The impact of selection and chronological bias on test decisions in survival analysis

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Motivation: clinical trials

The objective of any clinical trial is to provide an unbiased comparison of the differences between two treatments.

- Rosenberger and Lachin (2016)

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Dealing with bias

- Randomization is necessary to prevent bias
- . . . but not sufficient!

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- **Question**: How to measure bias?

  → Impact on test decision, e.g. type I error probability (ICH E9, 1998)

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Previous research : Continuous outcome

- Proschan (1994)
- Kennes et al. (2011)
- Tamm et al. (2012)
- Langer (2014)

} Selection bias

- Rosenkranz (2011)
- Tamm and Hilgers (2014)

} Chronological bias

- Uschner et al. (2015)

$\rightarrow$ Software tool

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- Uschner et al. (2015) $\rightarrow$ Software tool

Objective

Impact of bias on type I error probability for **time-to-event** trials

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Terminology and assumptions: randomization

- Two-armed randomized controlled trial, total sample size N
- Experimental (E), and control treatment (C)
- $\boldsymbol{t} = (t_1, \ldots, t_N) \in \{0, 1\}^N$ randomization sequence such that

$$t_i = \begin{cases} 0, & \text{if } i\text{th patient is assigned to } C \\ 1, & \text{if } i\text{th patient is assigned to } E \end{cases}$$

- $\boldsymbol{t}$ realization of random variable $\boldsymbol{T} = (T_1, \ldots, T_N)$

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Terminology and assumptions: distribution

- Group C of size n, group E of size m, $N = m + n$
- Exponentially distributed survival times $Z_1, \ldots, Z_N$ where

$$Z_i \sim \begin{cases} \mathrm{Exp}(\lambda_C), & \text{if } i\text{th patient is assigned to } C \\ \mathrm{Exp}(\lambda_E), & \text{if } i\text{th patient is assigned to } E \end{cases}$$

- All N events will be observed

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Test setting

- Two-sided hypotheses:

$$H_0: \quad {}^{\lambda_C}/_{\lambda_E} = 1 \quad \text{vs.} \quad H_1: \quad {}^{\lambda_C}/_{\lambda_E} \neq 1$$

- F-test is performed (Cox, 1953)
- Estimate λ_C/λ_E by MLEs $\hat{\lambda}_C/\hat{\lambda}_E$:

$$S_F = \frac{\hat{\lambda}_C}{\hat{\lambda}_E} = \frac{\overline{Z_E}}{\overline{Z_C}} \sim F(2m, 2n) \quad \text{under } H_0,$$

where $\overline{Z_C} = {}^1/_n \sum_{i=1}^N Z_i(1 - t_i)$ and $\overline{Z_E} = {}^1/_m \sum_{i=1}^N Z_i t_i$

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Approach

Objective

Impact of bias on type I error probability for time-to-event trials

1. Types of bias and biasing policy
2. Distribution F-test in the presence of bias
3. Applications

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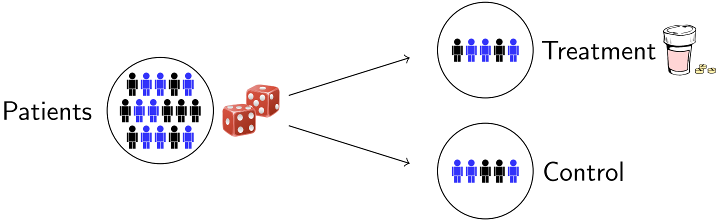
Issue: selection bias

- Selection bias endangering internal validity
- *Systematic baseline covariate imbalances across treatment groups* (Berger, 2005)



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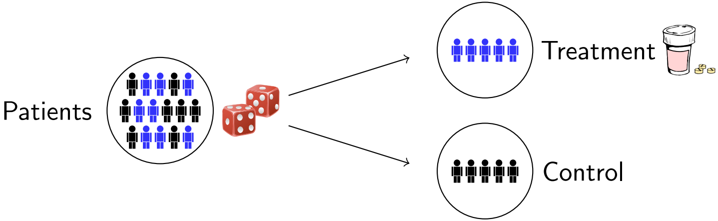

- Failed masking → third-order selection bias (Berger, 2005)

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Issue: chronological bias

- **Problem**: Patients are enrolled sequentially over time

  $\rightarrow$ Patients are treated sequentially over time

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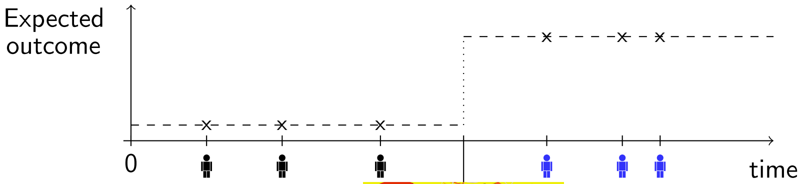
Stepwise time trend



