1.5em 0pt

A Bayesian sequential design with binary outcome

Yeojin Joo

May 28, 2019

Introduction

Sequential design?

- stop for efficacy when the superiority of a treatment is clearly established
- stop for futility when it is highly unlikely that efficacy can be established

A primary statistical concern is to control the overall type 1 error rate.

- The type 1 error rate may be inflated since multiple adaptations and multiple potential hypotheses may be considered.

Introduction

- Some researchers proposed a Bayesian sequential design that uses alpha-spending functions(BSDASF).
- The alpha-spending function allocates the type 1 error rate proportional to the amount of data used for interim analysis.

Introduction

- $t_j^* = n(t_j)/n$ where n is the allowed maximum sample size and $n(t_j)$ is the number of observations up to the jth interim analysis.

1. O'Brien-Fleming(OF) alpha-spending function: $\alpha_1(t^*) = 2 - 2\Phi(z_{\alpha/2}/\sqrt{t^*})$
2. Pocock alpha-spending function: $\alpha_2(t^*) = \alpha log\{1 + (e - 1)t^*\}$
3. Power alpha-spending function: $\alpha_3(t^*) = (t^*)^\gamma \alpha$
4. Equal alpha-spending funtion: $\alpha_4(t^*) = \alpha$

Introduction

In this paper, improved the BSDASF in the following aspects:

1. apply BSDASF to binary outcomes.
2. design a corresponding prior setting that enables incorporation of historical information.
3. investigate the effects of maximum sample size n on calculating decision rules.
4. propose a novel decision rule of stopping for futility.

Review of Bayesian sequential designs with alpha spending functions

- $\vec{X}_T$: a set of observations from the treatment group on the parameter μ_T
- $\vec{X}_C$: a set of observations from the congrol group on the parameter μ_C
- $H_0 : \mu_T \leq \mu_C$ vs $H_a : \mu_T > \mu_C$
- At the *jth* interim analysis, there are a total of $n(t_j)$ patients.
- $n(t_j) = n_T(t_j) + n_C(t_j)$
- $t_j^* = n(t_j)/n$: the information fraction at the *jth* interim analysis.

Review of Bayesian sequential designs with alpha spending functions

Algorithm 1. Sequential design with alpha-spending function α (BSDASF)
At the *jth* interim analysis, $j = 1, 2, ..., J$, $(t_j^* = 1)$

1. **Posterior updating** : Update $\pi(\mu_T|\vec{X}_{T_j})$ and $\pi(\mu_C|\vec{X}_{C_j})$ where $\vec{X}_{C_j} = (X_{C_1}, X_{C_2}, , .., X_{C_j})$ and $\vec{X}_{T_j} = (X_{T_1}, X_{T_2}, , .., X_{T_j})$
2. **Posterior probabilities** : Calculate the posterior probability of rejecting the null hypothesis, $P(\mu_T > \mu_C|\vec{X}_{T_j}, \vec{X}_{C_j})$
3. **Predictive posterior probabilities** :
   3.1 Generate data for the treatment group, $n/2 - n_T(t_j)$ and control group, $n/2 - n_C(t_j)$ from current posterior distributions.
   3.2 Pool generated and observed data and calculate the predictive posterior probability of rejecting null hypothesis, $Pre(\mu_T > \mu_C|\vec{X}_{T_j}, \vec{X}_{C_j}, n)$.

Review of Bayesian sequential designs with alpha spending functions

Algorithm 1. Sequential design with alpha-spending function α (BSDASF)

4. **Stopping for efficacy** :
   - If $P(\mu_T > \mu_C | \vec{X}_{T_j}, \vec{X}_{C_j}) \geq P_u(t_j^*)$, stop the trial for efficacy. Otherwise, go to step 5.
   - $P_u(t_j^*)$ is the critical value that uses an alpha-spending function to control the overall type 1 error rate.
5. **Stopping for futility** :
   - If $Pre(\mu_T > \mu_C | \vec{X}_{T_j}, \vec{X}_{C_j}, n) \leq P_l$, stop the trial for futility. Otherwise, continue the trial.
   - P_l is a preset decision bound, which depends on the goal and budget of the trial but not on t.

