Rothwell, R., Levin, G., Nie, L., Niu, J., Marathe, A., and Nikolov, N. (2019). Application of bayesian statistics to support approval of intravenous belimumab in children with systemic lupus erythematosus in the united states. In *2019 ACR/ARP Annual Meeting*.

SUPPORTING INFORMATION

APPENDIX SUPPLEMENTARY MATERIAL

Generalized Normal Cumulative Distribution Function

The CDF of a generalized normal random variable $\theta \sim \mathcal{GN}(\mu, \alpha, \beta)$ can be expressed as (Griffin, 2018)

$$P(\theta \leq q | \mu, \alpha, \beta) = \frac{1}{2} + \frac{\text{sign}(q - \mu)}{2} \int_0^{|q - \mu|^\beta} \frac{w^{1/\beta - 1}}{\alpha \Gamma(1/\beta)} \exp \left\{ - \left(\frac{1}{\alpha} \right)^\beta w \right\} dw \quad (\text{A.1})$$

Parameterizing the $\mathcal{GN}_p(\tilde{\mu}, q, \gamma)$ Distribution

The restrictions on the choice of $(p, \tilde{\mu}, q, \gamma)$ for the $\theta \sim \mathcal{GN}_p(\tilde{\mu}, q, \gamma)$ distribution to be well-defined:

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 patients in follow-up for monitoring frequencies of 8 or fewer, compared to approximately 6 patients 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 7 about here.]

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 θ_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 θ . 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 θ_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 about here.]

[Figure 9 about here.]

