The Impact of Bias on Different Randomization Procedures

David Schindler, Nicole Heussen, Diane Uschner, Ralf-Dieter Hilgers

Institute of Medical Statistics
RWTH Aachen University

March 15th, 2016

FP7 HEALTH 2013 - 602552

Introduction

- Choice of a randomization procedure does not follow scientific arguments up to now.
- Treatment comparisons should involve consideration of the potential contribution of bias to the *p*-value (ICH E9, 1998).
- Unequal performance of randomization procedures in the presence of
  - Selection bias
  - Chronological bias

FP7 HEALTH 2013 - 602552

Terminology

- Two-armed clinical trial with parallel group design and total sample size N, where N is an even number.
- Experimental treatment E and control treatment C.
- Let $\mathbf{T} = (T_1, \ldots, T_N)' \in \{0,1\}^N$ be a randomization sequence.
- Let $N_j(i)$ be the number of patients assigned to treatment group $j \in \{E, C\}$ after i allocations.

FP7 HEALTH 2013 - 602552

Model

Assuming a (random) bias vector $\mathbf{b} = (b_1, b_2, \ldots, b_N)^T$ the ith patient's response with $i \in \{1, 2, \ldots, N\}$ can be expressed as:

$$y_i = \mu_E \, T_i + \mu_C \, (1 - T_i) + b_i + \sigma \, \epsilon_i \, . \tag{1}$$

- The ith allocation is done as follows:

$$T_i = \begin{cases} 1, & \text{if patient } i \text{ is allocated to group } E \\ 0, & \text{if patient } i \text{ is allocated to group } C \end{cases} .$$

- Expected response μ_j under treatment $j \in \{E, C\}$.
- Errors $\epsilon_i \underset{iid}{\sim} \mathcal{N}(0, 1)$ and $\sigma \in \mathbb{R}^+$.

FP7 HEALTH 2013 - 602552

Test Statistic

We test the hypotheses

$$H_0 : \mu_E = \mu_C \text{ vs. } H_1 : \mu_E \neq \mu_C$$

with Student's t-test (under misspecification) and test statistic

$$W = \frac{\sqrt{\frac{N_E\,N_C}{N_E+N_C}}\,(\bar{y}_E - \bar{y}_C)}{\frac{1}{N_E+N_C-2}\left(\sum_{i=1}^{N} T_i\,(y_i - \bar{y}_E)^2 + \sum_{i=1}^{N}(1-T_i)\,(y_i - \bar{y}_C)^2\right)}$$

with $\bar{y}_E = \dfrac{1}{N_E}\displaystyle\sum_{i=1}^{N} y_i\,T_i,\ \bar{y}_C = \dfrac{1}{N_C}\displaystyle\sum_{i=1}^{N} y_i\,(1-T_i),$ and $N = N_E + N_C$.

FP7 HEALTH 2013 - 602552

Lemma (Langer (2014))

Under $H_0 : \mu_E = \mu_C$ the type-I-error probability in Model (1) (under misspecification) conditioned on the randomization sequence is

$$\begin{aligned} \alpha_\star :=& P\left(|W| > t_{N-2,1-\alpha/2} \middle| \mathbf{T}\right) \\ &= F_{N-2,\delta,\lambda}\left(t_{N-2,\alpha/2}\right) + 1 - F_{N-2,\delta,\lambda}\left(t_{N-2,1-\alpha/2}\right) \ , \end{aligned}$$

where $F_{N-2,\delta,\lambda}(x)$ is the distribution function of the doubly noncentral t-distribution with $N-2$ degrees of freedom and parameters

$$\delta = \frac{1}{\sigma}\sqrt{\frac{N_E\,N_C}{N_E + N_C}}\left(\bar{b}_E - \bar{b}_C\right) \text{ and } \lambda = \frac{1}{\sigma^2}\left[\sum_{i=1}^{N} b_i^2 - n_E\bar{b}_E^2 - n_C\bar{b}_C^2\right]$$

$$\text{with } \bar{b}_E = \frac{1}{N_E}\sum_{i=1}^{N} b_i\,T_i \text{ and } \bar{b}_C = \frac{1}{N_C}\sum_{i=1}^{N} b_i\,(1 - T_i)\,.$$

FP7 HEALTH 2013 - 602552

Simulations

Step 1: Generate 100.000 randomization sequences of a given randomization procedure.

Step 2: For each randomization sequence we compute the corresponding noncentrality parameters dependent on the bias.

Step 3: Compute $\alpha_\star$ of each randomization sequence.
$\Rightarrow$ Average of the $\alpha_\star$ values is an estimator for the type-I-error probability of a randomization procedure.

