Covariate-Adjusted Response Adaptive Designs for Semiparametric Survival Models

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Outline

Adaptive Designs in Clinical Trials

FDA Definition: Clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial.
ICH E20 Draft Guidelines : The term prospectively planned means that the potential trial adaptations are pre-specified in the clinical trial protocol prior to initiation of the trial.
Classification of adaptive designs

Adaptation Rules	**ICH E20 Terminology**
Adaptive Randomization Rule	Adaptation to Participant Allocation
Adaptive Sampling Rule	Sample Size Adaptation
Adaptive Stopping Rule	Early Trial Stopping
Adaptive Enrichment Rule	Adaptive Population Selection

Adaptive Randomization Rule: $\pi_{m+1,k} = Pr(\delta_{m+1} = T_k | \mathcal{D}_m)$.

Efron's Biased Coin Design and the Way Forward

Problem : Compromise between a perfectly balanced design and CRD
Efron's BCD(p) : If a new patient arrives at a stage when there are D Treatments more than Controls

- Assign treatment with p = 2/3, if D < 0
- Assign treatment with p = 1/2, if D = 0
- Assign treatment with p = 1/3, if D > 0

Limitations :

- It does not include balance over covariates.
- Efron (1980) is only limited to 2 covariates.
- Cannot work with continuous covariates and interactions.

Adaptive Randomization Methods :

1. **Restricted Randomization:** $\pi_{m+1,k} = Pr(\delta_{m+1} = T_k | \mathcal{X}_m)$.
2. **Minimization:** $\pi_{m+1,k} = Pr(\delta_{m+1} = T_k | \mathcal{X}_m, \mathcal{Z}_m, \mathcal{Z}_{m+1})$.
3. **RAR :** $\pi_{m+1,k} = Pr(\delta_{m+1} = T_k | \mathcal{X}_m, \mathcal{Y}_m)$.

The Motivation

Covariate-Adjusted Response Adaptive (CARA) Design

$\pi_{m+1,k} = Pr(\delta_{m+1} = T_k | \mathcal{X}_m, \mathcal{Y}_m, \mathcal{Z}_m, \mathcal{Z}_{m+1}).$

- The range of methods for CARA designs (Sverdlov *et.al* (2013), Mukherjee *et.al* (2023)) are limited in real-life survival trials.
- According to Sverdlov *et.al* (2013), even when the true distribution of the survival endpoints are not exponential, the proposed designs provide valid statistical inference provided the final analysis is done using the correct Accelerated Failure Time (AFT) Models.
- In real oncology survival trials primary analysis is infrequently analyzed using an AFT model
- Semiparametric CARA designs have been developed using the proportional hazard assumption between treatment arms.
- **ICH E20 :** "A RAR design would more likely show a false positive treatment effect if earlier-enrolled participants are more likely to be assigned to control than later-enrolled participants".

The Optimal Approach Towards Deriving a Target Allocation Proportion

Ethics

- Let $\alpha_k(t|\mathbf{z})$ be a measure of treatment failure at time t for an average patient with covariate $\mathbf{z}$ assigned to treatment k.
- Overall penalty of ethic can be $H(t|\mathbf{z}) = n_A\alpha_A(t|\mathbf{z}) + n_B\alpha_B(t|\mathbf{z})$.
- Some sensible choices of $\alpha_k(t|\mathbf{z})$ as per the experiment's needs can be;
  - $\alpha_k(t|\mathbf{z}) = 1$ for minimizing the trial size $H(t|\mathbf{z}) = n_A + n_B$,
  - or $\alpha_k(t|\mathbf{z}) = h_k(t|\mathbf{z})$ for minimizing the total hazards $H(t|\mathbf{z}) = n_A h_A(t|\mathbf{z}) + n_B h_B(t|\mathbf{z})$.

