Selecting an appropriate randomization procedure for a small population group trial on the basis of a linked optimization criterion

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Motivation

- No scientific evaluation of randomization procedures in the presence of several types of bias found in literature.
- Several demands on randomization procedures have been well studied independently of each other, but not simultaneously.
- Urgent need for a score that unifies several issues for measuring the different demands on the randomization process.

⇒ Propose a new framework for the selection of an appropriate randomization procedure based on desirability functions.

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Motivation

Examplary application of the new framework on

- Selection bias:
  - Assessed issue: correct guesses.
- Chronological bias
  - Assessd issue: type-I-error, power.
- Balancing behavior
  - Assessed issue: power loss due to differences in group sizes.

$\Rightarrow$ Propose a new framework for the selection of an appropriate randomization procedure based on desirability functions.

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Terminology

- Two-armed clinical trial with parallel group design with continuous endpoint and total sample size N.
- Experimental treatment E and control treatment C.
- Let $\boldsymbol{T} = (T_1, \ldots, T_N)' \in \{E, C\}^N$ be a randomization sequence and T_i be the ith element of $\boldsymbol{T}$.
- Let $N_s(i, \boldsymbol{T})$ be the number of patients assigned to $s \in \{E, C\}$ after i allocations.

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Selection bias

Assuming a balanced trial it is opportune for the experimenter to guess the ith allocation according to the convergence strategy:

(Blackwell and Hodges Jr., 1957)

$$g_{CS}(i, \boldsymbol{T}) = \begin{cases} E, & \text{if } N_E(i-1, \boldsymbol{T}) < N_C(i-1, \boldsymbol{T}) \\ \text{random guess}, & \text{if } N_E(i-1, \boldsymbol{T}) = N_C(i-1, \boldsymbol{T}) \\ C, & \text{if } N_E(i-1, \boldsymbol{T}) > N_C(i-1, \boldsymbol{T}) \end{cases}.$$

Expected proportion of Correct Guesses (CG) of $\boldsymbol{T}$ is defined as:

$$CG(\boldsymbol{T}) = \frac{\mathbb{E}\left(\sum_{i=1}^{N} \mathbb{1}_{\{T_i = g_{CS}(i, \boldsymbol{T})\}}\right)}{N}$$

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Chronological bias

Model for chronological bias: (Tamm and Hilgers, 2014; Rosenkranz, 2011)

$$\boldsymbol{Y} = \begin{pmatrix} 1 & \tilde{T}_1 & 1 \\ 1 & \tilde{T}_2 & 2 \\ \vdots & \vdots & \vdots \\ 1 & \tilde{T}_N & N \end{pmatrix} \begin{pmatrix} \mu \\ \xi \\ \vartheta \end{pmatrix} + \boldsymbol{\epsilon},$$

with $\boldsymbol{\epsilon} \sim \mathcal{N}(\mathbf{0}, \boldsymbol{I}_{N\times N})$ and $\tilde{T}_i := t(T_i) = \begin{cases} 1, & \text{if } T_i = E \\ -1, & \text{if } T_i = C \end{cases}$

- The trial is evaluated with a model including the effects μ and ξ, although the time effect $\vartheta \neq 0$ is present (misspecification).

  $\Rightarrow$ The type-I-error α and the power $(1-\beta)$ when testing $\xi = 0$ using a t-test is biased, due to not adjusting for ϑ.

Balancing behavior

Due to differences in group sizes $N_E(N, \boldsymbol{T}) - N_C(N, \boldsymbol{T})$ arising at the end of a clinical trial a **loss in the power** when conducting Student's t-test occurs.

Example:
Assuming a total sample size of $N = 50$, an effect size of $\Delta = 0.81$, and a type-I-error probability of $\alpha = 0.05$ it follows:

$N_E(N, \boldsymbol{T})$	25	24	23	20	15
$N_C(N, \boldsymbol{T})$	25	26	27	30	35
$1 - \beta_0(\boldsymbol{T})$	0.800	0.799	0.797	0.784	0.728

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Right-sided Derringer-Suich desirability function

Definition: (Derringer and Suich, 1980)

$$d_i(\boldsymbol{T}) := d(c_i(\boldsymbol{T})) = \begin{cases} 1, & \text{if } c_i(\boldsymbol{T}) \leq TV_i \\ \frac{USL_i - c_i(\boldsymbol{T})}{USL_i - TV_i}, & \text{if } TV_i < c_i(\boldsymbol{T}) < USL_i \\ 0, & \text{if } c_i(\boldsymbol{T}) \geq USL_i \end{cases}$$

- $c_i(\boldsymbol{T})$: value of the i-th issue for $\boldsymbol{T}$.
- TV_i: Target Value of the i-th issue.
- USL_i: Upper Specification Limit of the i-th issue.