BSDASF for binary outcome

- $X_{T_i} \overset{iid}{\sim} B(1, p_T)$, $X_{C_i} \overset{iid}{\sim} B(1, p_C)$ for $i = 1, 2, ..., n/2$.
- $H_0 : p_T \leq p_C$ vs $H_a : p_T > p_C$
- $\pi(p_C) = Beta(\alpha_c, \beta_C)$ according to prior knowledge such that $\frac{\alpha_c}{\alpha_C + \beta_C} = p_0$
- $\pi(p_T) = Beta(1, 1) = U(0, 1)$ (noninformative prior)

BSDASF for binary outcome

- $n_{T(t_j)}$, $n_{C(t_j)}$: The total of observations in the interim analysis at t_j
- Let $\vec{X}_{T_j} = (x_{T_1}, ..., x_{T_{n_{T(t_j)}}})'$, $\vec{X}_{C_j} = (x_{C_1}, ..., x_{C_{n_{C(t_j)}}})'$, then the posterior distributions for p_T and p_C are
$\pi(p_T|\vec{X}_{T_j}) = Beta(1 + \sum_{i=1}^{n_T(t_j)} x_{T_i}, 1 + n_T(t_j) - \sum_{i=1}^{n_T(t_j)} x_{T_i})$
$\pi(p_C|\vec{X}_{C_j}, \alpha_C, \beta_C) =$
$Beta(\alpha_C + \sum_{i=1}^{n_C(t_j)} x_{C_i}, \beta_C + n_C(t_j) - \sum_{i=1}^{n_C(t_j)} x_{C_i})$

BSDASF for binary outcome

- The Bayesian sequential design proposed for binary outcomes is similar to Algorithm 1.
- Step 5 of Algorithm 1 is modified so that the trial will be stopped for futility if $P(Pre(p_T > p_C | \vec{X}_{T_j}, \vec{X}_{C_j}, \alpha_C, \beta_C, n) > P_{uf}) < P_l$
- P_{uf} is preset as the threshold for rejecting the null hypothesis if all data are analyzed together. (ie, no interim analysis)
- P_l is a preset threshold that can be chosen to control power and actual sample size.

BSDASF for binary outcome

Algorithm 1.1 Calculate the predictive critical value P_{uf} with α, n

1. For $m = 1, 2, ..., N_{rep}$:
   (a) Generate $\vec{X}_T^m = (X_{T_1}^m, X_{T_2}^m, ..., X_{T_{n_T}}^m)' \overset{iid}{\sim} B(n_T, 0.5)$
   (b) Generate $\vec{X}_C^m = (X_{C_1}^m, X_{C_2}^m, ..., X_{C_{n_C}}^m)' \overset{iid}{\sim} B(n_C, 0.5)$
   (c) Calculate $P^m = P(p_T > p_C | \vec{X}_T^m, \vec{X}_C^m, \alpha_C, \beta_C)$
2. Denote $\vec{P} = (P^1, P^2, ..., P^{N_{rep}})'$
3. P_{uf} is set as the $(1-\alpha)th$ quantile of the $\vec{P}$

BSDASF for binary outcome

Algorithm 2. Calculate the critical value $P_u(t_j^*)$ at $t_j^*, j = 1, 2, ..., J$ with alpha-spending function $\alpha(t^*)$ and preset P_l

1. For $m = 1, 2, ..., N_{rep}$:
   (a) Generate $\vec{X}_T^m = (X_{T_1}^m, X_{T_2}^m, ..., X_{T_{n_T}}^m)' \overset{iid}{\sim} B(n_T, c)$
   (b) Generate $\vec{X}_C^m = (X_{C_1}^m, X_{C_2}^m, ..., X_{C_{n_C}}^m)' \overset{iid}{\sim} B(n_C, c)$
   (c) For j=1, 2, ..., J,
   Calculate $P^m(t_j^*) = P(p_T > p_C|\vec{X}_{T_j}^m, \vec{X}_{C_j}^m, \alpha_C, \beta_C)$, where $\vec{X}_{T_j}^m, \vec{X}_{C_j}^m$ is the first $n_T(t_j), n_C(t_j)$ elements of $\vec{X}_T^m, \vec{X}_C^m$
   (d) Denote $\vec{P}^m = (P^m(t_1^*), ..., P^m(t_J^*))$
   (e) For j=1, 2, ..., J,
   Calculate $P(Pre(p_T > p_C|\vec{X}_T, \vec{X}_C, \alpha_C, \beta_C) > P_{uf})$.
   If at any j, $\pi(p_T - p_C > 0|\vec{X}_{T_j}, \vec{X}_{C_j}, \alpha_C, \beta_C) \leq P_l$, set $P^m(t_{j'}^*) = 0$ for $j' = j + 1, j + 2, ..., J$.

