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Bayesian apative designs for clinical trials

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Introduction

- Bayesian adaptive design
  - proposed for a comparative two-armed clinical trial using decision-theoretic approaches.
  - At each interim analysis, the decision to terminate or to continue the trial is based on the expected loss function.
- In Berry&Ho(1988) and Lewis&Berry(1994), Bayesian designs are compared with frequentist group sequential designs using decision-theoretic approaches.
- Studies by Eales&Jesson(1992), Cressie&Biele(1994) and Barber&Jennison(2002) search for optimal group sequential designs under various settings using Bayesian decision-theoretic approaches.
- The maximum sample size/block size is predetermined for all these methods.

Introduction

In this paper,

(1) Generalized the Bayesian decision-theoretic approach by allowing the maximum sample size to be random
(2) Use loss functions that explicitly quantify the costs caused by false-positive and false-negative decisions.
    - maintain the desired frequentist properties such as type I and II error rates.
(3) Simultaneously consider efficacy, futility, and cost in the decision making.

Bayesian Adaptive Design with One-Step Backward Induction

- X_T : the treatment response
- X_C : the control response
- $2B_i$: the block size at each stage where B_i is the sample size for each treatment arm $(i = 1, 2, ...)$
- $\bar{X}_{T_i}, \bar{X}_{C_i}$: the observed means of the *ith* block for the two arms.
- Let θ be the parameter of interest, and let

$$X_i = \bar{X}_{T_i} - \bar{X}_{C_i} \sim F(.|\theta), \quad \int_{-\infty}^{\infty} x \, dF(x|\theta) = \theta$$

- prior $\pi(\theta)$ with a prior mean of $E(\theta|\pi) = \delta$

Bayesian Adaptive Design with One-Step Backward Induction

$$H_0 : \theta \leq \theta_0 \quad \text{versus} \quad H_1 : \theta > 0$$

- If $\theta > 0$, there is insufficient information to indicate a preference for any one of the treatments.
- A : actions of accepting the null hypothesis.
- R : actions of rejecting the null hypothesis.

$$L(\theta, A) = \begin{cases} 0, & \text{if } \theta \leq \theta_0 \\ \mathrm{K}_1, & \text{if } \theta > \theta_0 \end{cases} \quad L(\theta, R) = \begin{cases} \mathrm{K}_0, & \text{if } \theta \leq 0 \\ 0, & \text{if } \theta > 0 \end{cases}$$

Bayesian Adaptive Design with One-Step Backward Induction

- Let $\mathcal{X}_j = \{X_1, ..., X_j\}$ define the accumulated data up to step j
- Define the σ-algebra $\mathcal{F}_j = \sigma(\mathcal{X}_j)$,

$$E\{L(\theta, A|\mathcal{F}_j)\} = K_1 pr(\theta > \theta_0|\mathcal{F}_j)\}$$

$$E\{L(\theta, R|\mathcal{F}_j)\} = K_0 pr(\theta \leq 0|\mathcal{F}_j)$$

- Given the data up to the *jth* stage, a critical region R_j,

$$R_j = \{\mathcal{X}_j : \frac{pr(\theta \leq 0|\mathcal{F}_j)}{pr(\theta \leq \theta_0|\mathcal{F}_j)} \leq \frac{K_1}{K_0}\}, j = 1, 2, ...$$

Bayesian Adaptive Design with One-Step Backward Induction

- K_2 : the unit cost of enrolling a patient into the trial
- $L_{stop}(\mathcal{X}_j) = 2K_2 \sum_{i=1}^{j} B_i + min[E\{L(\theta, A)|\mathcal{F}_j\}, E\{L(\theta, R)|\mathcal{F}_j\}]$
- $L_{cont}(\mathcal{X}_j) = 2K_2 \sum_{i=1}^{j+1} B_i +$ $\mathrm{E}(\min[\mathrm{E}\{\mathrm{L}(\theta, A)|\mathcal{F}_{(j+1)}\}, E\{L(\theta, R)|\mathcal{F}_{(j+1)}\}]|\mathcal{F}_j)$

Bayesian Adaptive Design with One-Step Bakward Induction

- To search for the optimal adaptive design that minimizes the expected loss, use the following two-step strategy.

Step 1. If $L_{stop}(\mathcal{X}_j) \leq L_{cont}(\mathcal{X}_j)$, terminate the trial, and the maximum block size is j. Then if the accumulated data $\mathcal{X}_j$ is in the rejection region R_j, we conclude that the new treatment is more effective than the control.