FP7 HEALTH 2013 - 602552

Simulations

Step 1: Generate 100.000 randomization sequences of a given randomization procedure.

Step 2: For each randomization sequence we compute the corresponding noncentrality parameters dependent on the bias.

Step 3: Compute $\alpha_\star$ of each randomization sequence.
$\Rightarrow$ Average of the $\alpha_\star$ values is an estimator for the type-I-error probability of a randomization procedure.

FP7 HEALTH 2013 - 602552

Simulations

Step 1: Generate 100.000 randomization sequences of a given randomization procedure.

Step 2: For each randomization sequence we compute the corresponding noncentrality parameters dependent on the bias.

Step 3: Compute $\alpha_\star$ of each randomization sequence.
$\Rightarrow$ Average of the $\alpha_\star$ values is an estimator for the type-I-error probability of a randomization procedure.

FP7 HEALTH 2013 - 602552

Randomization Procedures

PBR(k) (Permuted Block Randomization with block length k) Within each block half of the patients are assigend to E and C.

RAR Random Allocation Rule, PBR with only one block.

CR Complete Randomization is accomplished by tossing a fair coin for each included patient.

TBD (Truncated Binomial Design) CR is used until $^N/_2$ patients are assigned to E or C, afterwards the randomization list is filled with the opposite treatment.

BSD(a) (Big Stick Design) CR with a reflecting boundary a.

FP7 HEALTH 2013 - 602552

Influence of Chronological Bias

Type-I-error probability of Student's t-test dependent on the randomization procedure when the ith response is affected by a linear time trend (Tamm and Hilgers (2014)) for $N = 8$ (exact):

$$b_i = \frac{(i-1)\,\vartheta}{N} \quad \text{with } \vartheta \in \mathbb{R}\,.$$

ϑ	CR	BSD(2)	TBD	RAR	PBR(2)
	$\bar{\alpha}_\star$	$\bar{\alpha}_\star$	$\bar{\alpha}_\star$	$\bar{\alpha}_\star$	$\bar{\alpha}_\star$
0	0.050	0.050	0.050	0.050	0.050
$1/2$	0.050	0.050	0.052	0.050	0.048
1	0.050	0.048	0.057	0.050	0.043
2	0.050	0.043	0.075	0.051	0.026

Calculations done with `randomizeR` (Schindler and Uschner, 2016).

- Nominal significance level α of the test is 5%.

FP7 HEALTH 2013 - 602552

Influence of Chronological Bias

Type-I-error probability of Student's t-test dependent on the randomization procedure when the ith response is affected by a linear time trend (Tamm and Hilgers (2014)) for $N = 8$ (exact):

$$b_i = \frac{(i-1)\,\vartheta}{N} \quad \text{with } \vartheta \in \mathbb{R}\,.$$

ϑ	CR $\bar{\alpha}_\star$	BSD(2) $\bar{\alpha}_\star$	TBD $\bar{\alpha}_\star$	RAR $\bar{\alpha}_\star$	PBR(2) $\bar{\alpha}_\star$
0	0.050	0.050	0.050	0.050	0.050
$1/2$	0.050	0.050	0.052	0.050	0.048
1	0.050	0.048	0.057	0.050	0.043
2	0.050	0.043	0.075	0.051	0.026

Calculations done with `randomizeR` (Schindler and Uschner, 2016).

- Nominal significance level α of the test is 5%.

FP7 HEALTH 2013 - 602552

Influence of Chronological Bias

Type-I-error probability of Student's t-test dependent on the randomization procedure when the ith response is affected by a linear time trend (Tamm and Hilgers (2014)) for $N = 60$ (simulated):

$$b_i = \frac{(i-1)\,\vartheta}{N} \quad \text{with } \vartheta \in \mathbb{R}\,.$$

ϑ	CR	BSD(2)	TBD	RAR	PBR(2)
	$\bar{\alpha}_\star$	$\bar{\alpha}_\star$	$\bar{\alpha}_\star$	$\bar{\alpha}_\star$	$\bar{\alpha}_\star$
0	0.050	0.050	0.050	0.050	0.050
1/2	0.050	0.048	0.055	0.051	0.048
1	0.050	0.042	0.069	0.050	0.041
2	0.049	0.026	0.115	0.051	0.024

Calculations done with `randomizeR` (Schindler and Uschner, 2016).

- Nominal significance level α of the test is 5%.

