A Bayesian adaptive design for clinical trials in rare diseases

Qingzhao Yu, et al.

Presented by 이종진

Seoul National University

ga0408@snu.ac.kr

may 28, 2019

- To treat the patients within trial as effectively as possible
- Modify the optimal design by incorporating randomisation and adding a constraint which forces a minimum number of patients on each treatment.

Problem setting

- Consider a two-armed clinical trial with a binary endpoint and a fintie number of patients, n.
- N_A, N_B are random, $n = N_A + N_B$
- Independent Bernoulli random variables, X, Y (denotes the patient's response either success or failure)

$$X \sim Bernoulli(\theta_A), Y \sim Bernoulli(\theta_B),\ for\ 0 \leq \theta_A, \theta_B \leq 1$$

RPW rule

- Well-known response-adaptive designs, *randomised play-the-winner*(RPW) rule.
- Initially, draw balls from an urn contains u balls of type A and B, respectively
- Allocate patient in the drawn treatments.
- A success on treatment A, or a failure on treatment B, add β type A and α type B balls in the urn ($0 \leq \alpha \leq \beta$, *are integers*)
- B success on treatment A, or a failure on treatment A, add β type B and α type A balls in the urn

Optimal design using dynamic programming(DP)

- The RPW is not contructed based on any formal optimality criterion.

  $\rightarrow$ Alternative approach which utilises dynamic programming

- Optimal design using dynamic programming(DP)

Optimal design using dynamic programming(DP)

- $\theta_A \sim \text{Beta}\left(s_{A,0}, f_{A,0}\right)$ and $\theta_B \sim \text{Beta}\left(S_{B,0}, f_{B,0}\right)$ for $0 \leq \theta_A, \theta_B \leq 1$
- For successes or failures on the treatments$(s_{A,t}, f_{A,t}, s_{B,t}, f_{B,t})$,
  $\theta_A | s_{A,t}, f_{A,t} \sim \text{Beta}\left(s_{A,0} + s_{A,t}, f_{A,0} + f_{A,t}\right)$ and
  $\theta_B | s_{B,t}, f_{B,t} \sim \text{Beta}\left(s_{B,0} + s_{B,t}, f_{B,0} + f_{B,t}\right)$, where
  $s_{A,t} + f_{A,t} + s_{B,t} + f_{B,t} = 1$
- $\widetilde{s}_{j,t} = s_{j,0} + s_{j,t}, \quad \tilde{f}_{j,t} = f_{j,0} + f_{j,t}$, where $j = A, B$
- $\frac{\widetilde{s}_{j,t}}{\widetilde{s}_{j,t} + \tilde{f}_{j,t}}$ is the posterior probability.
- Let $\delta_{j,t}$, for $t = 0, \ldots, n-1, j = A.B$

$$\delta_{j,t} = \begin{cases} 1, & \text{if patient } t+1 \text{ is allocated to treatment } j \\ 0, & \text{otherwise.} \end{cases}$$

Optimal design using dynamic programming(DP)

- $\frac{\widetilde{s}_{j,t}}{\widetilde{s}_{j,t}+f_{j,t}} \cdot \delta_{j,t}$ is the expected (one-period) reward.
- Let Π be the family of admissible designs π, which satisfie $\sum_j \delta_{j,t} = 1$ for all t
- Maximum expected total reward, i.e. maximum Bayes-expected number of successes, in the rest of the trial after t patients.
- $\mathcal{F}_t\left(s_A, f_A, s_B, f_B\right) :=$
$\max_{\pi \in \Pi} \mathbb{E}^{\pi}\left[\sum_{u=t}^{n-1} \sum_{j \in \{A,B\}} \frac{\widetilde{s}_{j,u}}{\widetilde{s}_{j,u}+\widetilde{f}_{j,u}} \cdot \delta_{j,u} | \widetilde{s}_{A,t} = s_A, \tilde{f}_{A,t} = f_A, \widetilde{s}_{B,t} = s_B, \tilde{f}_{B,t} = f_B\right]$

Optimal design using dynamic programming(DP)

- If treatment A is allocated to the t+1 patient,

$$\mathcal{F}_t^A(s_A, f_A, s_B, f_B) = \frac{s_A}{s_A + f_A} \cdot [1 + \mathcal{F}_{t+1}(s_A + 1, f_A, s_B, f_B)] + \frac{f_A}{s_A + f_A} \cdot \mathcal{F}_{t+1}(s_A, f_A + 1, s_B, f_B)$$

