Multiple-Stage Procedures in Covariate-Adjusted Response-Adaptive Designs

Eunsik Park[1] and Y-c Ivan Chang[2]

[1]Chonnam National University, Gwangju, Korea (Email: espark02@chonnam.ac.kr)
[2]Academia Sinica, Taipei, Taiwan

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Response-Adaptive (RA) Design

- In terms of ethical viewpoint, it is desirable if we can minimize the number of subjects allocated to the inferior treatments in the course of a clinical trial while useful and meaningful statistical inferences can still be made.
- The advantage of an RA design is that the information collected from previously entered subjects can be used to adjust the allocation probability such that a newly entered subject can have a better chance to be allocated to a superior treatment.
- Because of the sequential characteristic in this process, the sequential statistical methods should be used when analyzing this kind of data sets.
- Since the data collected in this manner are no longer independent, sequential methods that rely on assumption of independent observations are not valid anymore.

Covariate-Adjustment - I

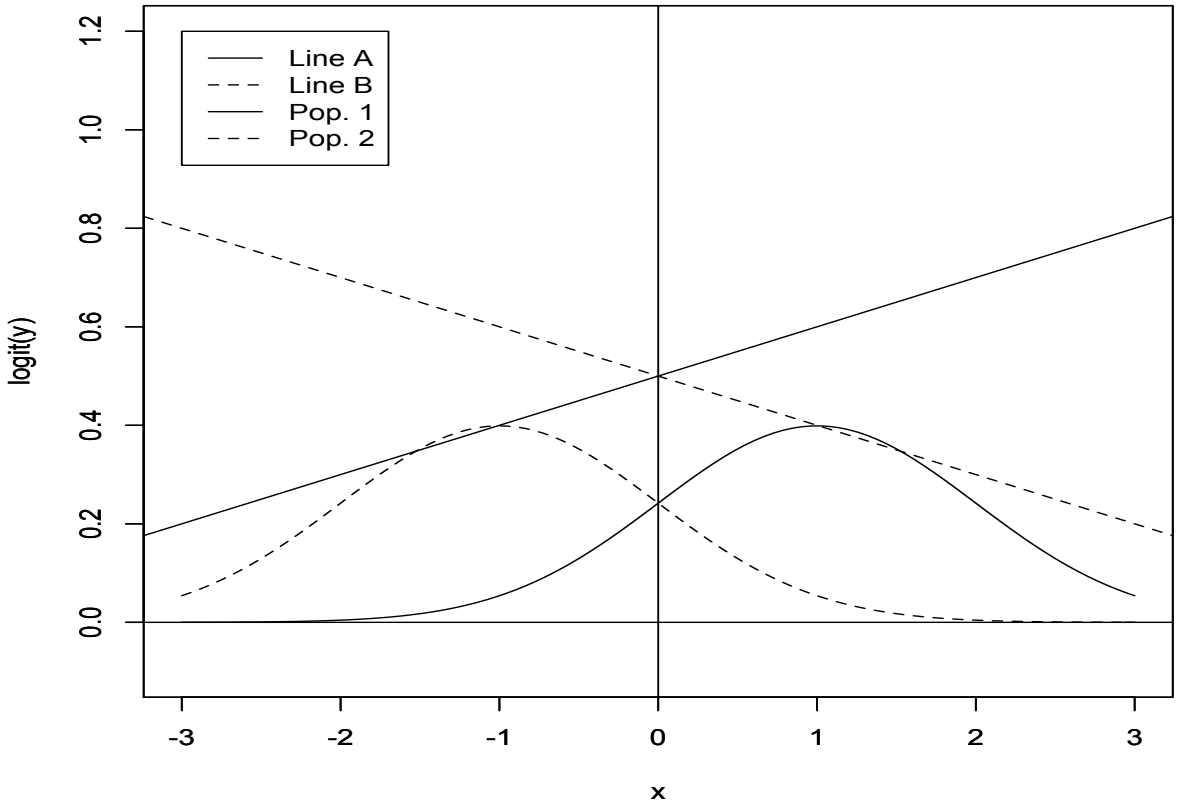

Figure: CARA design with two treatment slopes and two covariate populations.

