Bayesian Clinical Trials

Single Threshold Design Extension

Single Threshold Design Extension

- Single Threshold Design

Single Threshold Design Extension

- Single Threshold Design
- Single Threshold Design can be extended using different kinds of informative prior distributions

Single Threshold Design Extension

- Single Threshold Design
- Single Threshold Design can be extended using different kinds of informative prior distributions
- Bayesian modification of the Simon's design to control frequentist error rates and comparison with Tan and Machin's STD

Single Threshold Design Extension

- Single Threshold Design
- Single Threshold Design can be extended using different kinds of informative prior distributions
- Bayesian modification of the Simon's design to control frequentist error rates and comparison with Tan and Machin's STD
- a Bayesian two-stage design based on the pre-experimental control of the probability of having a large posterior probability that the true response rate exceeds a target value.

Single Threshold Design Extension

- Single Threshold Design
- Single Threshold Design can be extended using different kinds of informative prior distributions
- Bayesian modification of the Simon's design to control frequentist error rates and comparison with Tan and Machin's STD
- a Bayesian two-stage design based on the pre-experimental control of the probability of having a large posterior probability that the true response rate exceeds a target value.
- this probability is computed with respect to the prior predictive distribution of the data: this design can be considered a predictive version of the STD

Two-stage design

n_1 patients, $\quad Y = \begin{cases} 1 & \text{responder to drug} \\ 0 & \text{otherwise} \end{cases}$

- **First stage**

$$s_1 = \sum_{i=1}^{n_1} y_i \begin{cases} \leq r_1 & \text{experiment stops} \\ > r_1 & \text{enrolled additional } n_2 \text{ patients for 2nd stage} \end{cases}$$

-Second stage

$$s = \sum_{i=1}^{n_1+n_2} y_i \begin{cases} \leq r & \text{experiment stops} \\ > r & \text{drug candidate for phase III} \end{cases}$$

The predictive Single Threshold Design

- It takes the random nature of the data into account
- the posterior probabilities that θ exceeds θ_u in the two stages are considered random since they are functions of S1 and S, which are random variables

Predictive two-stage design

- Given the number of respondents s_1 at the end of stage 1, the posterior distribution of θ is

$$\pi_{n_1}(\theta|S_1 = s_1) \propto \pi(\theta) \times \text{Binomial}(s_1; n_1, \theta)$$

  which is a $\text{Beta}(\alpha + s_1, \beta + n_1 - s_1)$ in the usual conjugate analysis.

- Given the total number of respondents s at the end of stage 2, the posterior distribution of θ is

$$\pi_n(\theta|S_1 > r_1, S = s) \propto \pi(\theta|S_1 > r_1) \times \text{Binomial}(s; n, \theta)$$

  which is still $\text{Beta}(\alpha + s, \beta + n - s)$ in a conjugate analysis.

The single threshold design (Tan and Machin 2002)

-**Objective**: to choose the minimun sample size such that the posterior probability $\theta > \theta_u$ is greater or equal to a fixed threshold when the response rate is equal to θ_u + some small value $\epsilon > 0$

-Drug passes phase II if $\theta > \theta_u$ (target value) if:

$$\begin{cases} \min n_1 & \pi_{n_1}(\theta > \theta_u | S_1 = (\theta_u + \epsilon) n_1) \geq \lambda_1 \\ \\ \min n & \pi_n(\theta > \theta_u | S = (\theta_u + \epsilon) n) \geq \lambda_2 \end{cases}$$

where λ_1 and λ_2 are fixed probability thresholds.

Bayesian sample size determination

Bayesian sample size determination is a form of pre-posterior analysis, i.e. assessment of the value of data before they become available, in which the prior distribution role is twofold:

- to obtain $\pi(\theta|S)$ for posterior analysis
- to define the marginal (predictive) distribution $m(\theta; S) = \int_0^1 \text{Binomial}(s; n, \theta) \times \pi(\theta) d\theta$ for pre-posterior analysis
- Following Wang and Gelfand 2002, the fitting or analysis prior $\pi(\cdot|S)$ and the sampling or design prior $m(\cdot; S)$ do not necesarily have to coincide.