- $\mathcal{F}_t^B(s_A, f_A, s_B, f_B)$ can be expressed in the same way
- The value function satisifes the following recurrence known as the principle of optimality

$$\mathcal{F}_t(s_A, f_A, s_B, f_B) = \begin{cases} \max\{\mathcal{F}_t^A(s_A, f_A, s_B, f_B), \mathcal{F}_t^B(s_A, f_A, s_B, f_B)\} & 0 \le t \le n-1. \\ 0 & \text{t=n} \end{cases}$$

Optimal design using randomised dynamic programming (RDP)

- Natural step is to modify the optimal design by forcing actions to be randomised
- Action a=1, Allocated treatment A w.p. p and treatment B w.p. 1-p
- Action a=2, Allocated treatment A w.p. 1-p and treatment B w.p. p
- When a=1,

  $\mathcal{F}_t^1(s_A, f_A, s_B, f_B) = p \cdot \mathcal{F}_t^A(s_A, f_A, s_B, f_B) + (1-p) \cdot \mathcal{F}_t^B(s_A, f_A, s_B, f_B)$
- When a=2,

  $\mathcal{F}_t^2(s_A, f_A, s_B, f_B) = (1-p) \cdot \mathcal{F}_t^A(s_A, f_A, s_B, f_B) + p \cdot \mathcal{F}_t^B(s_A, f_A, s_B, f_B)$

- The value function satisfies

$$\mathcal{F}_t\left(s_A, f_A, s_B, f_B\right) = \begin{cases} \max\{\mathcal{F}_t^1\left(s_A, f_A, s_B, f_B\right), \mathcal{F}_t^2\left(s_A, f_A, s_B, f_B\right)\} & 0 \leq t \leq n-1. \\ 0 & \text{t=n} \end{cases}$$

Optimal design using constrained randomised dynamic programming (CRDP)

- In the paper, they modify the optimal design futher by adding a constraint to ensure that each treatment has at least l observations.
- Let $\mathbf{z}_t = (\widetilde{s}_{A,t}, \widetilde{f}_{B,t}, \widetilde{s}_{B,t}, \widetilde{f}_{B,t}, \widetilde{n}), \widetilde{n} = n - t$
- The action set, $\mathcal{A} = \{1, 2\}$
- $$\mathcal{R}^a(\widetilde{s}_{A,t}, \widetilde{f}_{B,t}, \widetilde{s}_{B,t}, \widetilde{f}_{B,t}, \widetilde{n} \geq 1) = \begin{cases} p \cdot \frac{\widetilde{s}_{A,t}}{\widetilde{s}_{A,t}+\widetilde{f}_{A,t}} + (1-p) \cdot \frac{\widetilde{s}_{B,t}}{\widetilde{s}_{B,t}+\widetilde{f}_{B,t}}, & \text{if } a{=}1 \\ (1-p) \cdot \frac{\widetilde{s}_{A,t}}{\widetilde{s}_{A,t}+\widetilde{f}_{A,t}} + p \cdot \frac{\widetilde{s}_{B,t}}{\widetilde{s}_{B,t}+\widetilde{f}_{B,t}}, & \text{if } a{=}2 \end{cases}$$

  Otherwise,

  $$\mathcal{R}^a(\widetilde{s}_{A,t}, \widetilde{f}_{B,t}, \widetilde{s}_{B,t}, \widetilde{f}_{B,t}, \widetilde{n} = 0) = \begin{cases} -n, & \text{if } s_{A,t} + f_{A,t} < l, \text{or } s_{B,t} + f_{B,t} < l, \\ 0, & \text{otherwise,} \end{cases}$$

- a When a=1:

$$\mathbf{z}_{t+1} = \begin{cases} (\widetilde{s}_{A,t}+1, \widetilde{f}_{A,t}, \widetilde{s}_{B,t}, \widetilde{f}_{B,t}, \widetilde{n}-1) & \text{w.p. } p \cdot \frac{\widetilde{s}_{A,t}}{\widetilde{s}_{A,t}+\widetilde{f}_{A,t}} \\ (\widetilde{s}_{A,t}, \widetilde{f}_{A,t}+1, \widetilde{s}_{B,t}, \widetilde{f}_{B,t}, \widetilde{n}-1) & \text{w.p. } p \cdot \frac{\widetilde{f}_{A,t}}{\widetilde{s}_{A,t}+\widetilde{f}_{A,t}} \\ (\widetilde{s}_{A,t}, \widetilde{f}_{A,t}, \widetilde{s}_{B,t}+1, \widetilde{f}_{B,t}, \widetilde{n}-1) & \text{w.p. } (1-p) \cdot \frac{\widetilde{s}_{B,t}}{\widetilde{s}_{B,t}+\widetilde{f}_{B,t}} \\ (\widetilde{s}_{A,t}, \widetilde{f}_{A,t}, \widetilde{s}_{B,t}, \widetilde{f}_{B,t}+1, \widetilde{n}-1) & \text{w.p. } (1-p) \cdot \frac{\widetilde{s}_{B,t}}{\widetilde{s}_{B,t}+\widetilde{f}_{B,t}} \end{cases}$$

- a When a=2:

$$\mathbf{z}_{t+1} = \begin{cases} (\widetilde{s}_{A,t}+1, \widetilde{f}_{A,t}, \widetilde{s}_{B,t}, \widetilde{f}_{B,t}, \widetilde{n}-1) & \text{w.p. } (1-p)\cdot \frac{\widetilde{s}_{A,t}}{\widetilde{s}_{A,t}+\widetilde{f}_{A,t}} \\ (\widetilde{s}_{A,t}, \widetilde{f}_{A,t}+1, \widetilde{s}_{B,t}, \widetilde{f}_{B,t}, \widetilde{n}-1) & \text{w.p. } (1-p)\cdot \frac{\widetilde{f}_{A,t}}{\widetilde{s}_{A,t}+\widetilde{f}_{A,t}} \\ (\widetilde{s}_{A,t}, \widetilde{f}_{A,t}, \widetilde{s}_{B,t}+1, \widetilde{f}_{B,t}, \widetilde{n}-1) & \text{w.p. } p\cdot \frac{\widetilde{s}_{B,t}}{\widetilde{s}_{B,t}+\widetilde{f}_{B,t}} \\ (\widetilde{s}_{A,t}, \widetilde{f}_{A,t}, \widetilde{s}_{B,t}, \widetilde{f}_{B,t}+1, \widetilde{n}-1) & \text{w.p. } p\cdot \frac{\widetilde{s}_{B,t}}{\widetilde{s}_{B,t}+\widetilde{f}_{B,t}} \end{cases}$$

Simulation studies

- $H_0 : \theta_A = \theta_B$ vs $H_0 : \theta_A \neq \theta_B$
- n = 75, (n=25, n=50, n=100)
- $\theta_A = 0.2$ (0.5, 0.8), $\theta_B \in \{0.1, \ldots, 0.9\}$
- 10,000 replications.
- Measure:

  Power/Type I error rate/Percentage of patients allocated to the superior treatment arm/ Average bias of the estimator / MSE of the estimator