Step 2. If $L_{stop}(\mathcal{X}_j) > L_{cont}(\mathcal{X}_j)$, continue to observe the $(j+1)th$ block and repeat Step 1 and 2.

- The total number of blocks to be observed in the trial, denoted by M , $P(M < \infty|\theta) = 1$. (by the martingale convergence theorem)

Connections with the frequentist designs

- The design parameters, $K_i, (i = 0, 1, 2)$ allow us to control the probabilities of type I and type II errors.
- If $\theta_0 = 0$, the probability of making a false-positive conclusion at stage j is $Pr(R_j|\theta = 0)$, where

$$R_j = \{\mathcal{X}_j : \frac{pr(\theta \leq 0|\mathcal{X}_j)}{pr(\theta > 0|\mathcal{X}_j)} \leq \frac{K_1}{K_0}\} = \{\mathcal{X}_j : pr(\theta \leq 0|\mathcal{X}_j) \leq \frac{K_1}{K_0 + K_1}\}$$

- If all related density functions satisfy the regularity conditions,

$$\pi(\theta|\mathcal{X}_j) \sim N(\delta_j, s_j^2) \text{ asymptotically.}$$

- $pr(\theta \leq 0|\mathcal{X}_j)$ is asymptotically distributed as $\mathbf{\Phi}(-\delta_j/s_j)$, where $\mathbf{\Phi}$ is the standard normal cdf.

Connections with the frequentist designs

- Under $\theta = \theta_0 = 0$, δ_j / s_j converges in distribution to Z.(Hartigan, 1983, Ch.11) Therefore,
$$pr(\theta \leq 0 | \mathcal{X}_j) \xrightarrow{d} \mathbf{\Phi}(Z)$$
- Since $\mathbf{\Phi}(Z) \sim U(0,1)$, rejection region R_j' under $\theta = 0$ is,
$$\begin{aligned} pr(R_j' | \theta = 0) &= pr(pr(\theta \leq 0 | \mathcal{X}_j) | \theta = 0) \leq \tfrac{K_1}{K_0 + K_1}) \\ &\to pr\{\mathbf{\Phi}(Z) \leq \tfrac{K_1}{K_0 + K_1}\} = \tfrac{K_1}{K_0 + K_1} \end{aligned}$$
- For $\theta_0 > 0$, R_j shrinks as θ_0 increases. Therefore,
$$\limsup_{j \to \infty} pr(R_j | \theta = 0) \leq \tfrac{K_1}{K_0 + K_1}$$
- If the overall sample size is sufficiently large, R_j depends on K_0/K_1
- For a given type I error rate, α
$$K_0/K_1 = (1 - \alpha)/\alpha, \text{ if we let } K_1/(K_0 + K_1) = \alpha$$

Connections with the frequentist designs

- High value of K_1 implies that future patients might benefit from a new effective treatment.
- However, the new treatment may be superseded within a few years, which would reduce the 'value' of the treatment, K_1.
- It is difficult explicitly to build this concern prospectively into a trial design.

Special Case 1: Noraml responses

- Derive a strict uppder boundary for continuous outcomes with a normal distribution.
- $X_i = \bar{X}_{T_i} - \bar{X}_{C_i} \sim N(\theta, \sigma^2/B_i)$
- $\theta \sim N(\delta, \sigma^2/B_0)$, where B_0 can be interpreted as a 'sample size' reflected by the prior information, $X_0 = \delta$
- After data from block j are observed, $\theta|\mathcal{X}_j \sim n(\delta_j, s_j^2)$ where,

$$\delta_j = \frac{\sum_{i=0}^{j} B_i X_i}{\sum_{i=0}^{j} B_i}, \quad s_j^2 = \frac{\sigma^2}{\sum_{i=0}^{j} B_i}$$

Special Case 1: Normal responses

- Then rejection region R_j, is given by

$$R_j = \{\mathcal{X}_j : \frac{pr(\theta \leq 0 | \mathcal{F}_j)}{pr(\theta \leq \theta_0 | \mathcal{F}_j)} \leq \frac{K_1}{K_0}\} = \{\mathcal{X}_j : \frac{\mathbf{\Phi}(-\delta_j/s_j)}{1 - \mathbf{\Phi}\{(\theta_0 - \delta_j)/s_j\}} \leq \frac{K_1}{K_0}\}$$

