Covariate-Adjusted Response-Adaptive Randomization Designs for Phase III Survival Trials

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Outline

1. Introduction

2. CARA Randomization for Survival Trials
   - Proposed designs
   - Operating characteristics
   - Comparison with the balanced randomization design

3. Discussion
Aspects of a Clinical Trial Design

**Statistical:**
- Randomization
- Blinding
- Balance
- Precision in estimation
- Power

**Logistical:**
- Study cost
- Study duration

**Ethical:**
- Overall Safety
- Min. treatment failures
- Min. “adverse” experience
Aspects of a Clinical Trial Design

In our presentation it is assumed that multiple objectives are pursued, including:

- **Randomized experiment** (to mitigate experimental biases)
- **Maximizing inferential aspects** (e.g., power of the hypothesis test)
- **Maximizing “ethical” aspects**
  - minimizing expected total hazard in the study
  - minimizing the number of inferior treatment assignments
Covariates in the Design of a Clinical Trial

Why adjust randomization for covariates?
- In most phase III comparative trials, study subjects are heterogeneous
- Important baseline covariates may have strong impact on responses to a model

Classes of randomization procedures that incorporate covariate data:
- Stratified randomization
- Covariate-adaptive randomization
- Covariate-adjusted response-adaptive randomization
Randomization Procedures that Account for Covariates

- **1970**: Efron’s BCD
- **1971**: Stratification (M. Zelen)
- **1974**: „Minimization“ (Taves, Pocock & Simon)
- **1974-75**: Wei’s UD
- **1978**: “Minimization” (Taves, Pocock & Simon)
- **1974**: Stratification (M. Zelen)
- **1971**: Efron’s BCD
- **1980**: Atkinson’s BCD
- **1982**: Smith’s BCD
- **1984**: Smith’s BCD
- **1990**: Bayesian biased coin (Ball et al.)
- **1993**: Bayesian biased coin (Ball et al.)
- **2000**: Treatment Effect Mappings (Rosenberger et al.; Bandyopadhyay & Biswas)
- **2001**: Treatment Effect Mappings (Rosenberger et al.; Bandyopadhyay & Biswas)
- **2005-06**: Bayesian CARA randomization (Thall & Wathen; Cheung et al.)
- **2007**: General CARA framework (L-X Zhang et al.)
- **2010**: Ongoing active research

**Covariate-adjusted response-adaptive (CARA) randomization**

**Optimal designs for linear models**

**Stratified randomization**

**Covariate-adaptive (CA) randomization**
CARA Randomization

- Two treatments: A and B
- n patients enter the trial sequentially and must be randomized to either A or B
- Response $Y_k \sim f_k(y_k|\theta_k, z)$, where $k = A, B$
- Let $T_m, Y_m, Z_m$ denote, respectively, the history of $m$ treatment assignments, responses, and covariates
- Patient ($m + 1$) enters the trial with covariate vector $z_{m+1}$ and is randomized to A with probability

$$\phi_{m+1} = \Pr(T_{m+1} = A|T_m, Y_m, Z_m, z_{m+1}), \quad m \geq 2m_0$$

The main purpose of CARA randomization is to balance the competing objectives of allocating greater number of study patients to the superior treatment, achieving high statistical efficiency in estimating treatment effects, and maintaining randomization.
CARA Randomization for Survival Trials

1. Look at the history preceding subject 7:

<table>
<thead>
<tr>
<th>Subject</th>
<th>T</th>
<th>Y</th>
<th>Z₁, Z₂, ..., Z₉</th>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>A</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>B</td>
<td>4*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>B</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Estimate treatment effects (A and B) based on data accrued thus far.

3. Assign the new patient to treatment A with probability conditional on the accrued data, and the covariate vector of the patient:

\[ \phi_7 = \Pr(T_7 = A | T_6, Y_6, Z_1, ..., Z_6, Z_7) \]

QUESTION: How to select \( \phi_7 \)?
CARA Randomization for Survival Trials

Existing work:


Objectives

1. Propose new CARA randomization procedures for survival intervention trials with exponential regression model with treatment-covariate interactions

2. Simulate the operating characteristics of the proposed procedures and compare them with the traditional balanced randomization design in terms of
   - Power and Type I error
   - Variability of allocation proportions
   - Number of inferior/superior treatment assignments
   - Number of deaths and total hazard
Consider a survival intervention trial comparing two treatments, $A$ and $B$.