Power/Type I error rate

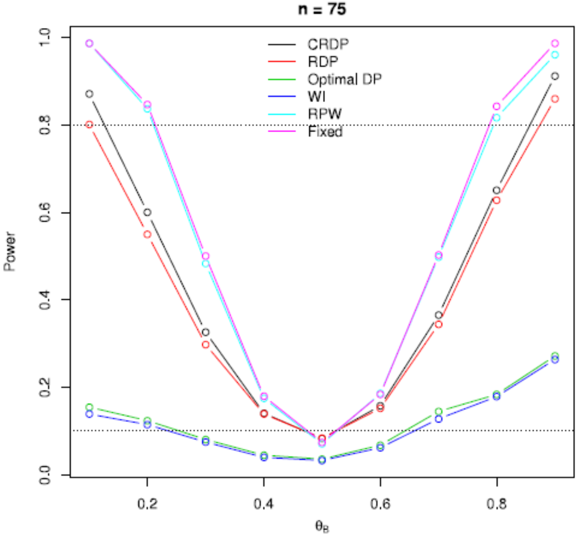
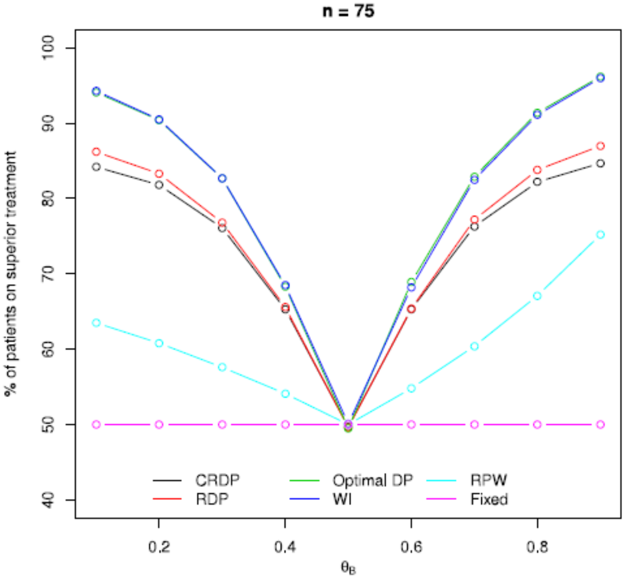
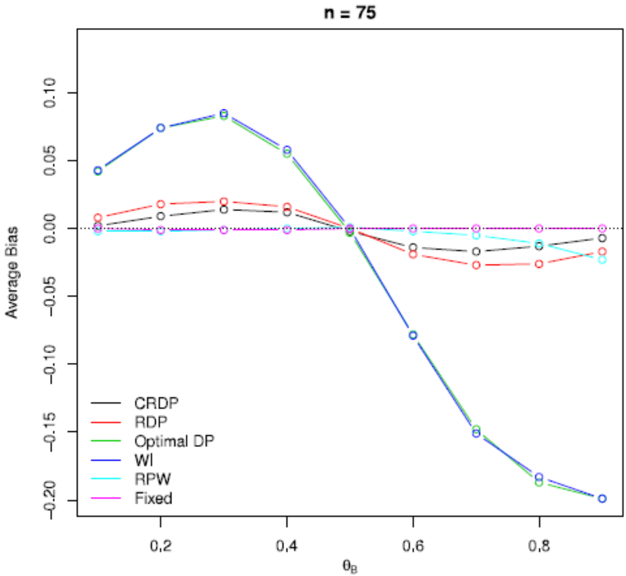


Figure: $\theta_A = 0.5$

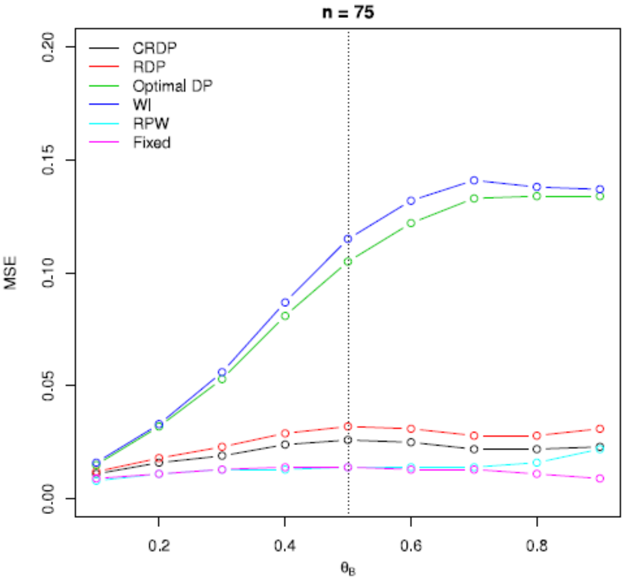
Percentage of patients allocated to the superior treatment arm



Average bias of the estimator



MSE of the estimator



A Bayesian sequential design with adaptive randomization for 2-sided hypothesis test

S. Faye Williamson, et al.

Presented by 이종진

Seoul National University

ga0408@snu.ac.kr

may 28, 2019

A Bayesian sequential design with adaptive randomization for 2-sided hypothesis test

- We consider a 2-sided test where the variances are unknown.
- Patients are allocated to the 2 arms with a randomization rate to achieve minimum variance for test statistics
- A Bayesian sequential design with adaptive randomization is not common

Settings

- $\overrightarrow{\mathbf{X}}_T$: n_T observations from the treatment(novel treatment) group. $\overrightarrow{\mathbf{X}}_C$: n_C observations from the control(established treatment) group.
- Assume $X_{Ti} \sim N\left(\mu_T, \sigma_T^2\right)$ for $i = 1, \ldots, n_T$,
$$X_{Ci} \overset{iid}{\sim} N\left(\mu_C, \sigma_C^2\right), \text{ for } i = 1, \ldots, n_C$$
- Purpose : Recruit patients for both group to test whether the mean efficacies of the novel and established treatments are equal $(\mu_T = \mu_C)$

