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

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

- Rosenberger and Lachin (2016)
Dealing with bias

- Randomization is necessary to prevent bias
- ...but not sufficient!
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**Question:** How to measure bias?
Dealing with bias

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

**Question:** How to measure bias?

→ Impact on test decision, e.g. type I error probability (ICH E9, 1998)
Previous research: Continuous outcome

- Proschan (1994)
- Kennes et al. (2011)
- Tamm et al. (2012)
- Langer (2014)
- Rosenkranz (2011)
- Tamm and Hilgers (2014)
- Uschner et al. (2015)

\{ Selection bias \\
\} Chronological bias

→ Software tool
Previous research: Continuous outcome

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\[ \text{Selection bias} \]
\[ \text{Chronological bias} \]

Objective

Impact of bias on type I error probability for \textit{time-to-event} trials
Terminology and assumptions: randomization

- Two-armed randomized controlled trial, total sample size $N$
- Experimental ($E$), and control treatment ($C$)
- $t = (t_1, \ldots, t_N) \in \{0, 1\}^N$ randomization sequence such that
  
  $$t_i = \begin{cases} 
  0, & \text{if } i\text{th patient is assigned to } C \\
  1, & \text{if } i\text{th patient is assigned to } E 
  \end{cases}$$

- $t$ realization of random variable $T = (T_1, \ldots, T_N)$
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
  
  $$Z_i \sim \begin{cases} 
  \text{Exp}(\lambda_C), & \text{if } i\text{th patient is assigned to } C \\
  \text{Exp}(\lambda_E), & \text{if } i\text{th patient is assigned to } E 
  \end{cases}$$
- All $N$ events will be observed
Test setting

- Two-sided hypotheses:
  \[ H_0 : \frac{\lambda_C}{\lambda_E} = 1 \quad \text{vs.} \quad H_1 : \frac{\lambda_C}{\lambda_E} \neq 1 \]

- F-test is performed (Cox, 1953)

- Estimate \( \frac{\lambda_C}{\lambda_E} \) 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 \( \overline{Z}_C = \frac{1}{n} \sum_{i=1}^{N} Z_i(1 - t_i) \) and \( \overline{Z}_E = \frac{1}{m} \sum_{i=1}^{N} Z_i t_i \)
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
Issue: selection bias

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

Systematic baseline covariate imbalances across treatment groups (Berger, 2005)

Failed masking $\rightarrow$ third-order selection bias (Berger, 2005)
Issue: chronological bias

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

Stepwise time trend

Expected outcome

0 1 2 3 4 5 6 7 8

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

![Monotone time trend](image)

→ **Chronological bias**
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)

- **Chronological bias:**
  - Monotone time trend present

- No treatment effect, $\lambda := \lambda_E = \lambda_C$
Biasing policy

Selection and chronological bias

Distribution of $i$th enrolled patient: $Z_i \sim \text{Exp}(\lambda_i)$ with

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

- $N_E(i - 1)$ 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
Biased distribution of the F-statistic

**Biased distribution**

Given: randomization sequence $t$, biasing factor $\delta$, monotone time trend $\theta$, $N = n + m$ 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

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

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\]

⇒ Assess impact of bias for particular randomization sequence
Comparison of randomization procedures

- Distinct randomization procedures yield distinct randomization sequences
- Each randomization sequence yields type I error probability
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- Distinct randomization procedures yield distinct randomization sequences
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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 $\alpha_0 = 0.05$
Conclusions and outlook

- Biasing policy: model selection and chronological bias, if $Z_1, \ldots, Z_N \sim \text{Exp}$
- 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!
References I