Covariate-Adjustment - II

- Due to innovation of genomic technologies and the nature of developing targeted drug, it is natural to incorporate the available individual information of covariates that have strong influence on responses to a model, since they may be associated with the efficacy of treatments.
- Traditionally, we use an RA design by assuming there is no treatment-covariate interaction effect where the slopes are equal; i.e., the lines A and B in the Figure should be parallel.
- However, if there is an interaction between treatment and covariate, that's anther reason to consider CARA design besides the ethical reason. In this case, the RA design cannot detect the differences of treatment effects since it assumes no interaction between covariates and treatments.

Covariate-Adjustment - III

- Furthermore, the method with RA design will make incorrect treatment allocation; That is, it can only be correct in one side of population, but wrong in the other side. Thus, in this case, the CARA design should perform better than the RA design.

Multi-Stage Design

- The effective sample size for a clinical trial with adaptive design is usually not available and the multi-stage design is therefore an adequate choice for making efficient and valid statistical inference.
- A multi-stage procedure is proposed for estimating the treatment effect under a covariate-adjusted response-adaptive design.

Treatment Allocation in a Sequential CARA Design

- Our goal is to estimate the treatment effects under such a CARA design in a clinical trial such that the estimates satisfy a prescribed precision and the number of subjects allocated to the superior treatment can be maximized.
- To balance the ethical consideration and the efficiency of the estimate, we adopt and modify the idea of Bandyopadhyay et al.(2007) by using an utility function and varying the parameters sequentially in different stages depending on the precision of the estimate, respectively.

Confidence Ellipsoid & Stopping Rule - Sequential Design

- Define $R_\delta = \{\theta \in \Theta : n(\hat{\theta} - \theta)^T V^{-1}(\hat{\theta} - \theta) \leq C_\alpha^2\}$, where C_α^2 is the constant such that $P(\chi^2(p \times K) \geq C_\alpha^2) \leq \alpha$.
- If we require that the maximum axis of R_δ ($\delta > 0$) is no larger than 2δ, then the minimum sample size to achieve this goal is

$$n \geq C_\alpha^2 \Lambda_{\max}(V)/\delta^2. \tag{1}$$

- Replacing the unknown V in Equation (1) by its estimate $\hat{V}$ (to be defined later), it suggests a stopping rule to construct such a fixed size confidence ellipsoid:

$$\tau_\delta = \inf\{n \geq n_0 : n \geq C_\alpha^2 \Lambda_{\max}(\hat{V})/\delta^2\}, \tag{2}$$

  where $n_0 \geq Km_0$ is the minimum initial sample size and m_0 is the initial sample size for each treatment.
- Let $\hat{R}_\delta = \{\theta \in \Theta : n(\hat{\theta} - \theta)^T \hat{V}^{-1}(\hat{\theta} - \theta) \leq C_\alpha^2\}$, then $\lim_{n\to\infty} P(\theta \in \hat{R}_\delta) = 1 - \alpha$.

Subset of Parameters - Sequential Design

Let H be a $p \times h$ matrix that specifies the contrasts with $0 < \text{Rank}(H) = h \leq p$ and $\gamma = H'\theta$.

- Let

$$R_{\delta_\gamma} = \{\gamma \in R^h : n(\hat{\gamma} - \gamma)' V_\gamma^{-1} (\hat{\gamma} - \gamma) \leq C_{\alpha,\gamma}^2\}. \tag{3}$$

- Then the optimal sample size and its corresponding stopping time are

$$n_{\gamma,opt} = \text{ first } n \text{ such that } n \geq \frac{C_{\alpha,\gamma}^2 \Lambda_{\max}(V_\gamma)}{\delta_\gamma^2} \tag{4}$$

and

$$\tau_{\delta_\gamma} = \inf\{n \geq n_0 : n \geq \frac{C_{\alpha,\gamma}^2 \Lambda_{\max}(\hat{V}_\gamma)}{\delta_\gamma^2}\}. \tag{5}$$

Confidence Ellipsoid & Stopping Rules - Multi-Stage Design

- Plugging in the estimate of V based on the initial sample size, say $\hat{V}_{n_0}$, we now have an estimate of sample size τ_1

$$\tau_1 \equiv \tau_{1,\delta} = \inf\{n \geq n_0 : n \geq \frac{C_\alpha^2 \Lambda_{\max}(\hat{V}_{n_0})}{\delta^2}\}$$

