Towards Structured Use of Bayesian Sequential Monitoring in Clinical Trials

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Abstract

The text of your abstract. 200 or fewer words.

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

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1 Introduction

Things to discuss:

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

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

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

2 Methods

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

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

2.1.1 Bayesian hypothesis testing based on posterior probabilities

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

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

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

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

It has been said that "the purpose of a trial is to collect data that bring to conclusive consensus at termination opinions that had been diverse and indecisive at the *outset*" (Kass and Greenhouse (1989), emphasis added). These opinions manifest as priors $\pi(\theta, \psi)$ for which their relation to $P(\theta \in \Theta_i | \pi(\theta, \psi))$ $i \in \{0, 1\}$ is examined. Note this quantity does not depend on the data $\mathbf{D}$ and therefore reflect a-priori opinion. A skeptical prior is an informative or subjective prior that gives substantial preference to H_0 such that it is "all but convinced" that H_0 is true a-priori. This prior $\pi_S(\theta, \psi) \equiv \pi_S$ has the property that $P(\theta \in \Theta_0 | \pi_S) \geq \delta$ (equivalently $P(\theta \in \Theta_1 | \pi_S) < 1 - \delta$). The choice of $\delta \in [0, 1]$ is motivated by *a compelling level of evidence* as it relates to θ, although in this setting the "evidence" reflects a theoretical opinion rather than empirical judgement. For example, if $\delta = 0.95$, then this choice of skeptical prior places 95% prior probability that $\theta \in \Theta_0$. An enthuastic prior $\pi_E(\theta, \psi) \equiv \pi_E$ similarly gives preference to H_1 through the property that $P(\theta \in \Theta_1 | \pi_E) \geq \delta$ (equivalently $P(\theta \in \Theta_0 | \pi_E) < 1 - \delta$). For purposes of interpretation, a *skeptical person* is someone whose a-priori opinions of θ are reflected through a skeptical prior and a *enthuastic person* is someone whose a-priori opinions of θ are reflected through an ethuastic prior. The prior distributions discussed are generally "non-informative" over the nuisance parameters.

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

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

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

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

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

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

$$E(\theta|\mathbf{D}, \pi_I) = \omega \cdot E(\theta|\mathbf{D}, \pi_S) + (1 - \omega) \cdot E(\theta|\mathbf{D}, \pi_E).$$

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

$$\xi = E[1\{P(\theta \in \Theta_1|\mathbf{D}_1, \mathbf{D}, \pi_I) \geq \delta\}]$$

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

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

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

3 Examples – (EVAN)

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

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

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

Monitoring priors for this trial will be made using the concepts of a skeptical prior and an enthuastic prior. Recall a skeptic is “all but convinced” that H_0 is true a-priori, therefore $P(\theta \in \Theta_0|\pi_S) \geq \delta$. An optimist is “all but convinced” that H_1 is true a-priori, therefore $P(\theta \in \Theta_1|\pi_E) \geq \delta$.

Beta priors for θ will be used to provide closed-form expressions of the posterior distributions via Beta-Binomial conjugacy. The Beta distribution has two shape parameters. These parameters can be determined uniquely by specifying the desired mean and variance of the distribution. It is intuitive to center the skeptical and enthuastic priors around the quantities θ_0 and θ_A respectively, so that $E(\pi_S) = \theta_0$ and $E(\pi_E) = \theta_A$. The variance for the skeptical and enthuastic priors is then uniquely determined through by the choice of threshold δ. In particular, let $\pi_S(\theta) \sim \mathcal{B}(\alpha, \beta)$ be Beta distributed with shape parameters (α, β). There is a single choice of (α, β) such that:

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

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

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

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

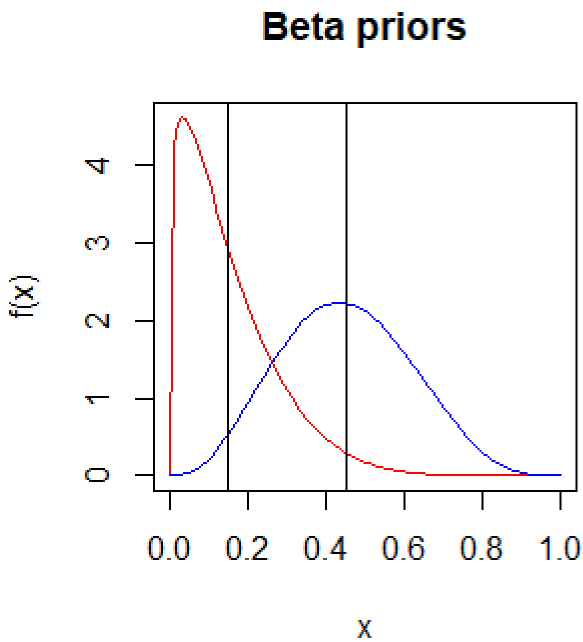
in which case $\delta = \int_{\Theta_0} \pi_S(\theta)d\theta$ is a deterministic quantity.

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

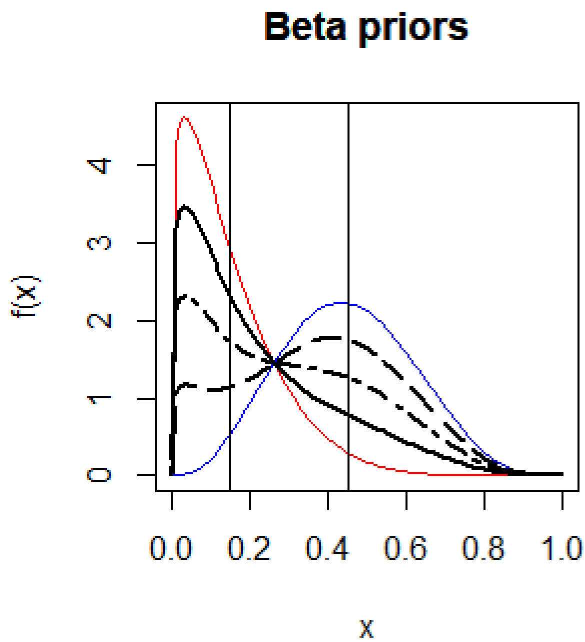
$$H_0 : \theta \leq 0.15$$
$$H_1 : \theta > 0.15$$
$$\pi_S(\theta) \sim \mathcal{B}()$$
$$\pi_E(\theta) \sim \mathcal{B}()$$
$$\text{efficacy criteria:} P(\theta > 0.15|\mathbf{D}, \pi_S) \geq 0.95$$
$$\text{futility criteria:} P(\theta \leq 0.35|\mathbf{D}, \pi_E) \geq 0.95$$
$$\text{exhausted resources:} N = XX \text{ patient outcomes obtained}$$

Vary decay rate will affect bias not Type I/II error. Not dissimilar to Frequentist: flatter-Pocock, mass at null-OBF.

Graph of π_S and π_E (very rough draft):



Graph of inference mixture for $\omega \in \{0, 1/4, 1/2, 3/4, 1\}$ (very rough draft)



Include 4 different sequential monitoring strategies. *Include details for how Bayesian monitoring has good frequentist properties even with frequent interim analyses.*

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

Interesting because prior is on risk difference while also being non-informative on control group. Will need numerical integration to evalutate posteriors.

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

$$
\begin{aligned}
P &\to \beta_0 \text{ (placebo)} \\
C &\to \beta_0 + \beta_1 \text{ (control)} \\
A &\to \beta_0 + \beta_1 + \beta_2 \text{ (active)} \\
H_0 &: \beta_2 - \delta\beta_1 \leq 0
\end{aligned}
$$

Parameters of interest (β_1, β_2), nuisance parameters (β_0, σ^2).

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

Will use MCMC to evaluate posteriors.

4 Discussion – (MATT/EVAN)

SUPPLEMENTARY MATERIAL

5 BibTeX

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