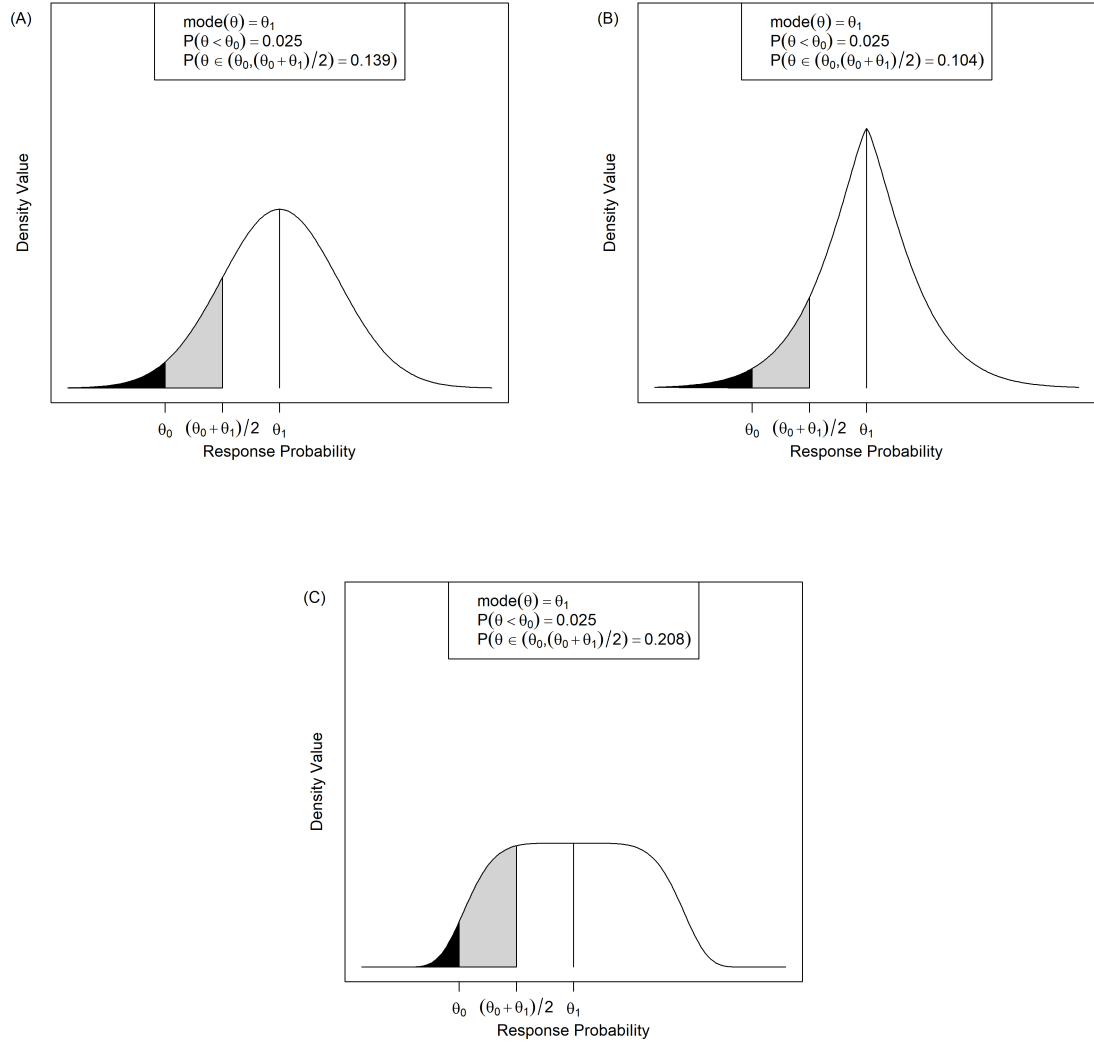


Figure 1. A, $\mathcal{GN}_{p=0.025}(\tilde{\mu} = \theta_1, q = \theta_0, \gamma = 1)$. B, $\mathcal{GN}_{p=0.025}(\tilde{\mu} = \theta_1, q = \theta_0, \gamma = 0.75)$, C, $\mathcal{GN}_{p=0.025}(\tilde{\mu} = \theta_1, q = \theta_0, \gamma = 1.5)$

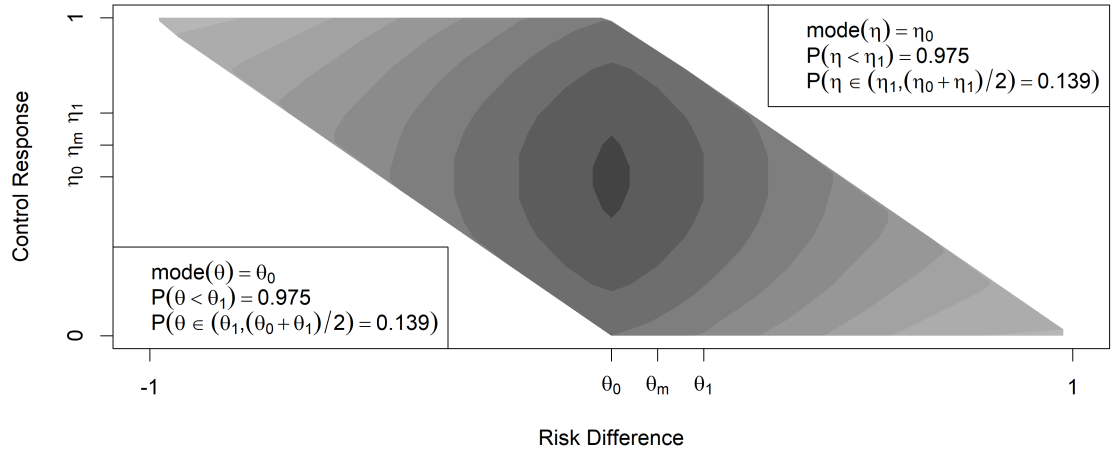


Figure 2. Joint distribution $\pi(\theta, \eta) = \pi(\theta) \times \pi(\eta|\theta)$, where $\pi(\theta) \sim \mathcal{GN}_{p=0.975, \Theta=[-1,1]}(\tilde{\mu} = \theta_0, q = \theta_1, \gamma = 1)$ and $\pi(\eta|\theta) \sim \mathcal{GN}_{p=0.975, H=[\max(-\theta, 0), \min(1, 1+\theta)]}(\tilde{\mu} = \eta_0, q = \eta_1, \gamma = 1)$.