- Then we sample additional $r \cdot (\tau_1 - n_0)$ subjects and allocate them based on previous estimate $\hat{\theta}_{n_0}$ according to the allocation rule.
- If $r < 1$, we sample a fraction of the additional samples. Then we can re-estimate the sample size based on the new sample size τ_1;

$$\tau_2 \equiv \tau_{2,\delta} = \inf\{n \geq \tau_1 : n \geq \frac{C_\alpha^2 \Lambda_{\max}(\hat{V}_{\tau_1})}{\delta^2}\}.$$

- If we consider three-stage procedure, then collect $[\tau_2 - \tau_1]^+$ new samples based on the allocation rule and its related parameters.

Subset of Parameters - Multi-Stage Design

Let H be a $p \times h$ matrix that specifies the contrasts with $0 < \text{Rank}(H) = h \leq p$ and $\gamma = H'\theta$.

- Let confidence ellipsoid and the optimal sample size are

$$R_{\delta_\gamma} = \{\gamma \in R^h : n(\hat{\gamma} - \gamma)' V_\gamma^{-1} (\hat{\gamma} - \gamma) \leq C_{\alpha,\gamma}^2\} \text{ and} \tag{6}$$

$$n_{\gamma,opt} = \text{ first } n \text{ such that } n \geq \frac{C_{\alpha,\gamma}^2 \Lambda_{\max}(V_\gamma)}{\delta_\gamma^2}. \tag{7}$$

- Then the stopping times are

$$\tau_1 \equiv \tau_{1,\delta_\gamma} = \inf\{n \geq n_0 : n \geq \frac{C_{\alpha,\gamma}^2 \Lambda_{\max}(\hat{V}_{n_0,\gamma})}{\delta_\gamma^2}\} \text{ and} \tag{8}$$

$$\tau_2 \equiv \tau_{2,\delta_\gamma} = \inf\{n \geq \tau_1 : n \geq \frac{C_{\alpha,\gamma}^2 \Lambda_{\max}(\hat{V}_{\tau_1,\gamma})}{\delta_\gamma^2}\}. \tag{9}$$

Utility Function - I

Utility function for K treatments is defined as

$$U(p) = \log|\hat{I}_{n+1}| - \eta\left\{\sum_{k=1}^{K} p_k \log\left(\frac{p_k}{\pi_k(\hat{\theta},\xi)}\right)\right\}, \qquad (10)$$

where $\pi_k(\hat{\theta},\xi)$ is the estimate of $\pi_k(\theta,\xi)$ denoting the estimate of the allocation probability for treatment k upto current stage n.

- For given ξ and the current estimate of θ, the optimal allocation rule is to find the vector of probabilities $p = (p_1,\ldots,p_K)$ that maximize the utility function above. That is the design at the $(n+1)$th stage is to allocate the $(n+1)$th subject to the treatment that maximizes the utility function.

Utility Function - II

- In the utility function, the first term is in log *n* scale, which is log determinant of the information matrix. If $\eta = 0$, then the new subject is selected to maximize the Fisher information matrix.
- If η goes to ∞, then the optimal value of *p* is to maximize the relative entropy function – the second term of (10)
- Hence, the parameter η can be used to adjust the ethical and efficiency balance. Here we adopt the idea of utility function to balance the needs for estimation precision of treatment effects and the ethical consideration. It leads to the (locally) D-optimal design.

Selection of Sequentially Varying T_n and η_n

The second term in the utility function has $\pi_k(\hat{\theta}, \xi)$. Modifying the utility function by Bandyopadhyay et al. (2007), $\pi_k(\hat{\theta}, \xi)$ can be defined as follows with $K = 2$ for the illustration purpose.

$$\pi_1(\hat{\theta}, \xi) = J\left(\frac{\xi'\hat{\theta}_1 - \xi'\hat{\theta}_2}{T_n}\right) \quad \text{and} \quad \pi_2(\hat{\theta}, \xi) = 1 - \pi_1(\hat{\theta}, \xi),$$

where $J(t)$ can be any symmetric function.

- $\pi_k(\hat{\theta}, \xi)$ largely depends on T_n. T_n and η can be random and depend on the variance of parameter estimates, which can be a function of standard deviation of estimate.