- Since $\frac{\mathbf{\Phi}(-\delta_j/s_j)}{1 - \mathbf{\Phi}\{(\theta_0 - \delta_j)/s_j\}}$ is a decreasing function of δ_j, and

$$\sup_{\delta_j} \frac{\mathbf{\Phi}(-\delta_j/s_j)}{1 - \mathbf{\Phi}\{(\theta_0 - \delta_j)/s_j\}} = \infty, \ \inf_{\delta_j} \frac{\mathbf{\Phi}(-\delta_j/s_j)}{1 - \mathbf{\Phi}\{(\theta_0 - \delta_j)/s_j\}} = 0$$

- Therefore, $\exists! c_j$ such that $R_j = \{\mathcal{X}_j : \delta_j \geq c_j\}$ or, equivalently,

$$c_j = \arg\{x : \frac{\mathbf{\Phi}(-\delta_j/s_j)}{1 - \mathbf{\Phi}\{(\theta_0 - \delta_j)/s_j\}} - \frac{K_1}{K_0} = 0\}$$

Special Case 1: Normal responses

- $h = \mathbf{\Phi}^{-1}\{K_1/(K_0 + K_1)\}$, It is interest to obtain h corresponding to a given α
- Under the null $\theta = 0$, $-\frac{\delta_j}{s_j} \sim N(-\frac{n_0\delta}{\sigma\sqrt{n_j}}, \frac{n_j - n_0}{n_j})$
- The probability of rejecting the null hypotheses at the *jth* interim analysis is

$$pr(R_j|\theta = 0) = pr(\delta_j/s_j > h|\theta = 0) = \mathbf{\Phi}\{\frac{h\sigma\sqrt{n_j} + n_0\delta}{\sigma\sqrt{n_j - n_0}}\}$$

- $\mathbf{\Phi}\{\frac{h\sigma\sqrt{n_j} + n_0\delta}{\sigma\sqrt{n_j - n_0}}\}$ increases when $\sqrt{n_j} \leq -h\sigma/\delta$, decreases when $\sqrt{n_j} \geq -h\sigma/\delta$

Special Case 1: Normal responses

When $\sqrt{n_j} \leq -h\sigma/\delta$,

- The function has maximum at $\sqrt{n_j} = -h\sigma/\delta$, therefore

$$\sup_{n_j} \boldsymbol{\Phi}\{\frac{h\sigma\sqrt{n_j}+n_0\delta}{\sigma\sqrt{n_j-n_0}}\} \leq \boldsymbol{\Phi}\{\frac{\sqrt{(h^2\sigma^2-n_0\delta^2}}{\sigma\sqrt{n_j-n_0}}\}$$

- $h^2\sigma^2 - n_0\delta^2 \geq 0$, as long as $n_0 \leq n_j$
- Therefore, $h_1 = -(z_\alpha^2 + \frac{n_0\delta^2}{\sigma^2})^{\frac{1}{2}}$

When $\sqrt{n_j} > -h\sigma/\delta$,

- since $n_j \geq n_1$, for $j \geq 1$, When $\sqrt{n_1} > -h\sigma/\delta$

$$\sup_{n_j} \boldsymbol{\Phi}\{\frac{h\sigma\sqrt{n_j}+n_0\delta}{\sigma\sqrt{n_j-n_0}}\} \leq \boldsymbol{\Phi}\{\frac{h\sigma\sqrt{n_1}+n_0\delta}{\sigma\sqrt{n_1-n_0}}\}$$

- Therefore, $h_2 = \frac{z_{1-\alpha}\sigma\sqrt{n_1-n_0}-n_0\delta}{\sigma\sqrt{n_1}}$

Special Case 1: Normal responses

For any given significance level α, we can determine K_0/K_1, based on this upper bound:

$$\frac{K_0}{K_1} = \begin{cases} \{1\text{-}\mathbf{\Phi}(\mathrm{h}_1)\}/\mathbf{\Phi}(h_1), & \text{if } \sqrt{n_1} \leq \sqrt{\{(\sigma/\delta)^2 z_\alpha^2 + n_0\}} \\ \{1\text{-}\mathbf{\Phi}(\mathrm{h}_2)\}/\mathbf{\Phi}(h_2), & \text{if } \sqrt{n_1} > \sqrt{\{(\sigma/\delta)^2 z_\alpha^2 + n_0\}} \end{cases}$$