Settings

- $\mu_C|\sigma_C^2 \sim N(\mu_0, \sigma_C^2/\tau)$,

  μ_0 : from the prior information. τ : controling the similarity between μ_0, μ_C
- $\sigma_C^2 \sim inv - \chi^2(\nu_0, \sigma_0^2)$

  ν_0, σ_0^2 : from prior information,

  σ_0^2 : an estimation of σ_C^2, ν_0 : control extend of dependency on the prior
- 'non-informative prior' for μ_T, σ_T^2, $p\left(\mu_T, \sigma_T^2\right) \propto \left(\sigma_T^2\right)^{-1}$
- At the jth interim analysis,

  $n(t_j) = n_T(t_j) + n_C(t_j)$: the number of patients recruited

  $\overrightarrow{\mathbf{x}}_{T_j}, \overrightarrow{\mathbf{x}}_{C_j}$: $n_T(t_j)$, and $n_C(t_j)$ number of observations
- Information fraction at the jth interim analysis, $t_j^* = n(t_j)/n$, where n is the maximum allowed sample size.

- Conditional on the interim data at t_j,

$p\left(\mu_T, \sigma_T^2 | \overrightarrow{\mathbf{x}}_{Tj}\right) \sim$
$\left(\sigma_T^2\right)^{-1} \times \exp\left[-\frac{1}{2\sigma_T^2}\left\{\left(n_T\left(t_j\right)-1\right)s_{Tj}^2 + n_T\left(t_j\right)\left(\overline{x}_{Tj}-\mu_T\right)^2\right\}\right]$, where
$\overline{x}_{T_j} = \left(n_{T_j}\left(t_j\right)\right)^{-1}\sum_{i=1}^{n_{T_j}(t)} x_{T_i}$ and
$s_{T_j}^2 = \left(n_{T_j}\left(t_j\right)-1\right)^{-1}\sum_{i=1}^{n_{T_j}(t)}\left(x_{Ti}-\overline{x}_{Tj}\right)^2$

- Conditional on the interim data at t_j,

$p\left(\mu_C, \sigma_C^2 | \overrightarrow{\mathbf{x}}_{Cj}, \tau, \mu_0, v_0, \sigma_0^2\right) \sim N - \ln v - \chi^2\left(\mu_{nj}, \sigma_{nj}^2/\tau_{nj}; v_{nj}, \sigma_{nj}^2\right)$,where
$\mu_{nj} = \frac{\tau}{\tau+n_C\left(t_j\right)}\mu_0 + \frac{n_C\left(t_j\right)}{\tau+n_C\left(t_j\right)}\overline{x}_{Cj}, \quad \tau_{nj} = \tau + n_C\left(t_j\right), \quad v_{nj} = v_0 + n_C\left(t_j\right)$
$v_{nj}\sigma_{nj}^2 = v_0\sigma_0^2 + \left(n_C\left(t_j\right)-1\right)s_{Cj}^2 + \frac{\tau n_C\left(t_j\right)}{\tau+n_C\left(t_j\right)}\left(\overline{x}_{Cj}-\mu_0\right)^2, \quad \overline{x}_{Cj} =$
$\frac{1}{n_C\left(t_j\right)}\sum_{i=1}^{n_C\left(t_j\right)} x_{Ci}$

Posterior distribution

- The marginal posterior distributions for σ_t and σ_C

$$p\left(\sigma_T^2 | \overrightarrow{\mathbf{x}}_{Tj}\right) \sim \text{Inv}-\chi^2\left(n_T\left(t_j\right)-1, s_{Tj}^2\right)$$

$$p\left(\sigma_C^2 | \overrightarrow{\mathbf{x}}_{Cj}, \tau, \mu_0, v_0, \sigma_0^2\right) \sim \text{Inv}-\chi^2\left(\nu_{nj}, \sigma_{nj}^2\right)$$

- The conditional posterior distributions for μ_T and μ_C

$$p\left(\mu_T | \sigma_T^2, \overrightarrow{\mathbf{x}}_{TJ}\right) \sim N\left(\overline{x}_{Tj}, \sigma_T^2 / n_T\left(t_j\right)\right)$$

$$p\left(\mu_C | \sigma_C^2, \overrightarrow{\mathbf{x}}_{Cj}, \tau, \mu_0, v_0, \sigma_0^2\right) \sim N\left(\mu_{nj}, \sigma_C^2 / \tau_{nj}\right)$$

