Towards Structured Use of Bayesian Sequential Monitoring in Clinical Trials

Evan Kwiatkowski[†], Eugenio Andraca-Carrera[‡],
Mat Soukup[‡], Matthew A. Psioda[†*]

† Department of Biostatistics, University of North Carolina,
McGavran-Greenberg Hall, CB#7420,
Chapel Hill, North Carolina, U.S.A.

‡ Division of Biometrics VII, Office of Biostatistics
Center for Drug Evaluation and Research,
US Food and Drug Administration,
Silver Spring, Maryland, USA

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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)

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)

- Define generally in terms of $\boldsymbol{\theta} = (\gamma, \boldsymbol{\psi})$ where γ is a parameter of interest and $\boldsymbol{\psi}$ is a nuisance parameter (possible vector valued).
- Define *Monitoring* Priors and *Inference* Priors.
- Make connection between Inference priors and two-part mixture prior and BMA.
- Define *Skeptical* and *Enthusiastic* monitoring priors and how each would be used.

- I would have a generic graphic to illustrate the types of priors and the mixture.

Suppose the parameter space is Θ and consider testing the hypothesis $H_0 : \theta \in \Theta_{H_0}$ versus $H_1 : \theta \in \Theta_{H_1}$, where $\Theta = \Theta_{H_0} \cup \Theta_{H_0}$ and $\Theta_{H_0} \cap \Theta_{H_0} = \emptyset$. Let D denote the data collected in the experiment and let $\pi \equiv \pi(\theta)$ denote a prior distribution for θ.

Consider a-priori beliefs about the true value of θ before data is collected. Define the skeptical viewpoint as being "all but convinced" that $\theta \in \Theta_{H_0}$ and similarly the enthuastic viewpoint as being "all but convinced" that $\theta \in \Theta_{H_1}$. These viewpoints can be made rigorous by associating them with priors $\pi_{Skeptical}$ and $\pi_{Enthuastic}$ such that $P(\theta \in \Theta_0 | \pi_{Skeptical})$ and $P(\theta \in \Theta_1 | \pi_{Enthuastic})$ reflect a high amount of certainty.

These viewpoints can be used in monitoring the trial once data is collected. It is reasonable to stop the trial for efficacy if the posterior distribution of θ given the skeptical prior is sufficiently contained in Θ_1, that is, if $P(\theta \in \Theta_1 | D, \pi_{Skeptical})$ is close to 1.. Similarly, it is reasonable to stop the trial for futility if the posterior distribution of θ given the enthuastic prior is sufficiently contained in Θ_0, that is, if $P(\theta \in \Theta_0 | D, \pi_{Enthuastic})$ is close to 1. Intuitively, if an individual had the prior belief that there was no effect but once presented with data, updates their opinion via Bayes rule and now is strongly convinced there is an effect, then efficacy can be accepted. The prior belief can be seen as a pessimistic viewpoint that has to be overwhelmed with evidence.

Once the trial is stopped based on the monitoring priors, or at the planned end of the trial, it is necessary to use a prior to make final inference on θ. It is inadvisable to use either the skeptical or enthuastic prior for inference since they are admittedly biased opionions in the direction of the null or the alternative for monitoring purposes. For inference purposes it is better to use an impartial prior $\pi_{Inference}$. Define $p(D|\pi) = \int L(\theta|D)\pi(\theta)d\theta$ to be the marginal likelihood for the data given the prior π. One can average the posterior means

from the analyses using the skeptical and enthuastic priors, such that,

$$\pi_{Inference} = \frac{p(D|\pi_{Skeptical})\pi_{Skeptical} + p(D|\pi_{Enthuastic})\pi_{Enthuastic}}{p(D|\pi_{Skeptical}) + p(D|\pi_{Enthuastic})}$$

Let $\omega = p(D|\pi_{Skeptical}/(p(D|\pi_{Skeptical}) + p(D|\pi_{Enthuastic}))$. Then

$$E(\theta|D, \pi_{Inference}) = \omega \times E(\theta|D, \pi_{Skeptical}) + (1-\omega) \times E(\theta|D, \pi_{Enthuastic})$$

For example, consider testing the hypothesis $H_0 : \theta \leq \theta_0$ versus $H_1 : \theta > \theta_0$ where θ is a treatment effect of interest. A standard Bayesian decision rule would reject H_0 when $P(\theta > \theta_0|D) \geq 0.95$.

Let $p(H_0)$ and $p(H_1)$ denote the prior probabilities for H_0 and H_1, where $p(H_0)+p(H_1) = 1$. Let D denote the data collected in the experiment. Let $\pi = \pi(\theta)$ denote a prior distribution for θ and define $p(D|\pi) = \int_\theta L(\theta|D)\pi(\theta)d\theta$ be the marginal likelihood for the data given the prior π.

For example, consider testing the hypothesis $H_0 : \theta \leq \theta_0$ versus $H_1 : \theta > \theta_0$ where θ is a treatment effect of interest. Suppose an effect $\theta_1 > \theta_0$ 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 $\theta = \theta_1$. A standard Bayesian decision rule would rejectg H_0 when $P(\theta > \theta_0|D) \geq 0.95$ which will result in a type one error rate of 0.05 (approximately) if $\theta = \theta_0$ when the analysis prior is non-informative (a so-called reference or flat prior).

2.2 Futility Monitoring Using Probability of Success (EVAN – draft on 6/21)

- Futility monitoring using POS is about stopping early when their is a high likelihood of a study being inconclusive at the end of the study.

- Since the final analysis uses the *Inference* prior, POS should be based on the inference prior.
- Develop the framework for POS and show how it is a weighted average POS based on the skeptical and enthusiastic priors.

3 Examples – (EVAN)

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

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