with K_0/K_1 defined above,

$$\sup_j pr(R_j|\theta = 0) \leq \alpha$$

Special Case 1: Normal responses

- The loss incurred in terminating the trial at the *jth* stage is
  $L_{stop}(\mathcal{X}_j) = 2K_2 \sum_{i=1}^{j} B_i + min[K_1\{1 - \mathbf{\Phi}(-\frac{\delta_j}{s_j})\}, K_0\mathbf{\Phi}(-\frac{\delta_j}{s_j})]$
- The relevant predictive distribution of X_{j+1} is
  $$X_{j+1}|\mathcal{X}_j \sim N(\delta_j, s_j^2 + \frac{\sigma^2}{B_{j+1}})$$
- Compute the posterior mean and posterior variance of θ recursively as
  $$\delta_{j+1} = \frac{n_j\delta_j + B_{j+1}x_{j+1}}{n_j + B_{j+1}}, \quad s_{j+1}^2 = \frac{\sigma^2}{n_j + B_{j+1}}$$
- Then, the predicted loss of continuing and observing one more block is,
  $L_{cont}(\mathcal{X}_j) = 2K_2 \sum_{i=1}^{j+1} B_i$

$$+\int_{-\infty}^{+\infty} min[K_1\{1 - \mathbf{\Phi}(-\frac{\delta_{j+1}}{s_{j+1}})\}, K_0\mathbf{\Phi}(-\frac{\delta_{j+1}}{s_{j+1}})]d\mathbf{\Phi}\{\frac{x_{j+1} - \delta_j}{(s_j^2 + \sigma^2/B_{j+1})^2}\}$$

Special Case 2: Binary responses

- $X_{T_i}|p_t \sim B(B_i, p_t), \quad X_{C_i}|p_c \sim B(B_i, p_c)$
- $p_t \sim Beta(a_t, b_t), \quad p_c \sim Beta(a_c, b_c)$
- The difference in efficacy is $\theta = p_t - p_c$, and the density function for θ is

$$\pi(\theta|a_t, b_t, a_c, b_c)$$

$$= \begin{cases} \int_{-\theta}^{1} q(\theta + x, a_t, b_t) q(x, a_c, b_c) dx, & \text{if } -1 < \theta < 0, \\ \int_{0}^{1-\theta} q(\theta + x, a_t, b_t) q(x, a_c, b_c) dx, & \text{if } \quad 0 < \theta < 1 \end{cases}$$

where $q(x, a, b)$ is the density function of the beta distribution.

Special Case 2: Binary responses

- At the end of the jth stage, the sufficient statistic denoted by
$$(s_{t_j}, f_{t_j}, s_{c_j}, t_{c_j}), \text{ where } s_{t_j} + f_{t_j} = s_{c_j} + f_{c_j} = \sum_{i=1}^{j} B_i$$
- s_{t_j}, f_{t_j} : the total numbers of successes and failures observed on the treatment arm up to stage j
- s_{c_j}, f_{c_j} : the total numbers of successes and failures observed on the control arm up to stage j

Special Case 2: Binary responses

- The expected losses for the two decisions, A and R, are

$$E\{L(\theta, A)|\mathcal{X}_j\} = K_1 \int_{\theta_0}^{1} \pi(\theta|a_{t_j}, b_{t_j}, a_{c_j}, b_{c_j})d\theta,$$
$$E\{L(\theta, R)|\mathcal{X}_j\} = K_0 \int_{-1}^{0} \pi(\theta|a_{t_j}, b_{t_j}, a_{c_j}, b_{c_j})d\theta$$

where

$$a_{t_j} = a_t + s_{t_j},\ b_{t_j} = b_t + f_{t_j},\ a_{c_j} = a_c + s_{c_j},\ b_{c_j} = b_t + f_{c_j}$$

- Transform the integrals,

$$E\{L(\theta, A)|\mathcal{X}_j\} = K_1 \int_{0}^{1-\theta} q(x, a_{c_j}, b_{c_j})\{1 - Q(\theta_0 + x, a_{t_j}, b_{t_j})\}dx$$
$$E\{L(\theta, R)|\mathcal{X}_j\} = K_0 \int_{0}^{1} q(x, a_{c_j}, b_{c_j})Q(x, a_{t_j}, b_{t_j})dx$$

where $Q(., a, b)$ is the cumulative distribution function of Beta(a, b)

Special Case 2: Binary responses

- The predictive distribution of $s_{t_{j+1}}, s_{c_{j+1}}$ given s_{t_j}, s_{c_j},
$$pr(s_{t_{j+1}}, s_{c_{j+1}} | s_{t_j}, s_{c_j}) =$$
$$\binom{B_{j+1}}{s_{t_{j+1}} - s_{t_j}} \binom{B_{j+1}}{s_{c_{j+1}} - s_{c_j}} \frac{\beta(a_{t_{j+1}}, b_{t_{j+1}})}{\beta(a_{t_j}, b_{t_j})} \frac{\beta(a_{c_{j+1}}, b_{c_{j+1}})}{\beta(a_{c_j}, b_{c_j})}$$
- It is possible to derive an absolute upper boundary for binary outcomes to control the type I error rate, as in the case of normal outcomes.