- The conditional posterior distribution of $\mu_T - \mu_C$

$$p\left(\mu_T - \mu_C | \sigma_T^2, \overrightarrow{\mathbf{x}}_{Tj}, \sigma_C^2, \overrightarrow{\mathbf{x}}_{Cj}, \tau, \mu_0, v_0, \sigma_0^2\right) \sim N\left(\overline{x}_{Tj} - \mu_{nj}, \sigma_T^2 / n_T\left(t_j\right) + |\sigma_C^2 / \tau_{nj}\right)$$

- The conditional posterior probability of $|\mu_T - \mu_C| > \delta$

$$\text{pr}\left(|\mu_T - \mu_C| > \delta | \sigma_T^2, \overrightarrow{\mathbf{x}}_{Tj}, \sigma_C^2, \overrightarrow{\mathbf{x}}_{Cj}, \tau, \mu_0, v_0, \sigma_0^2\right) = 1 - \Phi_{u,\sigma}(\delta) + \Phi_{u,\sigma}(-\delta)$$

where $\Phi_{u,\sigma}(x)$ is cdf of normal distribution with mean $u = \overline{x}_{Tj} - \mu_{nj}$ and variance $\sigma^2 = \sigma_T^2 / n_T\left(t_j\right) + \sigma_C^2 / \tau_{nj}$

The randomization method

- randomization rate can be changed adaptively after each interim analysis, to achieve greater testing power at fixed total sample size.
- newly nrecruited $n(t_{j+1}) - n(t_j)$ patients to be assigned to the treatment group is

$$r_T(t_j) = \min\left\{\max\left(\frac{\hat{\sigma}_{Tj} n_C(t_j) + \hat{\sigma}_{Tj}\tau + \hat{\sigma}_{Tj}(n(t_{j+1}) - \hat{\sigma}_{Cj} n_T(t_j)}{(\hat{\sigma}_{Tj} + \hat{\sigma}_{Cj})(n(t_{j+1}) - n(t_j))}, 0\right), 1\right\}$$

  , where $\hat{\sigma}_{Tj}$ and $\hat{\sigma}_{Cj}$ are the estimates of σ_T and σ_C from the jth interim analysis
- Assigning patients to the treatment group at this randomization rate can achieve the minimum variance estimation for the test statistic, $\hat{\mu}_T - \hat{\mu}_C = \overline{x}_{Tj} - \mu_{nj}$

Bayesian sequential design with adaptive randomization(BSDAR)

- To control the study-wide overall type I error, alpha spending functions are used.
- It is function of information fraction, $f\left(t_j^*\right)$ and t_j^* is the information fraction at the jth interim analysis, then $f(1)=\alpha$
- 4 types of alpha spending functions:
  1. O'Brien-Fleming alpha spending function $\left(\alpha_1\left(t^*\right)=2-2\Phi\left(z_{\alpha/2}/\sqrt{t^*}\right)\right)$, where Φ is cdf of standard normal.
  2. Pocock alpha spending function $\left(\alpha_2\left(t^*\right)=\alpha\log\left\{1+(e-1)t^*\right\}\right)$
  3. Uniform alpha spending function $\left(\alpha_3\left(t^*\right)=t^*\alpha\right)$
  4. Equal alpha spending function, the traditional method that sets equal critical values for all t^*.

Bayesian sequential design with adaptive randomization(BSDAR)

1. Update the marginal posterior probability distributions of σ_T and σ_C, $p\left(\sigma_T^2|\overrightarrow{\mathbf{x}}_{Tj}\right)$ and $p\left(\sigma_C^2|\overrightarrow{\mathbf{x}}_{Cj},\tau,\mu_0,\nu_0,\sigma_0^2\right)$
2. Update the conditional posterior probability distributions of μ_T and μ_C, $p\left(\mu_T|\sigma_T^2,\overrightarrow{\mathbf{x}}_{Tj}\right)$ and $p\left(\mu_C|\sigma_C^2,\overrightarrow{\mathbf{x}}_{Cj},\tau,\mu_0,v_0,\sigma_0^2\right)$
3. Calculate the posterior probability of rejecting the null hypothesis, $\mathrm{p}\left(|\mu_T-\mu_C|>\delta|\sigma_T^2,\overrightarrow{\mathbf{x}}_{Tj},\sigma_C^2,\overrightarrow{\mathbf{x}}_{Cj},\tau,\mu_0,v_0,\sigma_0^2\right)$
4. Stopping for efficacy: $\mathrm{p}\left(|\mu_T-\mu_C|>\delta|\sigma_T^2,\overrightarrow{\mathbf{x}}_{Tj},\sigma_C^2,\overrightarrow{\mathbf{x}}_{Cj},\tau,\mu_0,v_0,\sigma_0^2\right)\geq p_u\left(t_j^*\right)$, The choice of $p_u\left(t_j^*\right)$, depending on t_j and the choice of α
5. If the stopping decision is not made and the maximum sample size not reached, continue the trial and assign the newly recruited patients to the treatment group at the randomization rate $r_T\left(t_j\right)$

