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)

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, let $\pi \equiv \pi(\theta)$ denote a prior distribution for θ, and let $p(\theta|D, \pi)$ denote the posterior distribution of θ given a particular prior distribution.

Before any 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 $P(\theta \in \Theta_1|\pi_{Enthuastic})$ are sufficiently close to 1. Although these viewpoints are highly certain, we require that $\pi(\theta) > 0$ for all $\theta \in \Theta$.

These viewpoints can be used in monitoring the trial once data is collected. It is reasonable to The efficacy critiera is $P(\theta \in \Theta_1|D, \pi_{Skeptical}) \geq c_1$, and the futility criteria is $P(\theta \in \Theta_0|D, \pi_{Enthuastic}) \geq c_2$, where c_1 and c_2 are the thresholds reflecting strong belief in the skeptical and enthuastic viewpoints respectively.

A standard Bayesian decision rule would reject H_0 when $P(\theta \in \Theta_1|D) \geq 0.95$.

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