Simulation

- Through Monte Carlo simulations, compare the performance of the proposed design with the existing group sequential designs, including
  (1) the frequentist designs of Pocock (1977)
  (2) O'BrienFleming (1979)
  (3) the adaptive self-designing trial of Shen Fisher (1999)
- Pocock and O'Brien-Fleming trials predetermine the maximum sample size.
- 'Bayes Adapt I' : K_0/K_1 is determined by the equation on p.16
- 'Bayes Adapt II' : K_0/K_1 is determined by the equation on p.10

Simulation

Table 1: *Monte Carlo simulation. The comparison of power and average sample number between the Bayesian designs and other group sequential designs with one-sided* $\alpha = 0{\cdot}025$, *and true* $\theta = 0$ *at null and* $\theta = 0{\cdot}5$ *under the alternative*

		$B=6$				$B=8$			
Design	δ	$\hat{\alpha}$	ASN_α	$1-\hat{\beta}$	ASN_β	$\hat{\alpha}$	ASN_α	$1-\hat{\beta}$	ASN_β
Pocock	0·4	0·025	163·6	0·984	74·4	0·025	156·3	0·977	78·8
OBF	0·4	0·022	68·6	0·985	84·4	0·025	70·9	0·984	83·7
Self-designing	0·4	0·012	84·4	0·911	87·0	0·010	92·9	0·931	90·0
Bayes Adapt I	0·4	0·014	49·7	0·934	72·7	0·012	59·3	0·959	79·5
Bayes Adapt II	0·4	0·016	51·1	0·938	72·0	0·017	60·4	0·961	78·3
Pocock	0·5	0·025	105·6	0·911	66·6	0·024	109·8	0·924	71·7
OBF	0·5	0·024	47·7	0·929	65·5	0·024	49·7	0·937	69·1
Self-designing	0·5	0·013	62·5	0·888	78·5	0·014	71·4	0·918	83·9
Bayes Adapt I	0·5	0·012	45·8	0·921	69·4	0·016	54·4	0·946	75·5
Bayes Adapt II	0·5	0·018	47·8	0·930	68·2	0·017	54·9	0·951	73·7
Pocock	0·6	0·026	70·6	0·766	55·8	0·025	78·7	0·817	62·2
OBF	0·6	0·025	35·0	0·810	50·8	0·214	37·3	0·848	55·9
Self-designing	0·6	0·013	51·9	0·836	70·3	0·014	59·9	0·869	74·6
Bayes Adapt I	0·6	0·013	42·0	0·905	66·6	0·013	49·2	0·928	71·7
Bayes Adapt II	0·6	0·020	45·3	0·914	64·6	0·020	51·3	0·942	69·7
Pocock	0·7	0·025	47·4	0·598	42·7	0·026	47·6	0·614	45·2
OBF	0·7	0·024	26·7	0·670	38·1	0·023	28·9	0·668	39·9
Self-designing	0·7	0·014	43·9	0·761	61·3	0·014	49·3	0·772	65·1
Bayes Adapt I	0·7	0·015	39·8	0·889	63·9	0·015	45·9	0·920	68·9
Bayes Adapt II	0·7	0·022	42·7	0·907	61·6	0·021	48·9	0·932	66·1

ASN_α and ASN_β are average sample numbers under $\theta = 0$ and $\theta = 0{\cdot}5$, respectively. OBF, O'Brien–Fleming design. Bayes Adapt I, K_0/K_1 is determined by formula (2·8); Bayes Adapt II, K_0/K_1 satisfies the equation $K_1/(K_1+K_0) = \alpha$; for both designs, $K_2/K_1 = 0{\cdot}1^4 B\delta^3$.