- Trial has a fixed duration $D$ and a fixed recruitment period $R < D$
- Patient arrival times are uniform over $(0, R)$
- $T_k =$ survival time, exponential with mean $\lambda_k = \exp(\theta^\prime_k z), \, k = A, B$
- $C =$ censoring time, uniform over $(0, D)$
- Observed response $t_k = \min(T_k, C, D - R)$ and $\delta_k = 1_{\{t_k = T_k\}}$
- It is assumed that sufficient amount (60% or more) of response data is accrued during the recruitment phase to apply adaptation for responses
Proposed CARA Design I

- **Step 1.** Derive an optimal allocation for a model without covariates (e.g. Zhang and Rosenberger, 2007):

  \[
  \frac{n_A}{n_B} = \frac{\sqrt{\lambda^3_A / \epsilon_A}}{\sqrt{\lambda^3_B / \epsilon_B}}.
  \]

- **Step 2.** Use covariate-adjusted version of the optimal allocation as the target:

  \[
  \pi_A(\theta_A, \theta_B, z) = \frac{\sqrt{\lambda^3_A(z) / \epsilon_A(z)}}{\sqrt{\lambda^3_A(z) / \epsilon_A(z)} + \sqrt{\lambda^3_B(z) / \epsilon_B(z)}},
  \]

  where \( \lambda_k(z) = \exp(\theta'_k z) \) and \( \epsilon_k(z) = \Pr(T_k \leq C|\theta_k, z) \).

- **Step 3.** Based on data from \( m \) patients, obtain \((\hat{\theta}_{m,A}, \hat{\theta}_{m,B})\). Then allocate patient \((m + 1)\) with covariate \( z_{m+1} \) to treatment \( A \) with probability

  \[
  \phi_{m+1} = \pi_A(\hat{\theta}_{m,A}, \hat{\theta}_{m,B}, z_{m+1}).
  \]
Proposed CARA Design II

- Assign patient \((m + 1)\) with covariate \(z_{m+1}\) to treatment \(A\) with probability

\[
\phi_{m+1} = \frac{F_k \cdot \left\{ d(A, \hat{\theta}_m, z_{m+1}) \right\}^{1/\gamma}}{\sum_{k=A}^B F_k \cdot \left\{ d(k, \hat{\theta}_m, z_{m+1}) \right\}^{1/\gamma}},
\]

where \(F_A = \{1 + \exp((\hat{\theta}_{m,B} - \hat{\theta}_m, A)'z_{m+1})\}^{-1}\) is the hazard ratio \((B\ vs.\ A)\), \(F_B = 1 - F_A\), and

\[
d(k, \theta_k, z) = z'M_{m,k}^{-1}z\epsilon_k(z)
\]

is the directional derivative of the \(D\)-optimal criterion \(\log|M^{-1}|\).

- \(\gamma = 0 \rightarrow \) most efficient \((D\text{-optimal})\) design
- \(\gamma = \infty \rightarrow \) most “ethical” \((\text{Treatment Effect Mapping})\) design
- \(\gamma = 0.25 \rightarrow \) “tradeoff” design
Simulation Study

- 5 competing randomization procedures
  - Pocock and Simon's procedure (PS)
  - Covariate-adjusted Zhang-Rosenberger optimal target (ZR)
  - “Most ethical” design with $\gamma = \infty$ (TEM)
  - “Most efficient” design with $\gamma = 0$ (eff)
  - “Tradeoff” design with $\gamma = 0.25$ (tradeoff)

- Covariate structure: 3 independent covariates
  - Gender $\sim$ Bernoulli($p = 0.5$)
  - Age $\sim$ Uniform[18, 75]
  - Cholesterol level $\sim$ Normal($\mu = 200, \sigma = 30$)

- Trial as in Zhang and Rosenberger (2007): $R = 1, D = 1.5936$ (a patient recruited at time 0 with mean survival time= 1 has 50% chance of either die or being censored)
Simulation Assumptions

Table: 3 experimental scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Population Mean $A$</th>
<th>Population Mean $B$</th>
<th>Hazard Ratio $B$ vs. $A$</th>
<th>Hazard Ratio $B$ vs. $A$ (Males)</th>
<th>Hazard Ratio $B$ vs. $A$ (Females)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Alternative I</td>
<td>1.00</td>
<td>1.55</td>
<td>0.65</td>
<td>0.35</td>
<td>0.94</td>
</tr>
<tr>
<td>Alternative II</td>
<td>1.00</td>
<td>0.73</td>
<td>1.37</td>
<td>0.75</td>
<td>2.00</td>
</tr>
</tbody>
</table>
Simulation Assumptions

Mean Hazard Ratio B vs. A

- Null case
- Alternative I
- Alternative II

Population: Male, Female

Mean Hazard Ratio B vs. A

- Null case
- Alternative I – Male
- Alternative I – Female
- Alternative II – Male
- Alternative II – Female

Age:

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Simulation Details

- Age and Cholesterol Level are discretized into 2 and 3 levels, respectively, for Pocock-Simon implementation.

- First \( m = 80 \) patients are randomized to treatments using Pocock-Simon’s procedure to accrue data for estimating model parameters.

- Next, patients are assigned to treatment groups using CARA randomization.

- Sample size is chosen empirically such that Pocock-Simon’s procedure results in \( \sim 90\% \) power under a given alternative.

- Priority queue data structures were utilized to account for staggered entries and delayed responses, and a continuous monitoring scheme for updating history of responses was implemented.