BSDASF for binary outcome

Algorithm 2. Calculate the critical value $P_u(t_j^*)$ at $t_j^*, j = 1, 2, ..., J$ with alpha-spending function $\alpha(t^*)$ and preset P_l

2 Denote $\mathbf{P}_1 = (\vec{P}^1, \vec{P}^2, ..., \vec{P}^{N_{rep}})'$, $N_{rep} \times J$ matrix

3 $P_u(t_1^*)$ is set as the $(1 - \alpha(t_1^*))th$ quantile of the 1st column of matrix $\mathbf{P}_1$

4 For $j = 2, 3, ...J$:

   (a) Let $\mathbf{P}_j$ be a matrix composed of the rows of $\mathbf{P}_{j-1}$ such that $(j-1)st$ element of the row be smaller than or equal to $P_u(t_{j-1}^*)$

   (b) $P_u(t_j^*)$ is set as the $(1 - \Delta\alpha(t_j^*))th$ quantile of the *jth* column of matrix $\mathbf{P}_j$, where $\Delta\alpha(t_j^*) = \alpha(t_j^*) - \alpha(t_{j-1}^*)$

BSDASF for binary outcome

Algorithm 3. Power calculation for BSDASFB with alpha-spending function $\alpha(t^*)$. WLOG, let $p_T = d + c, p_C = c$

1. For $m = 1, 2, ..., N_{rep}$:
   (a) Draw $\vec{X}_T^m = (X_{T_1}^m, X_{T_2}^m, ..., X_{T_{n_T}}^m)' \overset{iid}{\sim} B(n_T, d + c)$
   (b) Draw $\vec{X}_C^m = (X_{C_1}^m, X_{C_2}^m, ..., X_{C_{n_C}}^m)' \overset{iid}{\sim} B(n_C, c)$
   (c) For j=1, 2, ..., J,
   Calculate $P^m(t_j^*) = P(p_T > p_C | \vec{X}_{T_j}^m, \vec{X}_{C_j}^m, \alpha_C, \beta_C)$, where $\vec{X}_{T_j}^m, \vec{X}_{C_j}^m$ is the first $n_T(t_j), n_C(t_j)$ elements of $\vec{X}_T^m, \vec{X}_C^m$
   (d) Denote $\vec{P}^m = (P^m(t_1^*), ..., P^m(t_J^*))$
   (e) For j=1, 2, ..., J,
   Calculate $P(Pre(p_T > p_C | \vec{X}_T, \vec{X}_C, \alpha_C, \beta_C) > P_{uf})$.
   If at any j, $\pi(p_T - p_C > 0 | \vec{X}_{T_j}, \vec{X}_{C_j}, \alpha_C, \beta_C) \leq P_l$, set $P^m(t_{j'}^*) = 0$ for $j' = j + 1, j + 2, ..., J$.

BSDASF for binary outcome

Algorithm 3. Power calculation for BSDASFB with alpha=spending function $\alpha(t^*)$. WLOG, let $p_T = d + c, p_C = c$

2 Denote $\mathbf{P}_1 = (\vec{P}^1, \vec{P}^2, ..., \vec{P}^{N_{rep}})'$, $N_{rep} \times J$ matrix

3 For $j = 2, ..., J+1$, Let $\mathbf{P}_j$ be a matrix composed of the rows of $\mathbf{P}_{j-1}$ such that the $(j-1)st$ element of the row be smaller than or equal to $P_u(t^*_{j-1})$

4 β=(the number of rows of matrix $\mathbf{P}_{j+1})/N_{rep}$.

5 Power=$1 - \beta$

Simulation-Sensitivity Analysis

- Assess how the decision boundary($P_u(t^*)$) changes with choice of α_C
- Larger α_C is associated with more confidence in that prior p_o.
- 2 conditions: $(1) p_0 = p_C = 0.5$ and $(2) p_0 \neq p_C$

Simulation-Sensitivity Analysis

$$(1)\ p_0 = p_C = 0.5$$

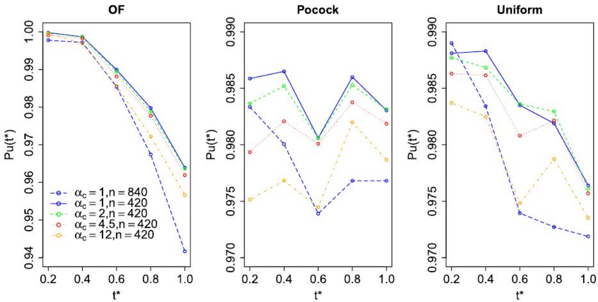


Figure: Comparison of critical values $P_u(t^*)$ for BSDASFB at different α_C, when $p_0 = p_C = 0.5$, d$n = 840$ and $n = 420$