Efficiency

- Define an indicative measure of difference in treatment effect in the presence of covariates, .

$$\mathbf{z}^T\{\mathbf{z}^T J_A^{-1}(\beta_A)\mathbf{z}\}\mathbf{z}e^{2\beta_A^T\mathbf{z}} + \mathbf{z}^T\{\mathbf{z}^T J_B^{-1}(\beta_B)\mathbf{z}\}\mathbf{z}e^{2\beta_B^T\mathbf{z}} = \kappa > 0,$$

Derived CARA Target Allocation Proportions

Minimizing Trial Size (Neyman Allocation Proportion)

$$\pi^S_{A1}(\beta_A, \beta_B, \mathbf{z}) = \frac{\sqrt{\epsilon_B(\mathbf{z};\beta_B)Va_A\{\widehat{h}_A(t|\mathbf{z})\}}}{\sqrt{\epsilon_B(\mathbf{z};\beta_B)Va_A\{\widehat{h}_A(t|\mathbf{z})\}} + \sqrt{\epsilon_A(\mathbf{z};\beta_A)Va_B\{\widehat{h}_B(t|\mathbf{z})\}}}. \quad (1)$$

Minimizing Total Hazard

$$\pi^S_{A2}(\beta_A, \beta_B, \mathbf{z}) = \frac{\sqrt{\epsilon_B(\mathbf{z};\beta_B)h_B(t|\mathbf{z})Va_A\{\widehat{h}_A(t|\mathbf{z})\}}}{(\sqrt{\epsilon_B(\mathbf{z};\beta_B)h_B(t|\mathbf{z})Va_A\{\widehat{h}_A(t|\mathbf{z})\}} + \sqrt{\epsilon_A(\mathbf{z};\beta_A)h_A(t|\mathbf{z})Va_B\{\widehat{h}_B(t|\mathbf{z})\}})}. \quad (2)$$

CARA Randomization Methods

Covariate-Adjusted Doubly Adaptive Biased Coin Design

$$j_{m+1}\left\{\frac{N_A(m)}{m},\hat{\pi}_m,\hat{\rho}_{Am}\right\} = \frac{\hat{\pi}_m\{\hat{\rho}_{Am}/\frac{N_A(m)}{m}\}^{\alpha}}{[\hat{\pi}_m\{\hat{\rho}_{Am}/\frac{N_A(m)}{m}\}^{\alpha}+(1-\hat{\pi}_m)\{(1-\hat{\rho}_{Am})/(1-\frac{N_A(m)}{m})\}^{\alpha}]} \quad (3)$$

when, $0<\frac{N_A(m)}{m}<1$.

For $\frac{N_A(m)}{m}=0, j_{m+1}\left\{\frac{N_A(m)}{m},\hat{\pi}_m,\hat{\rho}_{Am}\right\}=1$ and for $\frac{N_A(m)}{m}=1, j_{m+1}\left\{\frac{N_A(m)}{m},\hat{\pi}_m,\hat{\rho}_{Am}\right\}=0$.

Weighted Optimality Approach

$$\pi_A^S=\frac{p_A\{1+d(A,\beta_A,\mathbf{z}_{m+1})\}^{1/\eta}}{p_A\{1+d(A,\beta_A,\mathbf{z}_{m+1})\}^{1/\eta}+p_B\{1+d(B,\beta_B,\mathbf{z}_{m+1})\}^{1/\eta}}. \quad (4)$$

Covariate-Adjusted Efficient Randomized Adaptive Design (Mukherjee *et.al* 2023)

$$j_{m+1}\left\{\frac{N_A(m)}{m}, \hat{\pi}_m, \hat{\rho}_{Am}\right\} = \begin{cases} \alpha'\hat{\pi}_m & \text{if } \frac{N_A(m)}{m} > \hat{\rho}_{Am}, \\ \hat{\pi}_m & \text{if } \frac{N_A(m)}{m} = \hat{\rho}_{Am}, \\ 1-\alpha'(1-\hat{\pi}_m) & \text{if } \frac{N_A(m)}{m} < \hat{\rho}_{Am}, \end{cases} \tag{5}$$

$0 \leq \alpha' < 1$ is a constant that reflects the degree of randomization. A value of α' between 0.4 and 0.7 gives a family of CARA designs that are fully randomized and also asymptotically first-order efficient.