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$\Rightarrow$ Need a meaningful TV and USL dependent on the practical need.

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Investigated standard setting:

i	$c_i(\boldsymbol{T})$	TV_i	USL_i
1	$CG(\boldsymbol{T})$	0.50	0.75
2	$\alpha_{TT}(\boldsymbol{T})$	0.05	0.10
3	$\beta_{TT}(\boldsymbol{T})$	0.20	0.40
4	$\beta_0(\boldsymbol{T})$	0.20	0.21

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Properties of desirability scores

- Desirability scores are dimensionless and $\in [0, 1]$.
- Desirability scores are summarizeable with the geometric mean:

$$\bar{d}(\boldsymbol{T}) := \prod_{i=1}^{4} d_i(\boldsymbol{T})^{\omega_i} \text{ with } \sum_{i=1}^{4} \omega_i = 1.$$

- $\boldsymbol{T}$ with $\bar{d}(\boldsymbol{T}) = 0$ is called undesired randomization sequence.

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- Weights should be chosen dependent on the planned trial.
- Heuristical approach: Put one third of the weights on each demand.

$\Rightarrow \omega_1 = 1/3$, $\omega_2 = \omega_3 = 1/6$, and $\omega_4 = 1/3$

Correct guesses of PBR(4) for $N = 4$

- `randomizeR` was used for the evaluation (Schindler and Uschner, 2015).

j	$\boldsymbol{T}_j'$	$P(\boldsymbol{T}_j)$	$CG(\boldsymbol{T}_j)$	$d_1(\boldsymbol{T}_j)$
1	EECC	1/6	0.625	
2	ECEC	1/6	0.750	
3	CEEC	1/6	0.750	
4	ECCE	1/6	0.750	
5	CECE	1/6	0.750	
6	CCEE	1/6	0.625	
	average value:		0.708	

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

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1	EECC	$1/6$	0.625	0.500
2	ECEC	$1/6$	0.750	0.000
3	CEEC	$1/6$	0.750	0.000
4	ECCE	$1/6$	0.750	0.000
5	CECE	$1/6$	0.750	0.000
6	CCEE	$1/6$	0.625	0.500
	average value:		0.708	0.167

$$d_1(\boldsymbol{T}_1) = d(CG(\boldsymbol{T}_1)) = \frac{USL_1 - CG(\boldsymbol{T}_1)}{USL_1 - TV_1} = \frac{0.75 - 0.625}{0.75 - 0.5} = 0.5$$

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Correct guesses of PBR(4) for $N = 4$

- `randomizeR` was used for the evaluation (Schindler and Uschner, 2015).

j	$\boldsymbol{T}'_j$	$P(\boldsymbol{T}_j)$	$CG(\boldsymbol{T}_j)$	$d_1(\boldsymbol{T}_j)$
1	EECC	$1/6$	0.625	0.500
2	ECEC	$1/6$	0.750	0.000
3	CEEC	$1/6$	0.750	0.000
4	ECCE	$1/6$	0.750	0.000
5	CECE	$1/6$	0.750	0.000
6	CCEE	$1/6$	0.625	0.500
	average value:		0.708	0.167

$$\bar{d}_1(\boldsymbol{T}) = 1/6\,(0.5 + 0 + 0 + 0 + 0 + 0.5) = 0.167$$

Assessment of PBR(4) for $N = 4$

j	T'_j	$P(T_j)$	$d_1(T_j)$	$d_2(T_j)$	$d_3(T_j)$	$d_4(T_j)$	$\bar{d}(T_j)$
1	EECC	1/6	0.500	0.804	0.649	1.000	0.712
2	ECEC	1/6	0.000	1.000	0.668	1.000	0.000
3	CEEC	1/6	0.000	1.000	0.776	1.000	0.000
4	ECCE	1/6	0.000	1.000	0.776	1.000	0.000
5	CECE	1/6	0.000	1.000	0.961	1.000	0.000
6	CCEE	1/6	0.500	0.804	1.000	1.000	0.765
	average value:		0.167	0.935	0.805	1.000	0.246

Settings: $\vartheta = 1/4$, $\xi = 2.83$, $\alpha_0 = 0.05$, and $1 - \beta_0 = 0.8$.