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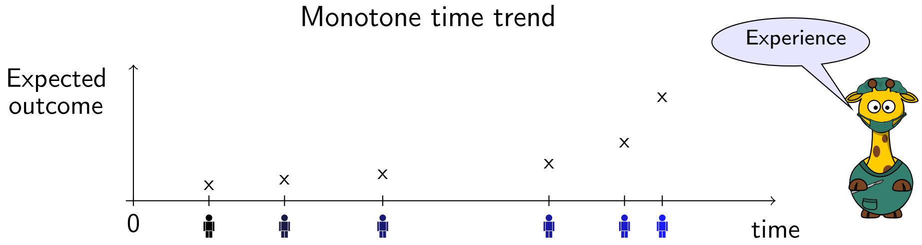

→ Chronological bias

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Biasing policy

Assumptions

- Selection bias:
  - Patients have different expected responses
  - Recruiter favors E and is able to decline enrollment
  - Guess pursuant to convergence strategy (Blackwell & Hodges, 1957)

Population

- Chronological bias:
  - Monotone time trend present
- No treatment effect, $\lambda := \lambda_E = \lambda_C$

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Biasing policy

Selection and chronological bias

Distribution of ith enrolled patient: $Z_i \sim \mathrm{Exp}(\lambda_i)$ with

$$\lambda_i = \begin{cases} \lambda\theta^{i-1}/\delta & \text{if} \quad N_E(i-1) > N_C(i-1) \\ \lambda\theta^{i-1} & \text{if} \quad N_E(i-1) = N_C(i-1) \\ \lambda\theta^{i-1}\delta & \text{if} \quad N_E(i-1) < N_C(i-1) \end{cases}$$

- $N_E(i-1)$ and $N_C(i-1)$ allocations to E and C after $i-1$ allocations
- $\delta \in (0,1)$ *biasing factor*, $\theta \in (0,1)$ *monotone time trend*

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Biased distribution

Given: randomization sequence $\boldsymbol{t}$, biasing factor δ, monotone time trend θ, $N = n + m$ patients. Assuming $\lambda_i \neq \lambda_j$ for all $i \neq j$, and defining special Lagrange basis polynomials

$$\ell_k(i) = \prod_{j \neq i, t_j = k} \frac{\lambda_j}{\lambda_j - \lambda_i}$$

the biased distribution is

$$F_{S_F | \boldsymbol{T} = \boldsymbol{t}}(z) = \begin{cases} \sum_{i=1}^{N} t_i \ell_1(i) \sum_{j=1}^{N} (1 - t_j) \ell_0(j) \left(1 - \frac{\lambda_j}{zm\lambda_i / n + \lambda_j}\right), & z > 0, \\ 0, & z \leq 0. \end{cases}$$

Biased distribution of the F-statistic

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$\Rightarrow$ Assess impact of bias for particular randomization sequence

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Comparison of randomization procedures

- Distinct randomization procedures yield distinct randomization sequences
- Each randomization sequence yields type I error probability

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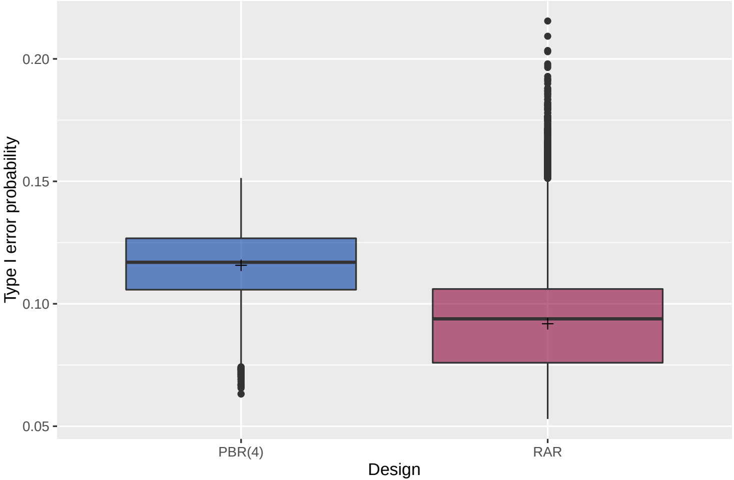
Investigated randomization procedures

RAR (Random allocation rule) Draw without replacement from an urn with $N/2$ marbles per group.

PBR(k) (Permuted block randomization) Randomize in blocks of length k, within each block like in RAR.

Comparison for $N = 20$

Setting: Two-sided F-test, H_0 true, biasing factor $\delta = 0.7$, monotone time trend $\theta = 0.95$, nominal significance level $\alpha_0 = 0.05$



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Conclusions and outlook

- Biasing policy: model selection and chronological bias, if $Z_1, \ldots, Z_N \sim \mathrm{Exp}$
- Formula: impact on test decision if F-test is performed and no censoring
- Formula can be generalized for $\lambda_C \neq \lambda_E$
- Compare distinct randomization procedures
- F-test with censoring
- Biasing policy can as well be applied for other test statistics

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Thank you!

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