Simulation Setup : Application to Logistic Models

- The purpose of the numerical study is to take a look at the performance of the estimate of treatment effect and the allocation of subjects.
- Assume logistic models with binary responses, treatments A and B and one continuous covariate X.
- Assume equal intercepts for both treatments $(\alpha_A, \alpha_B) = (0.1, 0.1)$ and regression coefficients $(\beta_A, \beta_B) = (-1, 1)$.
- Covariate is generated from mixed normal distribution with means 2 & $-$ 2 and equal variance 1 with respective probability 0.5.
- Since the treatment effect is defined as a function of differences of intercepts and regression coefficients between the two treatments, we apply the stopping rule for the contrasts of parameters, $\gamma = H'\theta$, where

$$H' = \begin{pmatrix} 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{pmatrix} \quad \text{and} \quad \theta = (\alpha_A, \alpha_B, \theta_A, \theta_B)'.$$

Simulation Results : RA vs. CARA Designs - 2-Stage Sampling

Table: 2-stage 95% confidence interval estimation by RA design with $\delta = 0.3$. T_{0V} and η_V indicate whether T_0 and η vary or not directly or inversely, respectively, proportional to standard deviation of treatment effect for new covariate. Results by CARA design is given in parenthesis.

$m0$	T_0	η	Variation		Stopping Time		Coverage Probability	Correct Allocation Probability
			T_{0V}	η_V	Mean	Standard Deviation		
15	1.0	0.0	N	N	30 (94)	2 (43)	1.00 (0.98, 0.99)	0.56 (0.47)
15	1.0	0.0	Y	N	30 (90)	0 (39)	1.00 (0.98, 0.99)	0.97 (0.46)
15	1.0	0.1	N	N	30 (93)	1 (37)	1.00 (0.99, 0.99)	0.50 (0.91)
15	1.0	0.1	N	Y	30 (90)	0 (42)	1.00 (0.98, 0.99)	0.40 (0.90)
15	1.0	0.1	Y	N	30 (89)	1 (36)	0.98 (0.98, 0.98)	0.67 (0.91)
15	1.0	0.1	Y	Y	30 (92)	1 (39)	1.00 (0.99, 0.99)	0.33 (0.89)
15	1.0	1.0	N	N	30 (92)	0 (42)	1.00 (0.98, 0.98)	. (0.92)
15	1.0	1.0	N	Y	30 (93)	1 (40)	1.00 (0.98, 0.99)	0.64 (0.92)
15	1.0	1.0	Y	N	30 (92)	0 (39)	1.00 (0.98, 0.99)	0.63 (0.93)
15	1.0	1.0	Y	Y	30 (92)	2 (53)	0.98 (0.98, 0.98)	0.56 (0.93)

Simulation Results : RA vs. CARA Designs - 3-Stage Sampling

Table: 3-stage 95% confidence interval estimation by RA design with $\delta = 0.3$. T_{0V} and η_V indicate whether T_0 and η vary or not directly or inversely, respectively, proportional to standard deviation of treatment effect for new covariate. Results by CARA design is given in parenthesis.

$m0$	T_0	η	Variation		Stopping Time		Coverage Probability	Correct Allocation Probability
			T_{0V}	η_V	Mean	Standard Deviation		
15	1.0	0.0	N	N	30 (66)	2 (35)	1.00 (0.97, 0.97)	0.35 (0.44)
15	1.0	0.0	Y	N	30 (65)	1 (21)	1.00 (0.96, 0.97)	0.49 (0.46)
15	1.0	0.1	N	N	30 (68)	2 (25)	0.98 (0.98, 0.99)	0.43 (0.90)
15	1.0	0.1	N	Y	30 (67)	0 (22)	1.00 (0.97, 0.98)	0.67 (0.90)
15	1.0	0.1	Y	N	30 (67)	0 (18)	1.00 (0.98, 0.99)	. (0.91)
15	1.0	0.1	Y	Y	30 (67)	1 (22)	1.00 (0.99, 0.99)	0.41 (0.89)
15	1.0	1.0	N	N	30 (71)	1 (39)	1.00 (0.97, 0.98)	0.30 (0.92)
15	1.0	1.0	N	Y	30 (66)	1 (18)	1.00 (0.97, 0.98)	0.58 (0.92)
15	1.0	1.0	Y	N	30 (70)	0 (23)	1.00 (0.96, 0.97)	0.67 (0.93)
15	1.0	1.0	Y	Y	30 (69)	0 (23)	1.00 (0.97, 0.98)	0.67 (0.93)