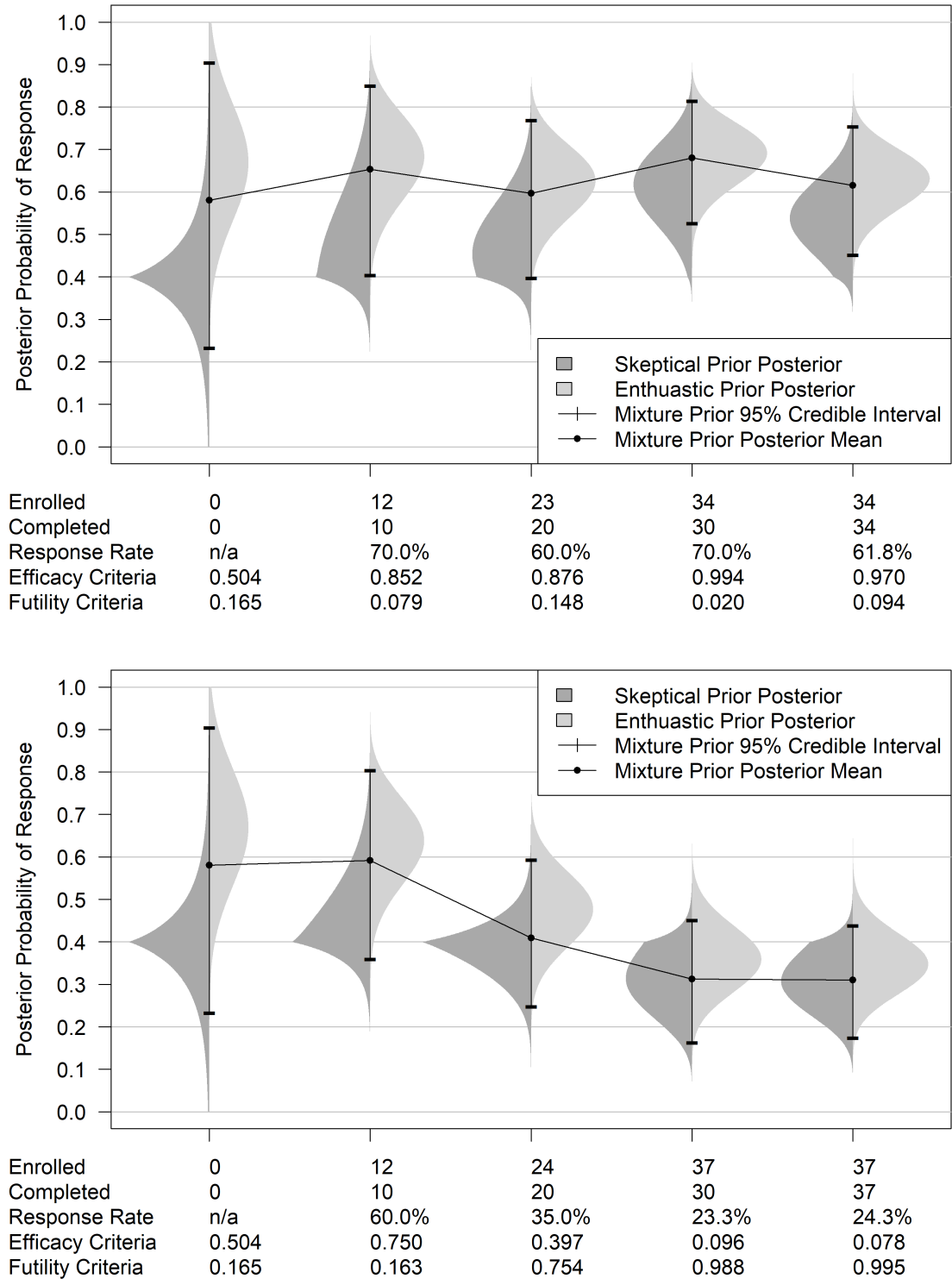


Figure 3. Example paths for the trial described in Section 3.1.2. A, Early stopping for efficacy. B, early stopping for futility.

