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)
    1. Foundational Bayesian sequential monitoring Cornfield (1966*a*) Cornfield (1966*b*) Neyman & Greenhouse (1967).
    2. Further development Freedman & Spiegelhalter (1989) Freedman & Spiegelhalter (1992) Spiegelhalter et al. (1993) Spiegelhalter et al. (1994) Fayers et al. (1997).
    3. Need to go further, and mention work on 3-arm Bayesian trials.
- 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)

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 $H_0 : \theta \in \Theta_{H_0} \equiv \Theta_0$ versus $H_1 : \theta \in \Theta_{H_1} \equiv \Theta_1$, where $\Theta = \Theta_{H_0} \cup \Theta_{H_1}$ and $\Theta_{H_0} \cap \Theta_{H_1} = \emptyset$. These hypotheses are adjudicated based on posterior probabilities of θ by evaluating $P(\theta \in \Theta_{H_i}|\mathbf{D}) = \int_{\Theta_{H_i}} p(\theta|\mathbf{D})d\theta$ for $i \in \{0,1\}$, where $p(\theta|\mathbf{D}) = \int_{\Psi} p(\theta,\psi|\mathbf{D})d\psi$.

Define δ 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 $P(\theta \in \Theta_{H_1}|\mathbf{D}) \geq \delta$.

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 monitor enrollment with an eye towards early termination.

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)). 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 $P(\theta \in \Theta_1 | \pi_S) < 1 - \delta$). 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 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 interm 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 is often non-informative or objective in the sense that it does not show a-priori preference to H_0 or H_1. This prior $\pi_I(\theta, \psi) \equiv \pi_I$ has the property that $P(\theta \in \Theta_0|\pi_I) \approx P(\theta \in \Theta_1|\pi_I)$. 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:

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

for $\omega \in [0, 1]$. Choosing $\omega = 1/2$ corresponds to an agnostic inference prior. Choosing ω based on posterior model probabilities of the null and alternative hypothesis 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 posterior distribution with an inference prior (e.g. posterior mean, credible intervals). Define $p(\mathbf{D}|\pi) = \int L(\theta|\mathbf{D})\pi(\theta)d\theta$ to be the marginal likelihood for the data given the prior π. The posterior mean using the inference prior will be a two-part mixture of the posterior means using the skeptical and enthuastic priors:

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

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 interm data. Let $p(\theta|D, \pi_I)$ denote the posterior distribution for θ based on the inference prior π_I and the current data D. Let ω denote the POS which is given as follows:

$$\omega = E[1\{P(\theta \in \Theta_1|D_1, D, \pi_I) \geq 1 - \delta\}]$$

where the expectation is taken with respect to the posterior predictive distribution $p(D_1)$ for future data D_1 (ongoing + subjects yet to enroll):

$$p(D_1) = \int p(D_1|\theta) \times \pi(\theta|D) d\theta.$$

One may stop the enrollment if ω is sufficiently small (i.e., $\omega < 0.05$). *Develop the framework for POS and show how it is a weighted average POS based on the skeptical and enthusiastic priors.*

This paper presents default parameterizations of prior distributions for inference and monitoring. The prior distributions depend on the type of data to be collected and on the hypotheses under consideration. For example, consider a superiority trial with continuous data which is assumed to be normally distributed. The skeptical prior is centered around the clinical inferiority boundary and the enthuastic prior is be centered around clinical superiority boundry. The variance of these priors is a nuisance parameter, and it is determined based on tail area considerations.

3 Examples – (EVAN)

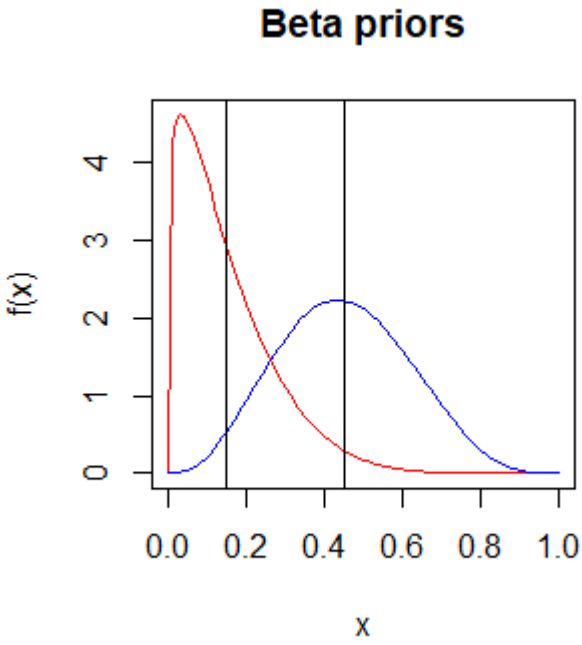
3.1 Single-Arm Oncology Proof-of-Activity Trial w/ Binary Endpoint

Consider a single-arm oncology proof-of-activity trial with a binary endpoint. The response rate is the treatment effect of interest. Consider testing the hypothesis $H_0 : \theta \leq \theta_0$ versus $H_1 : \theta > \theta_0$. Using the general notation $\Theta = [0, 1]$, $\Theta_{H_0} = [0, \theta_0]$, $\Theta_{H_1} = (\theta_0, 1]$. In this simple situation there are no nuisance parameters ψ.

A standard Bayesian decision rule would reject H_0 when $P(\theta > \theta_0|\mathbf{D}) \geq 0.95$ which will result in a type one error rate of 0.05 (approximately) if $\theta = \theta_0$ when the analysis prior is non-informative.

Suppose an effect $\theta_A > \theta_0$ is thought to be highly clinically relevant and plausible given what limited data is available. Consider a clinical trial with a single analysis and fixed sample size chosen that there is a high probability of proving H_1 when $\theta = \theta_A$. Motivated by a trial for Vemurafenib (Hyman et al. (2015)) let $\theta_0 = 0.15$ and $\theta_A = 0.45$.

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 $P(\theta \in \Theta_1|\pi_E) \geq \delta$. There are many ways to choose priors that have these properties. Beta priors will be used to provide closed-form expressions of the posterior distributions via Beta-Binomial conjugacy. The priors will be chosen so that the skeptical prior has expected value θ_0 and the enthuastic prior has expected value θ_A.



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

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

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%*
SIM578%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*