Simulation

- 'Bayes Adapt I' is more conservative than 'Bayes Adapt II'.
- The type 1 error rates of the proposed Bayesian designs are similar to that of the self-designing trial, but no additional futility stopping rule is required.
- The frequentist group sequential designs with the fixed maximum sample sizes lead to a substantial loss of power.
- The Bayesian-designs hold advantages over the self-designing trial in terms of both power and average sample number.

Simulation

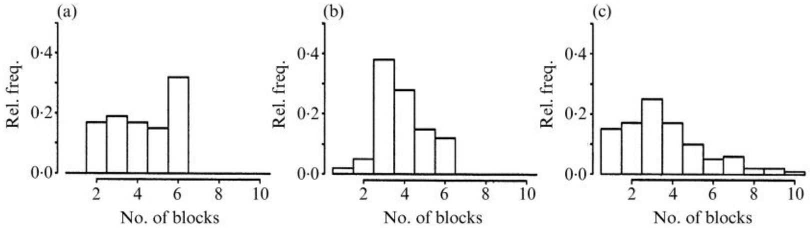

Fig. 1: Monte Carlo simulation. The histogram of the number of blocks as relative frequencies for (a) the Pocock design, (b) the O'Brien–Fleming design and (c) the Bayesian adaptive design, with $\theta = 0{\cdot}6$, $\delta = 0{\cdot}6$ and $B = 12$ for all the designs.

- Without a constraint on the maximum number of blocks, more than 75% of the trials using the proposed adaptive design are terminated with the number of blocks being four or fewer.

Simulation

Table 2: *Monte Carlo simulation. The comparison of power and average sample number between the proposed Bayesian optimal design and fixed sample design for binary responses: priors are* Be(1, 1), $\delta = 0{\cdot}4$, $p_t = p_c = 0{\cdot}5$ *for* H_0, $p_t = 0{\cdot}5 + \theta/2$ *and* $p_c = 0{\cdot}5 - \theta/2$ *for* H_1. *The ratio* K_0/K_1 *is* 19, *which satisfies the equation* $K_1/(K_1 + K_0) = \alpha$ *for* $\alpha = 0{\cdot}05$, *and the ratio* K_2/K_1 *is* 0·005

	Proposed Bayesian design II				Fixed sample design	
	$B = 16$		$B = 24$			
θ	pr(reject H_0)	ASN	pr(reject H_0)	ASN	pr(reject H_0)	ASN
0·40	0·921	46·0	0·973	55·0	0·906	46
0·36	0·874	50·4	0·945	57·3	0·835	46
0·32	0·801	52·3	0·875	60·9	0·741	46
0·28	0·710	54·0	0·812	64·4	0·631	46
0·00	0·047	40·2	0·047	56·2	0·050	46

ASN, average sample number.

Simulation

Table 3: *Monte Carlo simulation. The comparison of power and average sample number between the proposed Bayesian optimal design and the Lewis–Berry Bayesian design for binary responses:* $p_t = p_c = 0{\cdot}5$ *for* H_0, $p_t = 0{\cdot}5 + \delta/2$ *and* $p_c = 0{\cdot}5 - \delta/2$ *for* H_1. *The ratio* K_0/K_1 *is* 19, *which satisfies the equation* $K_1/(K_1 + K_0) = \alpha$ *for* $\alpha = 0{\cdot}05$, $K_2/K_1 = 0{\cdot}005$ *for* $\delta = 0{\cdot}4$, *and* $K_2/K_1 = 0{\cdot}00003$ *for* $\delta = 0{\cdot}2$

			Proposed Bayesian design II				Lewis–Berry design			
Priors	δ	B	$\hat{\alpha}$	ASN_α	$1-\hat{\beta}$	ASN_β	$\hat{\alpha}$	ASN_α	$1-\hat{\beta}$	ASN_β
Be(1, 1)	0·4	16	0·047	40·2	0·921	46·0	0·039	42·1	0·946	44·3
	0·2	16	0·030	131·4	0·926	171·7	0·035	155·9	0·960	161·4
Be(2, 2)	0·4	16	0·030	40·6	0·942	48·6	0·027	38·3	0·907	46·2
	0·2	16	0·026	125·5	0·917	171·9	0·034	152·3	0·958	162·1

- The proposed design has power similar to that LewisBerry's design, but the average sample number is slightly increased, by less than 5% under the alternative.
- However, the computation of the proposed design is much less intensive compared to that of LewisBerry's design, and the implementation is straightforward with one-step backward induction.
- The design of LewisBerry has a prespecified maximum number of blocks, while proposed design does not have such a restriction.