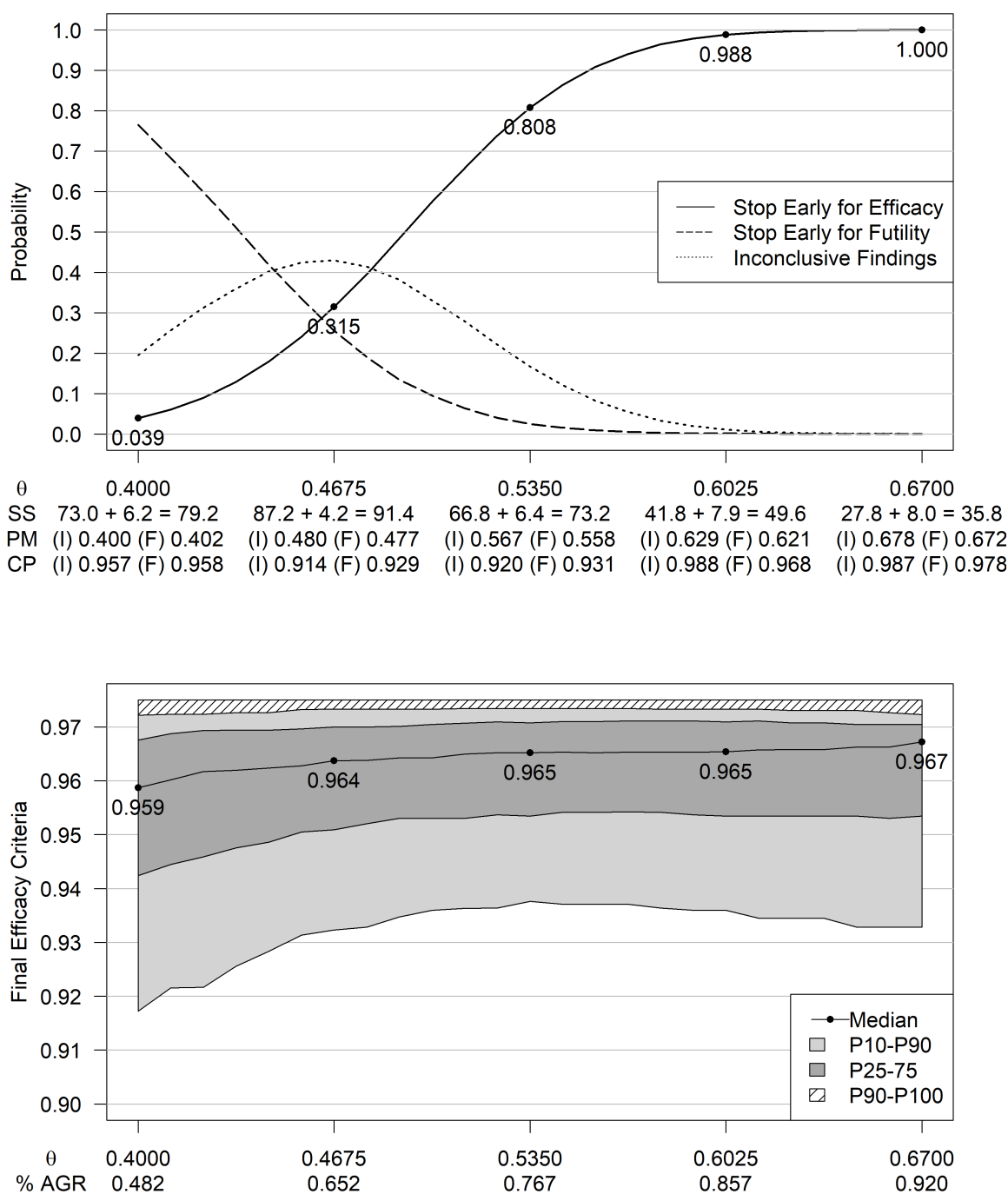


Figure 4. A, Sequential design properties. (SS; sample size, PM; posterior mean, CP; coverage probability, (I); interim analysis, (F); final analysis) B, Distribution of final posterior probability given interim stoppage and evidence decrease (% AGR; Percent of agreement between final and interim posterior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