Algorithm1 for $r_T\,(t_j)$

- For given rate $r_T(t_0)$)(usually 0.5), $\alpha(t^*)$
- Assume $\mu_T = \mu_C = c$
- Preset the planned total number of patients to be recruited at the jth interim analysis as $n(t_j)$.
- $n_T(t_1) = n(t_1) r_T(t_0)$ and $n_C(t_1) = n(t_1)(1 - r_T(t_0))$

Algorithm1 for $r_T\left(t_j\right)$

1. For $m = 1, \ldots, N_{rep}$:
   1.1 Generate $\overrightarrow{\mathbf{x}}_T^m = \left(x_{T1}^m, \ldots, x_{Tn_T}^m\right)^{\mathrm{T}}$ from $N\left(c, \sigma_T^{2*}\right)$
   1.2 Generate $\overrightarrow{\mathbf{x}}_C^m = \left(x_{C1}^m, \ldots, x_{Cn_c}^m\right)^{\mathrm{T}}$ from $N\left(c, \sigma_C^{2*}\right)$
   1.3 For $j = 1, \ldots, J-1$,
      1.3.1 Calulate the estimates of $\sigma_T^{\mathbf{2}}$ and $\sigma_C^{\mathbf{2}}$ based on their interim posterior distributions, denoting the estimates as $\hat{\sigma}_{Tj,m}^{\mathbf{2}}$ and $\hat{\sigma}_{Cj,m}^{\mathbf{2}}$
      1.3.2 Calculate $P^m(t_j^*) = \mathrm{pr}\left(|\mu_T - \mu_C| > \delta | \overrightarrow{\mathbf{x}}_{Tj}^m, \overrightarrow{\mathbf{x}}_{Cj}^m, \mu_{\mathbf{0}}, \tau, \hat{\sigma}_{Tj,m}^{\mathbf{2}}, \hat{\sigma}_{Cj,m}^{\mathbf{2}}, v_{\mathbf{0}}, \sigma_{\mathbf{0}}^{\mathbf{2}}\right)$ where $\overrightarrow{\mathbf{x}}_{Tj}^m$ is a vector of the first $n_T\left(t_j\right)$ elements of $\overrightarrow{\mathbf{x}}_T^m$ and $\overrightarrow{\mathbf{x}}_{Cj}^m$ the first $n_C\left(t_j\right)$ elements of $\overrightarrow{\mathbf{x}}_C^m$
      1.3.3 Calculate the randomization rate $r_T^m\left(t_j\right)$ based on estimates from 1.3.1
      1.3.4 Calculate the number of patients assigned to treatment group, $n_T\left(t_{j+\mathbf{1}}\right)^m = n_T\left(t_{j+\mathbf{1}}\right) - \left(n\left(t_{j+\mathbf{1}}\right) - n\left(t_j\right)\right) r_T^m\left(t_j\right)$
   1.4 At $j = J$, calculate
   $$P^m(t_j^*) = \mathrm{pr}\left(|\mu_T - \mu_C| > \delta | \overrightarrow{\mathbf{x}}_{Tj}^m, \overrightarrow{\mathbf{x}}_{Cj}^m, \mu_0, \tau, \hat{\sigma}_{Tj,m}^2, \hat{\sigma}_{Cj,m}^2, v_0, \sigma_0^2\right)$$
   1.5 Let $\overrightarrow{\mathbf{P}}^m = \left(P^m\left(t_1^*\right), \ldots, P^m\left(t_J^*\right)\right)$