Predictive version of the STD (Sambucini, 2008)

- The posterior probabilities that $\theta > \theta_u$ in the two stages are considered random since they are function of S_1 and S, which are random variables
- Determine two fixed thresholds probabilities γ_1 and γ_2 such that

$$\mathbb{P}\left[\pi_{n_1}(\theta > \theta_u | S_1 = (\theta_u + \epsilon)n_1) \geq \lambda_1\right] \geq \gamma_1 \tag{1}$$

and

$$\mathbb{P}\left[\pi_{n}(\theta > \theta_u | S = (\theta_u + \epsilon)n) \geq \lambda_2\right] \geq \gamma_2 \tag{2}$$

where $\mathbb{P}$ is the probability measure corresponding to the predictive (or marginal) distribution of the data

Analysis and Design prior

- **Analysis prior:** embodies the effective uncertainty on θ (it is used to form the posterior distribution for making inference)
- **Design prior:** describes a scenario under which a sensible sample size is established a priori according to a design criterion.

Objective: use of a subjective prior based on elicitation of expert opinions for design prior.

The predictie STD design 1^{st} stage

Given the target response rate θ_u, consider the r.v. $\pi_{n_1}(\theta > \theta_u | S_1)$

- given the probability thresholds (λ_1, γ_1), select the smallest sample size n_1^* such that $\forall n_1 > n_1^*$

$$\mathbb{P}[\pi_{n_1}(\theta > \theta_u | S_1) \geq \lambda_1] \geq \gamma_1$$

- $\mathbb{P}$ is the probability measure corresponding to the prior predictive distribution of S_1 induced by the design (sampling) prior:

$$\mathbb{P}[\pi_{n_1}(\theta > \theta_u | S_1) \geq \lambda_1] = \sum_{s_1 = \tilde{r}_1}^{n_1} m(S_1)$$

where $\tilde{r}_1$ is the smallest s_1 such that $\pi_{n_1}(\theta > \theta_u | s_1) \geq \lambda_1$.

- Once the optimal value n_1^* is selected, then $r_1^* = \tilde{r}_1 - 1$

The predictive STD design 2^{nd} stage

Given the target response rate θ_u, consider the r.v. $\pi_{n_1}(\theta > \theta_u | S)$

- given the probability thresholds (λ_2, γ_2), select the smallest $n*$ such that $\forall n > n^*$

$$\mathbb{P}[\pi_n(\theta > \theta_u | S) \geq \lambda_2] \geq \gamma_2$$

- $\mathbb{P}$ is the probability measure corresponding to the prior predictive distribution of S induced by the design (sampling) prior:

$$\mathbb{P}[\pi_n(\theta > \theta_u | S) \geq \lambda_2] = \sum_{s=\tilde{r}}^{n} m(s | S_1 > r^*)$$

where $\tilde{r}$ is the smallest s such that $\pi_n(\theta > \theta_u | s) \geq \lambda_2$.

- Once the optimal value n^* is selected, then $r^* = \tilde{r} - 1$

Examples

-Using the R routines find sample size at both stages for $\theta_u = 0.3$ when - analysis prior is non informative ($\pi_A = \theta_u - 0.1$) - design prior is an optimistic prior ($\pi_D = \theta_u + 0.1$) - for $n_D = 1$ and $n_D = 10$ - under $\lambda_1 = 0.6$, $\gamma_1 = 0.6$ - under $\lambda_2 = 0.8$, $\gamma_2 = 0.9$

Illustrative example

Let's consider the phase II clinical trial conducted by Foo et al. [17] at the National Cancer Centre in Singapore to evaluate the activity of gemcitabine in patients with metastatic nasopharyngeal carcinoma and previously treated with chemotherapy.

In a previous study, using a Simon's minimax design with $\{\theta_0 = 0.05, \theta_u = 0.2, \alpha = 0.05, \beta = 0.2\}$ find the recommended two stage sample size

Actual data

- The actual data showed seven responders out of the 13 patients in the first stage
- Therefore, the trial continued to the second stage, obtaining a cumulative number of 13 responders out of the total number (27 patients)
- Suppose now that we are interested in planning a new two-stage study to analyze the activity of gemcitabine. We can consider the data as a source of prior information

Prior information on θ_u

- Since the results of this previous study show a strong efficacy of the gemcitabine, in the new study we could specify a target value θ_u greater than 0.2 (the target response rate previously considered)
- The elicitation of the design prior can be based on the available actual data (13 responders out of 27 patients at the end of the second stage):
  - prior sample size $n_D = 27$ and a observed response rate $pi_0^D = \frac{13}{27}$
  - using a non-informative beta distribution as analysis prior (e.g. $\pi_0^A = \theta_u - 0.1$

Under this assumptions find the recommended sample size when $(\lambda_1, \gamma_1, \lambda_2, \gamma_2) = (0.7, 0.7, 0.8, 0.8)$