- When n was fixed, $P_u(t^*)$ decreased as α_C increased.
- When n was larger, $P_u(t^*)$ were larger

Simulation-Sensitivity Analysis

(2) $p_0 \neq p_C$

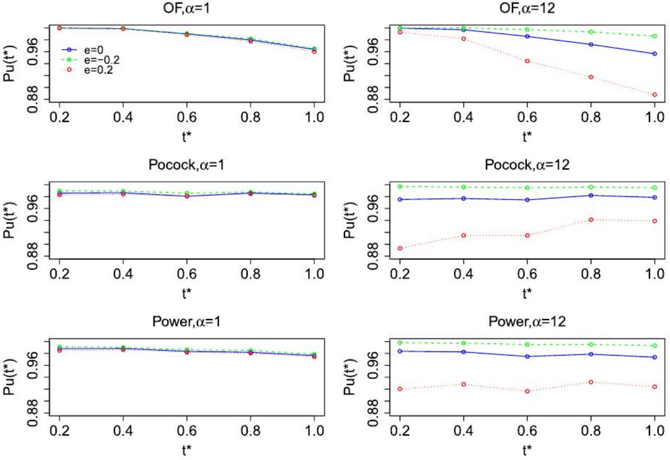


Figure: Comparison of critical values $P_u(t^*)$ when $\alpha_C = 1$ and $\alpha_C = 12$ at different $e(e = p_0 - p_C)$

Simulation-Sensitivity Analysis

- Based on the results of sensitivity analysis, we suggest setting α_C, β_C to small values, unless there is enough evidence to show the historical intormation is very similar to the experiment.
- Typically, α_C can be set at 1, and β_C be set such that $\frac{\alpha_C}{\alpha_C+\beta_C} = p_0$.

Methods Comparision studies

(1) Comparison of powers between the BSDASFB and the frequentist sequential design

- set $\alpha_C = \beta_C = 1, n = 100, e = 0, P_I = 0$

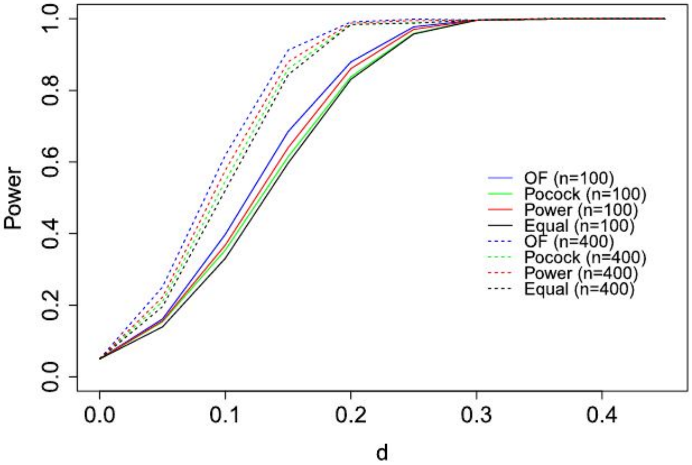
	Bayesian				Frequentist		
d ($p_T - p_C$)	OF	Pocock	Power	Equal	OF	Pocock	Power
0	0.0508	0.0495	0.0498	0.0496	0.0505	0.0499	0.0503
0.1	0.3786	0.3264	0.3498	0.3134	0.1536	0.1339	0.1403
0.2	0.8772	0.8284	0.8502	0.8128	0.3616	0.3082	0.3262
0.3	0.9886	0.9864	0.9878	0.9860	0.6598	0.5873	0.6130
0.4	1.0000	1.0000	1.0000	1.0000	0.9154	0.8747	0.8902

Abbreviation: OF, O'Brien-Fleming.