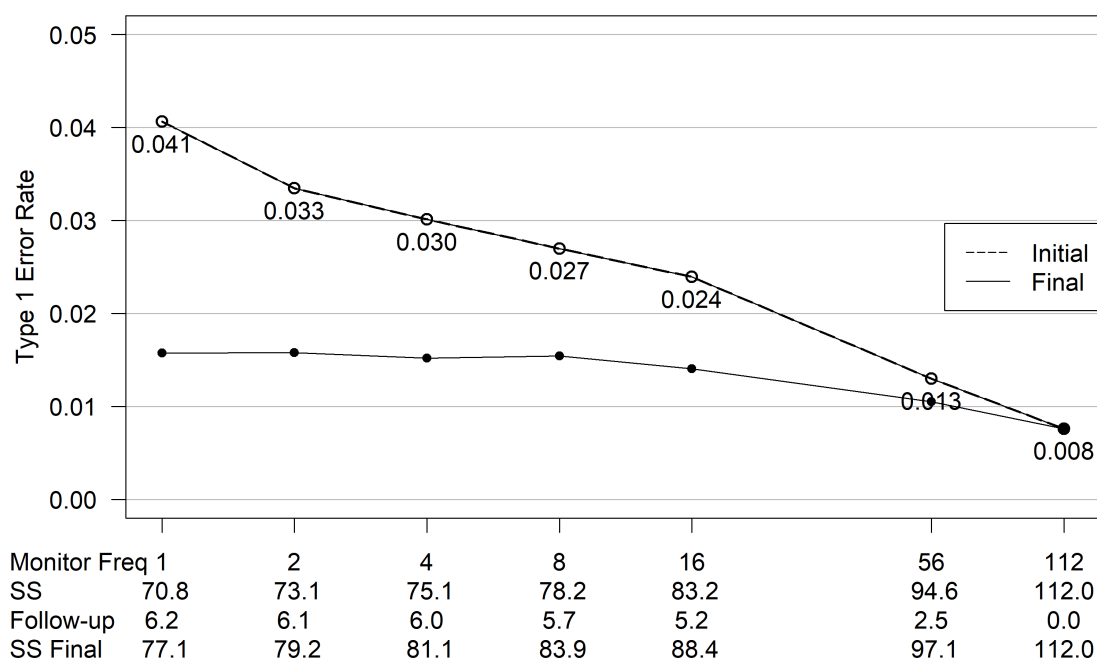


Figure 5. Probability of efficacy criteria being satisfied when $\theta = \theta_0$. SS; sample size. Monitor Freq; monitoring frequency.

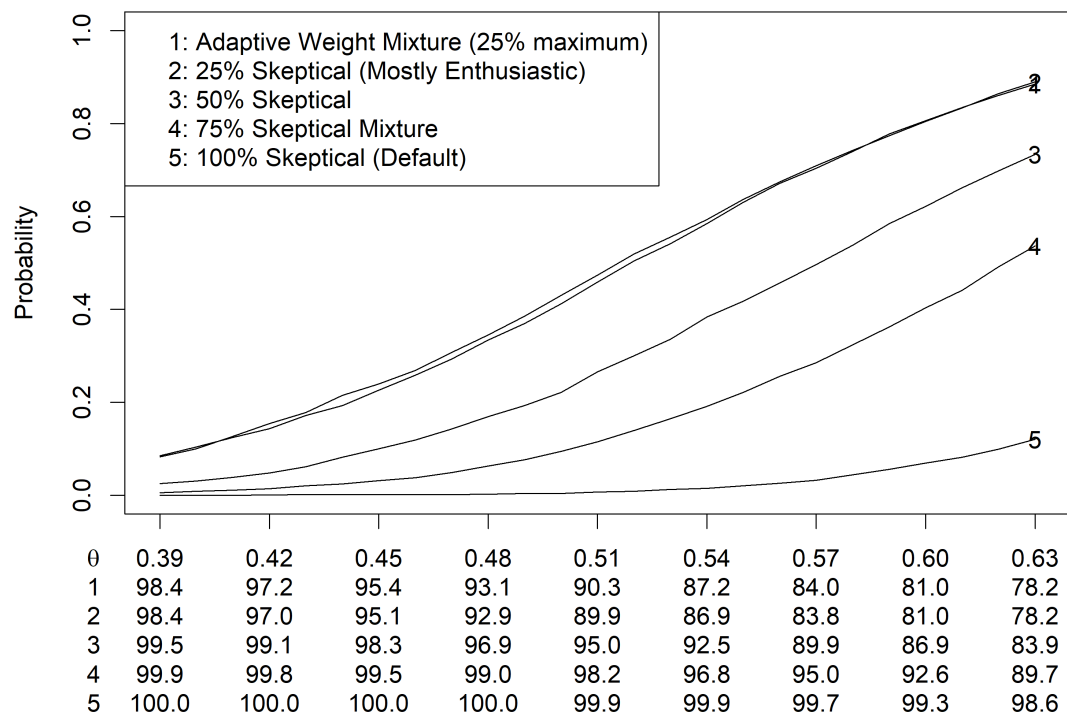


Figure 6. Probability of stopping for efficacy and associated sample sizes by true IP response rate θ with different choices of efficacy monitoring prior.