Simulation Results : RA vs. CARA Designs - Sequential Sampling

Table: Sequential 95% confidence interval estimation by RA design with $\delta = 0.3$. T_{0V} and η_V indicate whether T_0 and η vary or not directly or inversely, respectively, proportional to standard deviation of treatment effect for new covariate. Results by CARA design is given in parenthesis.

$m0$	T_0	η	Variation		Stopping Time		Coverage Probability	Correct Allocation Probability
			T_{0V}	η_V	Mean	Standard Deviation		
15	1.0	0.0	N	N	30(52)	0(9)	1.00 (0.97, 0.96)	0.50 (0.50)
15	1.0	0.0	Y	N	30(52)	1(10)	1.00 (0.96, 0.97)	0.47 (0.43)
15	1.0	0.1	N	N	30(56)	0(11)	1.00 (0.98, 0.98)	0.43 (0.91)
15	1.0	0.1	N	Y	30(55)	2(13)	1.00 (0.94, 0.98)	0.31 (0.90)
15	1.0	0.1	Y	N	30(55)	0(11)	1.00 (0.98, 0.98)	0.36 (0.92)
15	1.0	0.1	Y	Y	30(53)	0(12)	1.00 (0.94, 0.96)	0.38 (0.91)
15	1.0	1.0	N	N	30(54)	1(11)	1.00 (0.96, 0.96)	0.42 (0.91)
15	1.0	1.0	N	Y	30(58)	1(18)	1.00 (0.96, 0.96)	0.58 (0.93)
15	1.0	1.0	Y	N	30(57)	0(12)	1.00 (0.94, 0.94)	0.23 (0.95)
15	1.0	1.0	Y	Y	30(56)	0(10)	1.00 (0.98, 0.98)	0.30 (0.95)

Simulation Findings: RA vs. CARA Designs & Multiple-Stage vs. Sequential Designs

- When significant covariate adjustment is ignored, both multiple-stage and sequential designs stops early and correct treatment allocation can not be considered.
- When significant covariate adjustment is considered, both multiple-stage and sequential designs stops later and correct treatment allocation is very high when η is non-zero.
- Stopping times for 3-stage designs are earlier than 2-stage designs but with similar correct treatment allocation due to estimating coefficients once more.
- Stopping times for sequential sampling are earlier than multiple-stage designs but with similar correct treatment allocation due to estimating coefficients for every observation.

Simulation Findings - Multi-stage Sampling in CARA Designs : Stopping Time & Coverage Probability

- As η gets larger, stopping time doesn't get larger much due to large variation.
- Varying η doesn't give significantly different results compared to fixed η due to large stopping times.
- Stopping time is very large and unstable, when initial sample size m_0 is small such as 5, due to unstable regression coefficient estimates at the beginning stage.
- As initial sample size gets larger, stopping time gets earlier and its variation gets smaller.
- Coverage probabilities of treatment differences are mostly upward biased close to 1 due to many samples.

Simulation Findings - Multi-stage Sampling in CARA Designs : Correct Treatment Allocation

- As η gets larger, correct treatment allocation gets better with similar performance for positive η. This confirms that η plays a role as a tuning parameter for ethical consideration and small nonzero η is sufficient for correct allocation.
- Varying T_0 in stages depending on treatment effect variation doesn't yield sensitive changes in correct allocation due to large sample sizes.

Summary

- We propose a multiple-stage estimation scheme for the CARA design in clinical trials.
- We allow our allocation function and design to depend on not only the previous collected information and multi-stage estimates of treatment effects, but also the covariate information of individual subjects.
- The proposed stopping time is based on the martingale estimating equation, which is different from the classical sequential methods that usually rely on independent observations.
- The most important feature of the proposed stopping rule is that it guarantees the precision of the estimates of treatment effects, which is novel and has never been proposed in other CARA related literature.
- Our multi-stage procedure was illustrated by applying logistic models and can be applied to other generalized linear models.