

# Towards Structured Use of Bayesian Sequential Monitoring in Clinical Trials

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July 10, 2019

## 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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\*The authors gratefully acknowledge *please remember to list all relevant funding sources in the unblinded version*

# 1 Introduction

Things to discuss:

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

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

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

## 2 Methods

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

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

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

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

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

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

The posterior distribution of  $\theta$  depends on the choice of prior distribution  $\pi(\theta, \psi)$  since  $p(\theta, \psi|\mathbf{D}) = p(\mathbf{D}|\theta, \psi)\pi(\theta, \psi)/p(\mathbf{D})$  by Bayes rule. The specification of the prior distribu-

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

The use of monitoring based on changing the opinion of skeptical and enthusiastic priors has been described as overcoming a handicap (Freedman & Spiegelhalter (1989)) and providing a brake (Fayers et al. (1997)) on the premature termination of trials, or constructing

“an adversary who will need to be disillusioned by the data to stop further experimentation” (Spiegelhalter et al. (1994)).

Early termination of the trial is appropriate if diverse prior opinions about  $\theta$  would be in agreement given the interim data (e.g. the skeptical and enthusiastic person reach the same conclusion). 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 *enthusiastic person* becomes “all but convinced” that  $H_1$  is false ( $P(\theta \in \Theta_0 | \mathbf{D}, \pi_E) \geq \delta$ ).

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

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

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

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

skeptical and enthusiastic 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  $\theta$  based on the inference prior  $\pi_I$  and the current data  $\mathbf{D}$ . Let  $\xi$  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  $\xi$  is sufficiently small (i.e.  $\xi < 0.05$ ).

### 3 Examples – (EVAN)

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

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

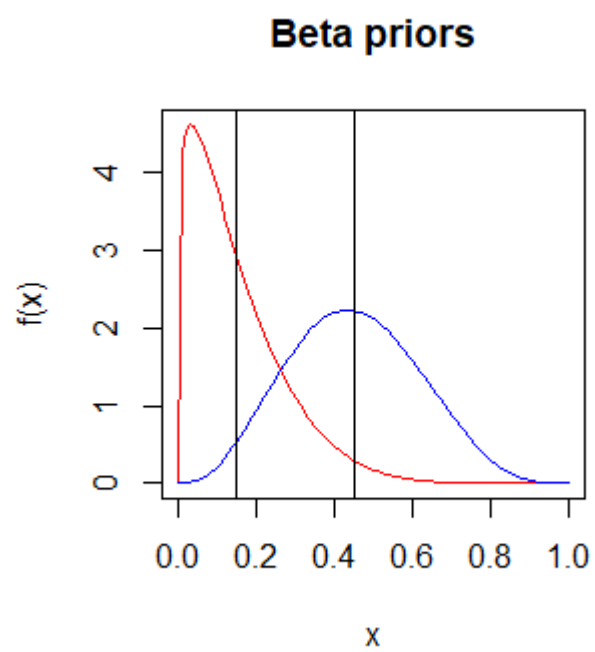
Consider testing the hypothesis  $H_0 : \theta \leq \theta_0$  versus  $H_1 : \theta > \theta_0$ . Using the general notation  $\Theta_0 = [0, \theta_0]$  and  $\Theta_1 = (\theta_0, 1]$ . Consider a highly clinically relevant treatment effect  $\theta_A > \theta_0$ . It is desirable that the trial have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

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

Beta priors for  $\theta$  will be used to provide closed-form expressions of the posterior distributions via Beta-Binomial conjugacy. The Beta distribution has two shape parameters. These parameters can be determined uniquely by specifying the desired mean and variance of the distribution. It is intuitive to center the skeptical and enthusiastic priors around the quantities  $\theta_0$  and  $\theta_A$  respectively, so that  $E(\pi_S) = \theta_0$  and  $E(\pi_E) = \theta_A$ . The variance for the skeptical and enthusiastic priors is then uniquely determined through by the choice of threshold  $\delta$ . Alternatively, the variance could be determined by specifying a desired quantile of the prior distributions which would then be reflected in  $\delta$ .