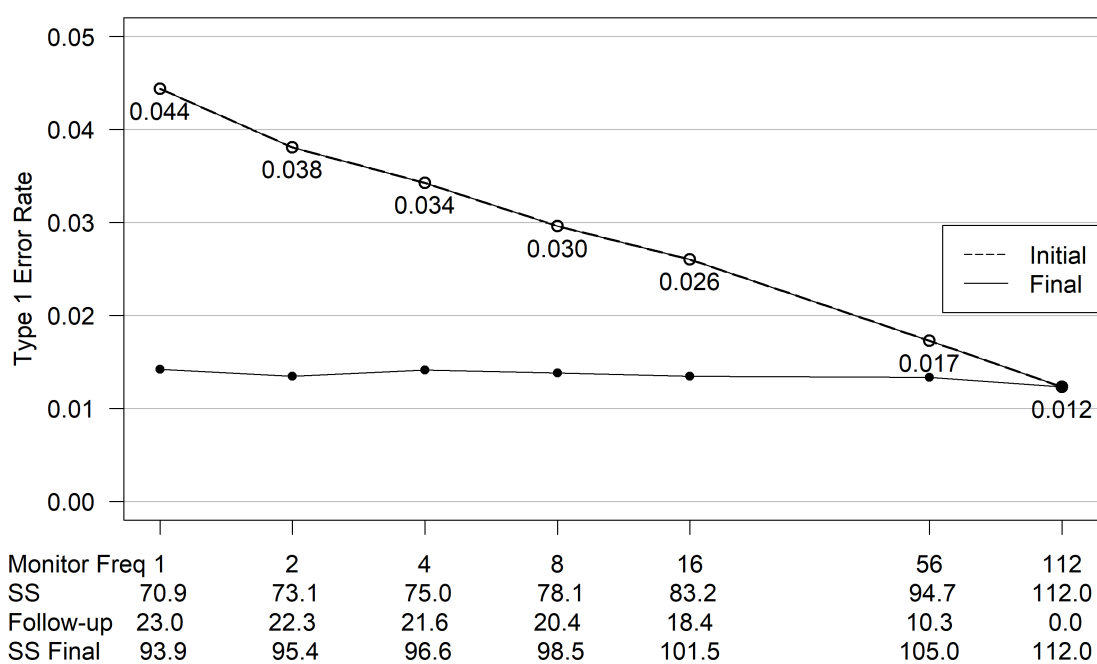


Figure 7. Single arm design from Example 3.1 with a longer follow-up period. Probability of efficacy criteria being satisfied when $\theta = \theta_0$. SS; sample size. Monitor Freq; monitoring frequency.