Simulation Study

- A covariate structure of three independent covariates generated: (Gender [Bernoulli, p = 0.381], Age [Uniform (40,80)], Cholestrol Level [Normal (200,400)]) following Rosenberger, Vidyashankar and Agarwal (2001).
- 800 patients have been considered to be failing due to a single cause.
- 110 (burn-in period) patients were initially equally randomized by Efron's (1971) method before adaptation.
- Arrival pattern here is simulated from a uniform (0,365), trial duration, D = 582 days.
- Generalized Type I Right Censoring times simulated from a uniform (0,582).
- Survival Times simulated from a Weibull model with scale parameter ($\mu_k(\mathbf{z})$) and the shape parameter (γ) to be $\mu_k(\mathbf{z})$ =exp($\beta_k^T \mathbf{z}$) and 2.08 respectively.
- The natural log transformed HR for a Weibull proportional hazard model represent the covariate-adjusted treatment effect, and is given by,

$$\log(HR) = [\gamma_B \log\{\hat{\mu}_B(\mathbf{z})\} - \gamma_A \log\{\hat{\mu}_A(\mathbf{z})\}],$$

- The theoretical median survival time ratios are 1 for Neutral Model, 36.88 for Positive Model and 0.027 for the Negative Model.

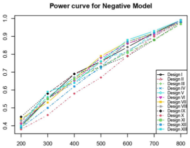
		Covariate effects					Target allocations	
Model	Treatment	β_0	β_1	β_2	β_3	log(HR)	$E(\pi^*_{A1})$	$E(\pi^*_{A2})$
Neutral	A	1.896	0.810	0.038	0.001	0	0.50	0.50
	B	1.896	0.810	0.038	0.001		0.50	0.50
Positive	A	5.5042	0.810	0.038	0.001	−7.419	0.62	0.55
	B	1.896	0.810	0.038	0.001		0.38	0.45
Negative	A	−1.7112	0.810	0.038	0.001	7.487	0.39	0.46
	B	1.896	0.810	0.038	0.001		0.61	0.54

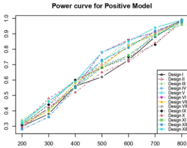
Competing Designs

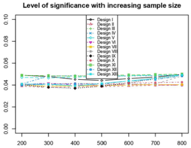
Designs	Competing Randomization Procedures
I	Completely Randomized Design (CRD)
II	Efron's Biased Coin Design with p = (2/3)
III	Pocock Simon Design with p = (3/4)
IV	CARA CADBCD with(1) as the Target
V	CARA CADBCD with(2) as the Target
VI	CARA CAERADE with(1) as the Target
VII	CARA CAERADE with(2) as the Target
VIII	CARA design based on (4) with $\eta = 0$
IX	CARA design based on (4) with $\eta = 0.1$
X	CARA design based on (4) with $\eta = 0.25$
XI	CARA design based on (4) with $\eta = \infty$
XII	RAR DBCD with(2) as the Target
XIII	RAR ERADE with(2) as the Target

Simulation Results

Model	Designs	N_A/n (SE)	N_AM–N_BM	N_AF–N_BF	Events	Type I error
Neutral	I	0.50 (0.018)	200–200	200–200	650	0.05
	II	0.50 (0.001)	200–200	200–200	650	0.04
	III	0.50 (0.009)	200–200	200–200	649	0.05
	IV	0.50 (0.014)	200–200	200–200	649	0.05
	V	0.50 (0.020)	200–200	200–200	650	0.05
	VI	0.50 (0.012)	200–200	200–200	650	0.04
	VII	0.50 (0.013)	200–200	200–200	650	0.04
	VIII	0.50 (0.013)	200–200	200–200	650	0.05
	IX	0.50 (0.016)	200–200	200–200	650	0.05
	X	0.50 (0.017)	200–200	200–200	650	0.04
	XI	0.50 (0.020)	200–200	200–200	650	0.05
	XII	0.50 (0.021)	200–200	200–200	650	0.05
	XIII	0.50 (0.015)	200–200	200–200	650	0.05
Models	**Designs**	**N_A/n (SE)**	**N_AM–N_BM**	**N_AF–N_BF**	**Events**	**Power**
Negative	I	0.50 (0.018)	200–200	200–200	334	0.99
	II	0.50 (0.001)	200–200	200–200	334	0.99
	III	0.50 (0.009)	200–200	200–200	334	0.99
	IV	0.45 (0.015)	179–221	181–219	332	0.99
	V	0.39 (0.020)	157–243	155–245	330	0.98
	VI	0.48 (0.013)	191–209	193–207	333	0.99
	VII	0.38 (0.018)	151–249	153–247	330	0.98
	VIII	0.48 (0.013)	192–208	192–208	333	0.99
	IX	0.45 (0.015)	182–218	178–222	332	0.98
	X	0.44 (0.016)	176–224	176–224	332	0.98
	XI	0.42 (0.028)	167–233	169–231	330	0.97
	XII	0.39 (0.019)	156–244	156–244	330	0.98
	XIII	0.40 (0.017)	160–240	160–240	330	0.99