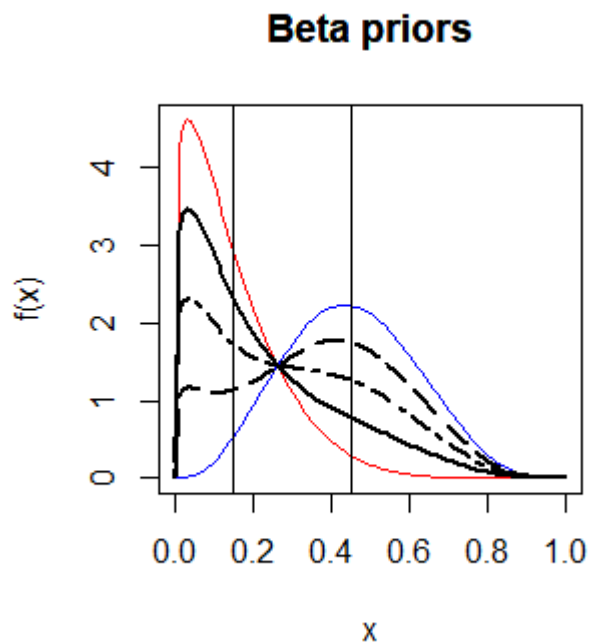
Motivated by a trial for Vemurafenib (Hyman et al. (2015)) let  $\theta_0 = 0.15$  and  $\theta_A = 0.45$ .

Graph of  $\pi_S$  and  $\pi_E$  (very rough draft):





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



*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 evaluate posteriors.

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

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

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

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

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

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

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

Will use MCMC to evaluate posteriors.

## 4 Discussion – (MATT/EVAN)

## SUPPLEMENTARY MATERIAL

### 5 BibTeX

#### References

Cornfield, J. (1966*a*), ‘A Bayesian Test of Some Classical Hypotheses, with Applications to Sequential Clinical Trials’, *Journal of the American Statistical Association* **61**(315), 577.

**URL:** <https://www.jstor.org/stable/2282772?origin=crossref>

Cornfield, J. (1966*b*), ‘Sequential Trials, Sequential Analysis and the Likelihood Principle’, *The American Statistician* **20**(2), 18.

**URL:** <https://www.jstor.org/stable/2682711?origin=crossref>

Fayers, P. M., Ashby, D. & Parmar, M. K. B. (1997), ‘Tutorial in Biostatistics: Bayesian Data Monitoring in Clinical Trials’, *Statistics in Medicine* **16**(12), 1413–1430.

**URL:** <http://doi.wiley.com/10.1002/%28SICI%291097-0258%2819970630%2916%3A12%3C1413%3A%3ASIM578%3E3.0.CO%3B2-U>

Freedman, L. S. & Spiegelhalter, D. J. (1989), ‘Comparison of Bayesian with group sequential methods for monitoring clinical trials’, *Controlled Clinical Trials* **10**(4), 357–367.

**URL:** <https://www.sciencedirect.com/science/article/pii/0197245689900019?via%3Dihub>

Freedman, L. S. & Spiegelhalter, D. J. (1992), ‘Application of bayesian statistics to decision making during a clinical trial’, *Statistics in Medicine* **11**(1), 23–35.

**URL:** <http://doi.wiley.com/10.1002/sim.4780110105>

Hyman, D. M., Puzanov, I., Subbiah, V., Faris, J. E., Chau, I., Blay, J.-Y., Wolf, J., Raje, N. S., Diamond, E. L., Hollebecque, A., Gervais, R., Elez-Fernandez, M. E., Italiano, A., Hofheinz, R.-D., Hidalgo, M., Chan, E., Schuler, M., Lasserre, S. F., Makrutzki, M., Sirzen, F., Veronese, M. L., Tabernero, J. & Baselga, J. (2015), ‘Vemurafenib in Multiple Nonmelanoma Cancers with *BRAF* V600 Mutations’, *New England Journal of Medicine* **373**(8), 726–736.

**URL:** <http://www.nejm.org/doi/10.1056/NEJMoa1502309>

Neyman, J. & Greenhouse, S. W. (1967), *Proceedings of the Berkeley Symposium on Mathematical Statistics and Probability.*, University of California Press.

**URL:** <https://projecteuclid.org/euclid.bsmsp/1200513830>

Spiegelhalter, D. J., Freedman, L. S. & Parmar, M. K. B. (1993), ‘Applying Bayesian ideas in drug development and clinical trials’, *Statistics in Medicine* **12**(15-16), 1501–1511.

**URL:** <http://doi.wiley.com/10.1002/sim.4780121516>

Spiegelhalter, D. J., Freedman, L. S. & Parmar, M. K. B. (1994), ‘Bayesian Approaches to Randomized Trials’, *Journal of the Royal Statistical Society. Series A (Statistics in Society)* **157**(3), 357.

**URL:** <https://www.jstor.org/stable/10.2307/2983527?origin=crossref>