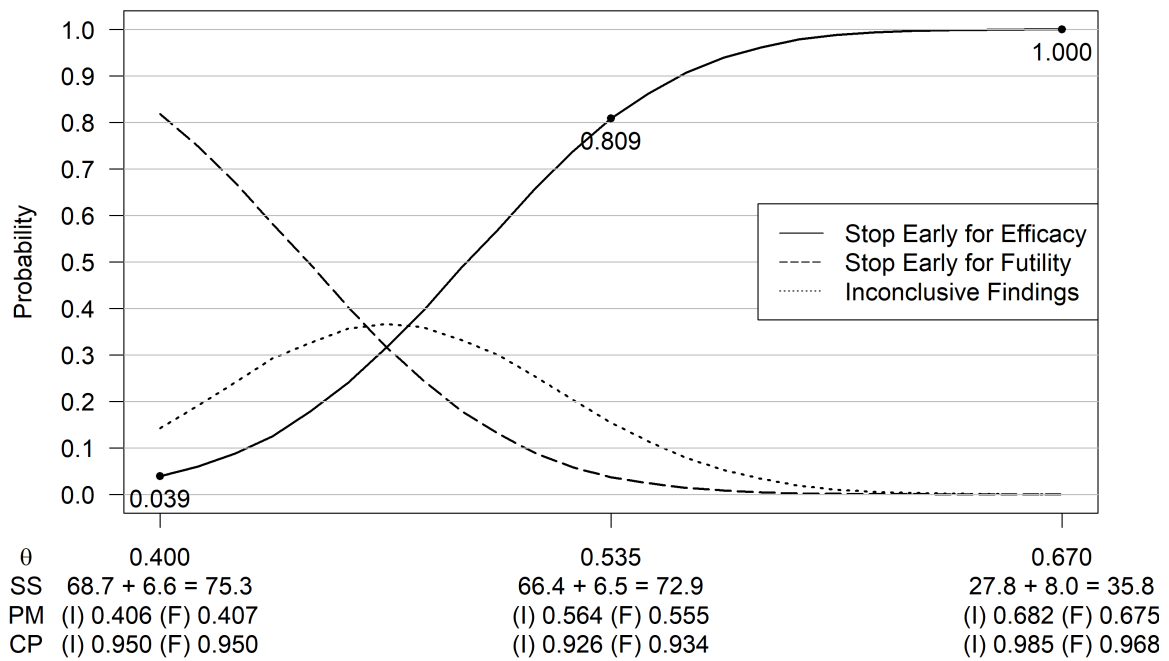
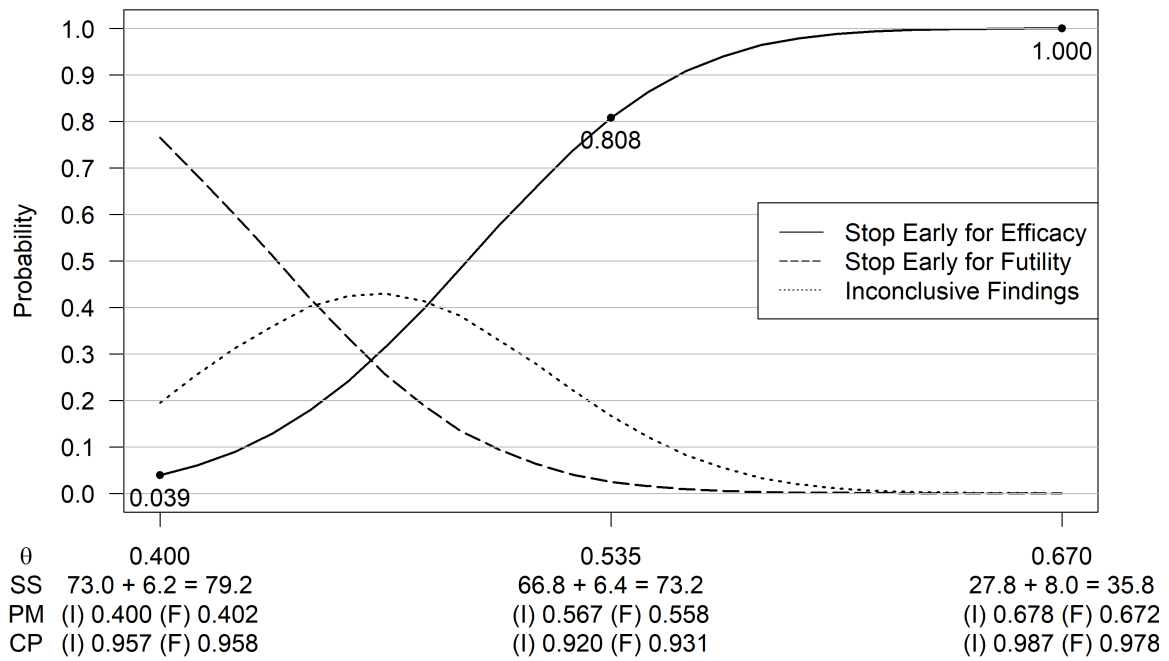


Figure 8. Modification of enthusiastic prior parameterization in Example 3.1. A, default enthusiastic prior (Figure 1(c)). B, flattened enthusiastic prior (Figure 1(d)). Both designs use concentrated skeptical prior (Figure 1(b)).