FP7 HEALTH 2013 - 602552

Influence of Selection Bias

Type-I-error probability of Student's t-test dependent on the randomization procedure when the ith response is affected by selection bias (Proschan, 1994) for $N = 8$ (exact):

$$b_i = \begin{cases} \eta, & \text{if } N_E(i-1) < N_C(i-1) \\ 0, & \text{if } N_E(i-1) = N_C(i-1) \\ -\eta, & \text{if } N_E(i-1) > N_C(i-1) \end{cases} \text{ with } \eta \in \mathbb{R}_+ .$$

ϑ	CR	BSD(2)	TBD	RAR	PBR(2)
	$\bar{\alpha}_\star$	$\bar{\alpha}_\star$	$\bar{\alpha}_\star$	$\bar{\alpha}_\star$	$\bar{\alpha}_\star$
0.30	0.050	0.051	0.053	0.055	0.063
0.60	0.052	0.055	0.061	0.068	0.098
1.19	0.056	0.065	0.083	0.103	0.207

Calculations done with `randomizeR` (Schindler and Uschner, 2016).

- Nominal significance level α of the test is 5%.

FP7 HEALTH 2013 - 602552

Influence of Selection Bias

Type-I-error probability of Student's t-test dependent on the randomization procedure when the ith response is affected by selection bias (Proschan, 1994) for $N = 60$ (simulated):

$$b_i = \begin{cases} \eta, & \text{if } N_E(i-1) < N_C(i-1) \\ 0, & \text{if } N_E(i-1) = N_C(i-1) \\ -\eta, & \text{if } N_E(i-1) > N_C(i-1) \end{cases} \text{ with } \eta \in \mathbb{R}_+ .$$

ϑ	CR	BSD(2)	TBD	RAR	PBR(2)
	$\bar{\alpha}_\star$	$\bar{\alpha}_\star$	$\bar{\alpha}_\star$	$\bar{\alpha}_\star$	$\bar{\alpha}_\star$
0.09	0.050	0.053	0.051	0.051	0.064
0.18	0.051	0.061	0.052	0.054	0.106
0.37	0.052	0.091	0.057	0.064	0.278

Calculations done with `randomizeR` (Schindler and Uschner, 2016).

- Nominal significance level α of the test is 5%.

FP7 HEALTH 2013 - 602552

Balancing Behavior

- Power loss due to unequally sized groups at the end of the clinical study depend on the randomization procedure and sample size N.
- For a study, which is planned with 80% power, we get:

N	CR	BSD(2)	TBD	RAR	PBR(2)
	$1-\beta_\star$	$1-\beta_\star$	$1-\beta_\star$	$1-\beta_\star$	$1-\beta_\star$
8	0.736	0.787	0.800	0.800	0.800
60	0.793	0.800	0.800	0.800	0.800

Calculations done with `randomizeR` (Schindler and Uschner, 2016).

FP7 HEALTH 2013 - 602552

Conclusion

- Randomization procedures differ in terms of their susceptibility to selection and chronological bias.
- The choice of an appropriate randomization procedure is the crucial point to prevent bias.
- Evaluation of randomization procedures should be part of the trial and analysis plan.
- We developed `randomizeR` (Schindler and Uschner, 2016) for making fair comparisons of randomization procedures concerning different types of bias and their balancing behavior.

The IDeAl project has received funding from the European Union's 7th Framework Programme for research, technological development and demonstration under Grant Agreement no 602552.

FP7 HEALTH 2013 - 602552

References I

Blackwell, D. and J. L. Hodges Jr. (1957). Design for the control of selection bias. *Annals of Mathematical Statistics 25*, 449–460.

ICH E9 (1998). Statistical principles for clinical trials. *Current Step 4 version dated 5 Februrary 1998. Available from:* `http://www.ich.org`.

Kennes, L. N., E. Cramer, R.-D. Hilgers, and N. Heussen (2011). The impact of selection bias on test decision in randomized clinical trials. *Statistics in Medicine 30*, 2573–2581.

Langer, S. (2014). *The modified distribution of the t-test statistic under the influence of selection bias based on random allocation rule*. master thesis, RWTH Aachen University.

Proschan, M. (1994). Influence of selection bias on type 1 error rate under random permuted block designs. *Statistica Sinica 4*, 219–231.

Rosenkranz, G. K. (2011). The impact of randomization on the analysis of clinical trials. *Statistics in Medicine 30*, 3475–3487.

References II

Schindler, D. and D. Uschner (2016). *randomizeR: Randomization for clinical trials*. R package version 1.1.

Tamm, M. and R.-D. Hilgers (2014). Chronological bias in randomized clinical trials under different types of unobserved time trends. *Methods of Information in Medicine 53*, 501–510.

FP7 HEALTH 2013 - 602552