Re-design a Survival Trial for Colorectal Cancer

- A total of 572 eligible patients were randomized in a 1:1 ratio cetuximab plus best supportive care (treatment A) and best supportive care alone (treatment B) for a period of 21 months based on data from Karapetis et al(2008) D = 27 months.
- The primary endpoint of this trial was overall survival (OS).
- The model-adjusted median OS was 6.1 months for treatment A versus 4.6 months for treatment B.
- The degree and the direction of the effect of cetuximab, differed between the levels of Kras mutation status.
- Patients with wild-type Kras tumours benefited from cetuximab (median overall survival 9.5 versus. 4.8 months; hazard ratio for death 0.55), whereas patients with a colorectal tumour bearing mutated K ras did not benefit from cetuximab (median overall survival 4.6 versus. 4.5 months; hazard ratio for death 0.98).
- A simulation study with 10,000 replications was conducted, to compare the CARA designs with the traditional balanced randomization procedure.
- Burn-in sample size : 110 patients using Efron's (1971) Biased Coin Design.

Designs	I	II	V	VII	VIII	XI	XIII
N_A/n (SE)	0.50(0.012)	0.50(0.001)	0.65(0.014)	0.65(0.011)	0.62(0.011)	0.68(0.025)	0.65(0.012)
N_{A-}–N_{B-}	171-171	146-146	248-102	242-104	233-110	257-102	186-100
N_{A+}–N_{B+}	115-115	140-140	124-98	130-96	122-107	132-81	186-100
Events	377	377	357	356	361	355	365
Power	0.99	0.99	0.98	0.99	0.99	0.96	0.99

SE: standard error.

Discussion

- The proposed CARA designs provide a robust strategy of designing a pivotal trial, where the ethical advantage of patient benefit can be achieved without compromising much on the validity of the statistical inference.
- Unlike the usual response-adaptive method, this provides a patient centric approach towards the development of personalized medicine as it considers the benefit of the patients for their individual covariate profile.

Publication: Statistical Methods in Medical Research

Mukherjee A, Jana S, Coad S. "Covariate-adjusted response-adaptive designs for semiparametric survival models."*Statistical Methods in Medical Research.* 2024;0(0). doi:10.1177/09622802241287704

- Operational challenges exists while implementing such adaptive randomization approach to a pivotal survival trial and one may not achieve substantial practical benefit in implementing such novel strategy for a two-arm survival trial.
- Such innovative methods are being used as the FDA complex innovative design pilot program with multiple arm trials and other Master Protocols.

Future Research

- This approach can serve as a steppingstone to enhance it into a multi-arm approach with studies handling time-to-event outcomes as their primary endpoint in the Master Protocol with the flexibility of adding and dropping arms during the trial process.
- Many clinical trials handle endpoints with competing events as their primary or key secondary endpoints.
- Such semi-parametric approach should be enhanced for trials with competing risk where patients are allocated to the better treatment arm to minimize the number of events to the main cause.

Publication: Statistics in Biopharmaceutical Research

Mukherjee, A., Sayantee, J. (2025). "Covariate-Adjusted Response Adaptive Designs for Competing Risk Survival Models."*Statistics in Biopharmaceutical Research*, 1–24. https://doi.org/10.1080/19466315.2024.2446233

- This approach can serve as a steppingstone to enhance it into a multi-arm approach with studies handling time-to-event outcomes as their primary endpoint in the Master Protocol with the flexibility of adding and dropping arms during the trial process.
- Ongoing work as a part of the ASA Randomization Working Group on developing CARA designs for Multi-arm Multi-Stage (MAMS) trials with co-primary endpoints. {Collaborators : Ayon Mukherjee (Eli Lilly), Alex Sverdlov (Novartis), Hongjian Zhu (Systimmune) and Rajenki Das (University of Cambridge)}

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