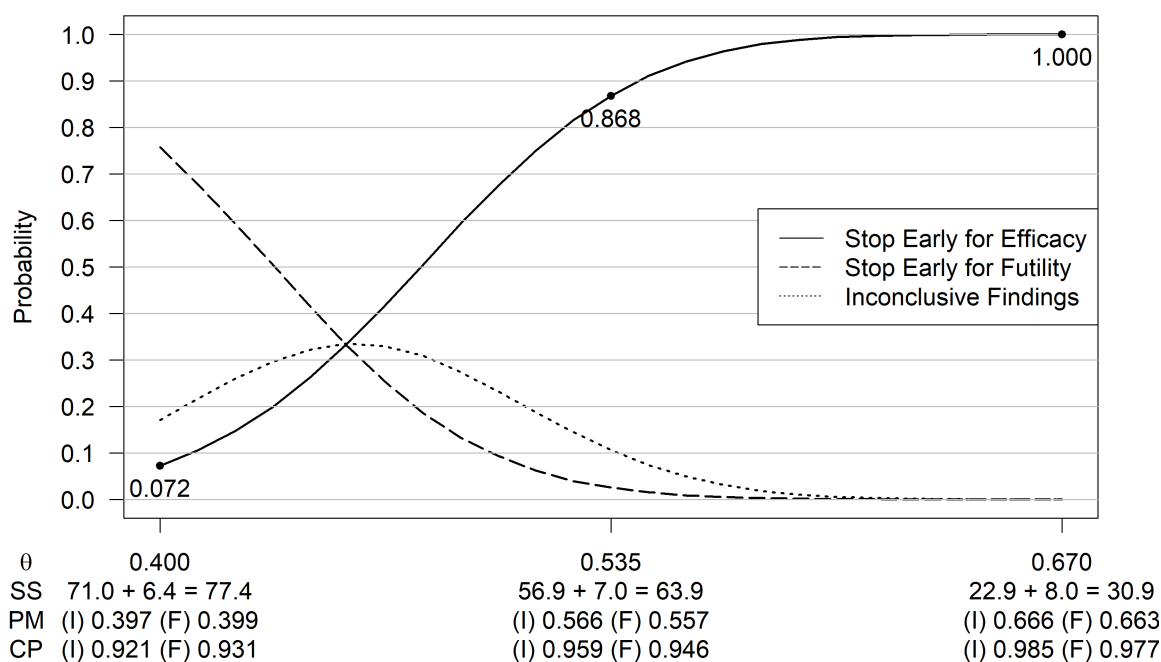
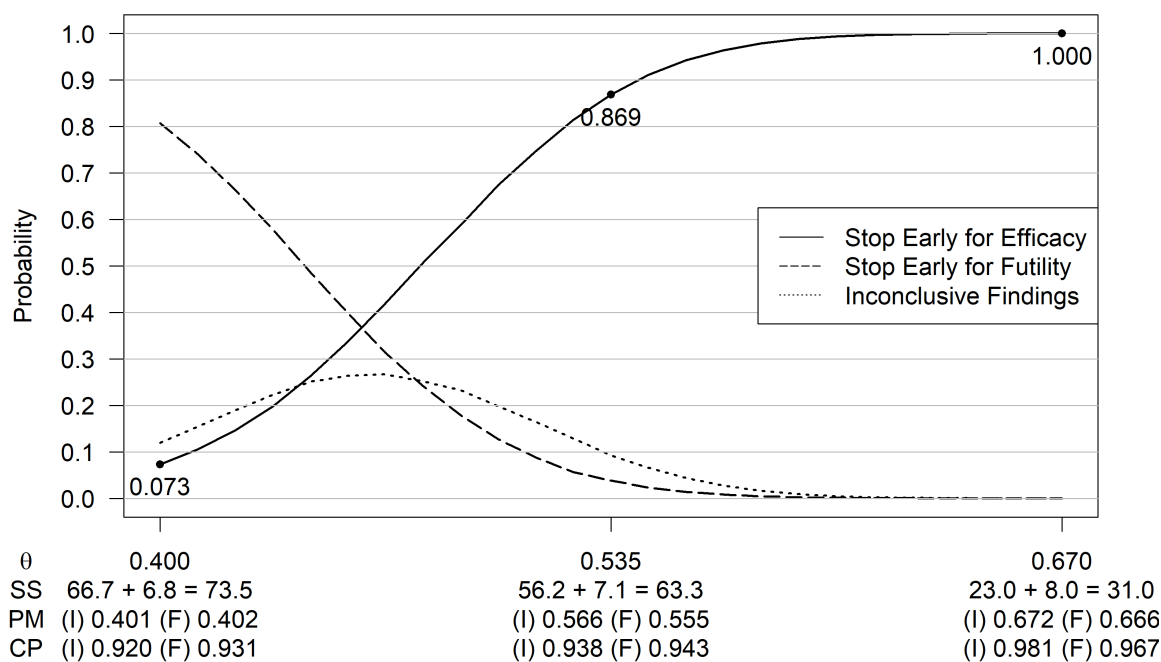


Figure 9. Modification of enthusiastic prior parameterization in Example 3.1. A, default enthusiastic prior (Figure 1(c)). B, flattened enthusiastic prior (Figure 1(d)). Both designs use default skeptical prior (Figure 1(a)).