- 5,000 replications for each experimental scenario in R.
Simulation Results

Figure: Allocation proportion $N_A(n)/n$
## Simulation Results

**Table:** Number of patients on Treatment A (SD)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>n</th>
<th>(B \text{ vs } A)</th>
<th>HR</th>
<th>PS</th>
<th>ZR</th>
<th>TEM</th>
<th>eff</th>
<th>tradeoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null</td>
<td>200</td>
<td>1.00</td>
<td></td>
<td>100 (1)</td>
<td>100 (6)</td>
<td>100 (6)</td>
<td>100 (4)</td>
<td>100 (5)</td>
</tr>
<tr>
<td>Alternative I†</td>
<td>200</td>
<td>0.65</td>
<td></td>
<td>100 (1)</td>
<td>76 (5)</td>
<td>84 (5)</td>
<td>100 (4)</td>
<td>86 (5)</td>
</tr>
<tr>
<td>Alternative II††</td>
<td>325</td>
<td>1.37</td>
<td></td>
<td>163 (1)</td>
<td>177 (8)</td>
<td>171 (8)</td>
<td>162 (5)</td>
<td>170 (6)</td>
</tr>
</tbody>
</table>

† \(B\) is “superior”  
†† \(A\) is “superior”
Simulation Results

Figure: Average numbers (+SD) of males and females on Treatment A
Simulation Results

**Table:** Average number of males and females on Treatment A (SD)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Gender</th>
<th>((B \text{ vs } A))</th>
<th>PS</th>
<th>ZR</th>
<th>TEM</th>
<th>eff</th>
<th>tradeoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null</td>
<td>Male</td>
<td>1.00</td>
<td>50 (4)</td>
<td>50 (5)</td>
<td>50 (5)</td>
<td>50 (5)</td>
<td>50 (5)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>1.00</td>
<td>50 (4)</td>
<td>50 (5)</td>
<td>50 (5)</td>
<td>50 (5)</td>
<td>50 (5)</td>
</tr>
<tr>
<td>Alternative I</td>
<td>Male</td>
<td>0.35†</td>
<td>50 (4)</td>
<td>28 (4)</td>
<td>35 (4)</td>
<td>52 (5)</td>
<td>38 (4)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.94†</td>
<td>50 (4)</td>
<td>48 (5)</td>
<td>49 (5)</td>
<td>48 (5)</td>
<td>48 (5)</td>
</tr>
<tr>
<td>Alternative II</td>
<td>Male</td>
<td>0.75†</td>
<td>81 (5)</td>
<td>65 (6)</td>
<td>71 (7)</td>
<td>84 (6)</td>
<td>73 (6)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>2.00‡‡</td>
<td>81 (5)</td>
<td>112 (8)</td>
<td>100 (8)</td>
<td>78 (6)</td>
<td>98 (7)</td>
</tr>
</tbody>
</table>

† \(B\) is “superior”
‡‡ \(A\) is “superior”
## Simulation Results

### Table: Type I Error, Power†, and Total Number of Deaths (SD)

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Characteristic</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null</td>
<td>Type I Error</td>
<td>PS</td>
</tr>
<tr>
<td></td>
<td>$D(n)$ (SD)</td>
<td>0.054</td>
</tr>
<tr>
<td>Alternative I</td>
<td>Power</td>
<td>0.928</td>
</tr>
<tr>
<td></td>
<td>$D(n)$ (SD)</td>
<td>87 (7)</td>
</tr>
<tr>
<td>Alternative II</td>
<td>Power</td>
<td>0.882</td>
</tr>
<tr>
<td></td>
<td>$D(n)$ (SD)</td>
<td>177 (9)</td>
</tr>
</tbody>
</table>

† Using test statistic $T = \left( \hat{\theta}_{m,A} - \hat{\theta}_{m,B} \right)' \left( \hat{M}_{m,A}^{-1} + \hat{M}_{m,B}^{-1} \right)^{-1} \left( \hat{\theta}_{m,A} - \hat{\theta}_{m,B} \right)$, which is asymptotically $\chi^2$ with df=$4 - 1$.
Conclusions

Several new CARA randomization designs were proposed

1. The proposed CARA procedures are more ethical than the balanced design:
   - For a trial of \( \geq 200 \) patients, on average, 14 – 16 more patients are allocated to the “superior” treatment with negligible (< 1%) loss in power
   - With treatment-covariate interactions, on average, greater number of patients receive the treatment which is “best” given their covariate profiles
   - Average number of deaths can be reduced with CARA randomization designs

2. Some of the proposed CARA procedures have good inferential properties:
   - Valid statistical inference (nominal Type I error is maintained)
   - ZR procedure is 5% less powerful than the balanced design
   - “Efficient” design is almost identical to the balanced design
   - TEM and “tradeoff” designs are very close to the balanced design in terms of power

3. The proposed designs are more variable than the balanced randomization design
Cautions/Limitations

- CARA randomization is not relevant for long-term survival trials with short recruitment period
- CARA randomization designs rely on the correctly specified parametric model
- Number of covariates must be limited, since m.l.e.’s may converge very slowly due to delayed responses
Current/Future Work

- Other parametric models (Weibull, log-logistic) and semi-parametric (Cox’s proportional hazards) model
- Robustness to model misspecification
- Different censoring schemes
- Time-dependent covariates
- Defining “optimality” given that patient covariate values are unknown in advance
- Bayesian CARA randomization
Some Useful References