Algorithm1 for $r_T(t_j)$

2. Denote $\mathbf{P}_1 = \left(\overrightarrow{\mathbf{P}}^1, \ldots, \overrightarrow{\mathbf{P}}^{N_{rep}}\right)^{\mathrm{T}}$, a $N_{rep} \times J$ matrix whose (i,j) element is the $P^m(t_j^*)$ calculated in the ith iteration of Step 1
3. $p_u(t_1^*)$ is set as the $(1 - \alpha(t_1^*))$ th quantile of the first column of matrix P_1
4. For $j = 2, \ldots J$
   4.1. Let P_j be *a* matrix composed of the rows of P_{j-1}, where the $(j-1)$th element of the row is smaller than or equal to $p_u\left(t_{j-1}^*\right)$
   4.2. $p_u(t_j^*)$ is set as the $(1 - \Delta\alpha(t_j^*))$ th quantile of the jth column of matrix P_j where $\Delta\alpha(t_j^*) = \alpha(t_j^*) - \alpha(t_{j-1}^*)$

Algorithm2 for power

- For given rate $r_T(t_0))$(usually 0.5), $\alpha(t^*)$
- $mu_C = c, \mu_T = d + c$
- Preset the planned total number of patients to be recruited at the jth interim analysis as $n(t_j)$.
- $n_T(t_1) = n(t_1)r_T(t_0)$ and $n_C(t_1) = n(t_1)(1 - r_T(t_0))$

Algorithm2 for power

1. For $m = 1, \ldots, N_{rep}$:
   1.1 Generate $\overrightarrow{\mathbf{x}}_T^m = \left(x_{T1}^m, \ldots, x_{Tn_T}^m\right)^{\mathrm{T}}$ from $N\left(\mu_C, \sigma_T^{2*}\right)$
   1.2 Generate $\overrightarrow{\mathbf{x}}_C^m = \left(x_{C1}^m, \ldots, x_{Cn_C}^m\right)^{\mathrm{T}}$ from $N\left(\mu_T, \sigma_C^{2*}\right)$
   1.3 For $j = 1, \ldots, J-1$
      1.3.1 Calulate the estimates of $\sigma_T^{\mathbf{2}}$ and $\sigma_C^{\mathbf{2}}$ based on their marginal interim posterior distributions
      1.3.2 Calculate $P^m(t_j^*) = \mathrm{pr}\left(|\mu_T - \mu_C| > \delta | \overrightarrow{\mathbf{x}}_{Tj}^m, \overrightarrow{\mathbf{x}}_{Cj}^m, \mu_{\mathbf{0}}, \tau, \hat{\sigma}_{Tj,m}^{\mathbf{2}}, \hat{\sigma}_{Cj,m}^{\mathbf{2}}, v_{\mathbf{0}}, \sigma_{\mathbf{0}}^{\mathbf{2}}\right)$ based on the first $n_T(t_j)$ elements of $\overrightarrow{\mathbf{x}}_T^m$ and $n_C\left(t_j\right)$ elements of $\overrightarrow{\mathbf{x}}_C^m$
      1.3.3 Calculate the randomization rate $r_T^m\left(t_j\right)$
      1.3.4 Calculate the number of patients assigned to treatment group, $n_T\left(t_{j+\mathbf{1}}\right)^m = n_T\left(t_{j+\mathbf{1}}\right) - \left(n\left(t_{j+\mathbf{1}}\right) - n\left(t_j\right)\right) r_T^m\left(t_j\right)$
   1.4 At j=J, calculate $P^m\left(t_j^*\right) = \mathrm{pr}\left(|\mu_T - \mu_C| > \delta | \overrightarrow{\mathbf{x}}_{Tj}^m, \overrightarrow{\mathbf{x}}_{Cj}^m, \mu_0, \tau, \hat{\sigma}_{Tj,m}^2, \hat{\sigma}_{Cj,m}^2, \hat{\sigma}_{Cj,m}^2, v_0, \sigma_0^2\right)$
   1.5 Let $\overrightarrow{\mathbf{P}}^m = \left(P^m\left(t_1^*\right), \ldots, P^m\left(t_J^*\right)\right)$

Algorithm2 for power

2 Let $\mathbf{P}_1 = \left(\overrightarrow{\mathbf{P}}^1, \ldots, \overrightarrow{\mathbf{P}}^{N_{rep}}\right)^{\mathrm{T}}$, a $N_{rep} \times J$ matrix

3 Let P_j be a matrix composed of the rows of P_{j-1} where the $(j-1)$th element of the row is smaller than or equal to $p_u\left(t^*_{j-1}\right)$, for $j = 2, \ldots, J+1$

4 $\beta =$ (the number of rows of matrixP_{J+1}) $/N_{rep}$

5 Power $= 1 - \beta$