Methods Comparision studies

(2) Comparison of BSDASFB with different alpha-spending functions

- set $\alpha_C = \beta_C = 1.e = 0$, $n = 100$, and $n = 400$



Methods Comparision studies

(2) Comparison of BSDASFB with different alpha-spending functions

		OF		Pocock		Power		Equal	
d	P_l	Size	Power	Size	Power	Size	Power	Size	Power
0.05	0	87.35	0.162	84.82	0.154	86.69	0.156	84.43	0.139
0.1	0	74.51	0.398	68.32	0.354	68.93	0.368	66.07	0.331
0.15	0	69.35	0.685	63.87	0.615	64.04	0.640	62.26	0.597
0.2	0	66.15	0.878	58.62	0.838	59.65	0.861	56.29	0.831
0.25	0	60.41	0.978	47.26	0.959	48.33	0.971	44.96	0.958
0.3	0	52.05	0.997	37.38	0.996	38.68	0.996	35.70	0.996
0.35	0	45.15	0.999	30.32	0.999	31.33	0.999	29.07	0.999
0.4	0	39.63	1	25.43	0.999	25.89	0.999	24.60	0.999
0.45	0	33.51	1	22.25	1	22.61	1	20.50	1

Methods Comparision studies

(2) Comparison of BSDASFB with different alpha-spending functions

- BSDASFB with OF requires more samples and has greatest power comparred to any other alpha-spending function.
- The OF alpha-spending function allocates less type 1 error rate at very early states, therefore, is less likely to stop the trial early.
- We suggest to use OF function.

Methods Comparision studies

(3) Comparison of powers and actual sample sizes at different d and P_I

		OF		Pocock		Power		Equal	
d	P_I	Size	Power	Size	Power	Size	Power	Size	Power
0.05	0	87.35	0.162	84.82	0.154	86.69	0.156	84.43	0.139
0.1	0	74.51	0.398	68.32	0.354	68.93	0.368	66.07	0.331
0.15	0	69.35	0.685	63.87	0.615	64.04	0.640	62.26	0.597
0.2	0	66.15	0.878	58.62	0.838	59.65	0.861	56.29	0.831
0.25	0	60.41	0.978	47.26	0.959	48.33	0.971	44.96	0.958
0.3	0	52.05	0.997	37.38	0.996	38.68	0.996	35.70	0.996
0.35	0	45.15	0.999	30.32	0.999	31.33	0.999	29.07	0.999
0.4	0	39.63	1	25.43	0.999	25.89	0.999	24.60	0.999
0.45	0	33.51	1	22.25	1	22.61	1	20.50	1
0.1	0.05	72.71	0.342	65.90	0.314	66.32	0.335	64.63	0.303
0.1	0.1	71.50	0.333	64.84	0.312	65.10	0.321	63.99	0.300
0.1	0.2	70.32	0.313	63.58	0.3118	64.66	0.301	63.30	0.299
0.2	0.05	65.08	0.800	58.15	0.769	59.10	0.788	56.05	0.759
0.2	0.1	64.76	0.772	57.90	0.755	58.52	0.762	55.80	0.739
0.2	0.2	64.25	0.719	57.55	0.711	58.03	0.713	55.68	0.705
0.3	0.05	51.82	0.973	37.10	0.971	38.25	0.972	35.12	0.970
0.3	0.1	51.16	0.966	36.88	0.965	37.79	0.965	34.82	0.964
0.3	0.2	50.57	0.939	36.25	0.938	37.10	0.938	34.30	0.938

- The power and actual sample size decreases as P_I increases.

Methods Comparision studies

(4) Comparison two stopping rules for futility

- Proposed : $P(Pre(p_T > p_C|\vec{X}_{T_j}, \vec{X}_{C_j}, \alpha_C, \beta_C, n) > P_{uf}) < P_l$
- ZY : $Pre(\mu_T > \mu_C|\vec{X}_{T_j}, \vec{X}_{C_j}, n) \leq P_l$

		$P_0(P_T = 0.5)$				$P_T(P_0 = 0.5)$			
		0.5	0.6	0.7	0.8	0.5	0.45	0.4	0.35
P_l	**OF**	Powers				Actual Sample Sizes			
0.21	Proposed	0.750	0.744	0.743	0.742	33.93	33.85	33.68	33.65
0.28	ZY	0.750	0.740	0.705	0.704	58.19	52.08	49.92	49.88
P_l	**Pocock**								
0.20	Proposed	0.750	0.741	0.733	0.731	32.60	32.51	32.24	32.15
0.27	ZY	0.750	0.724	0.695	0.686	56.53	50.39	48.18	48.13
P_l	**Power**								
0.20	Proposed	0.750	0.741	0.734	0.732	32.95	32.78	32.68	32.63
0.28	ZY	0.750	0.735	0.699	0.698	57.03	50.76	48.80	48.71
P_l	**Equal**								
0.15	Proposed	0.750	0.742	0.735	0.730	32.47	32.43	32.25	32.20
0.20	ZY	0.750	0.731	0.690	0.685	56.38	50.3	48.22	48.19