$d_1(T) = d(CG(T))$ $\quad d_2(T) = d(\alpha_{TT}(T))$ $\quad d_3(T) = d(1 - \beta_{TT}(T))$ $\quad d_4(T) = d(1 - \beta_0(T))$

$$\bar{d}(T_1) = \sqrt[3]{d_1(T_1)} \cdot \sqrt[6]{d_2(T_1)} \cdot \sqrt[6]{d_3(T_1)} \cdot \sqrt[3]{d_4(T_1)}$$
$$= \sqrt[3]{0.500} \cdot \sqrt[6]{0.804} \cdot \sqrt[6]{0.649} \cdot \sqrt[3]{1.000}$$
$$= 0.712$$

Assessment of PBR(4) for $N = 4$

j	$\boldsymbol{T}'_j$	$P(\boldsymbol{T}_j)$	$d_1(\boldsymbol{T}_j)$	$d_2(\boldsymbol{T}_j)$	$d_3(\boldsymbol{T}_j)$	$d_4(\boldsymbol{T}_j)$	$\bar{d}(\boldsymbol{T}_j)$
1	EECC	$1/6$	0.500	0.804	0.649	1.000	0.712
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Settings: $\vartheta = 1/4$, $\xi = 2.83$, $\alpha_0 = 0.05$, and $1 - \beta_0 = 0.8$.
$d_1(\boldsymbol{T}) = d(CG(\boldsymbol{T}))$ $d_2(\boldsymbol{T}) = d(\alpha_{TT}(\boldsymbol{T}))$ $d_3(\boldsymbol{T}) = d(1 - \beta_{TT}(\boldsymbol{T}))$ $d_4(\boldsymbol{T}) = d(1 - \beta_0(\boldsymbol{T}))$

$$\varnothing \bar{d}(\boldsymbol{T}) = 1/6\,(0.712 + 0 + 0 + 0 + 0 + 0.765) = 0.246$$

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Assessment of PBR(4) for $N = 4$

j	$\boldsymbol{T}'_j$	$P(\boldsymbol{T}_j)$	$d_1(\boldsymbol{T}_j)$	$d_2(\boldsymbol{T}_j)$	$d_3(\boldsymbol{T}_j)$	$d_4(\boldsymbol{T}_j)$	$\bar{d}(\boldsymbol{T}_j)$
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Settings: $\vartheta = 1/4$, $\xi = 2.83$, $\alpha_0 = 0.05$, and $1 - \beta_0 = 0.8$.
$d_1(\boldsymbol{T}) = d(CG(\boldsymbol{T}))$ $d_2(\boldsymbol{T}) = d(\alpha_{TT}(\boldsymbol{T}))$ $d_3(\boldsymbol{T}) = d(1 - \beta_{TT}(\boldsymbol{T}))$ $d_4(\boldsymbol{T}) = d(1 - \beta_0(\boldsymbol{T}))$

2/3 of the randomization sequences are undesired.

$\Rightarrow$ Approach for $N = 4$ not usefull.

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Investigated randomization procedures

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

RPBR(k) (Randomized Permuted Block Randomization with maximal block length k) PBR with random block lengths $2, 4, .., k$.

CR Complete randomization is accomplished by tossing a fair coin.

BSD(a) (Big Stick Design) CR allow for imbalance within the limit a.

Comparison for $N = 50$

Settings: $\vartheta = 1/50$, $\xi = 0.40$, $\alpha_0 = 0.05$, and $1 - \beta_0 = 0.8$.
Results based on 100.000 simulations.

Design	$\varnothing\bar{d}(\boldsymbol{T})$ (sd)	$P(\bar{d}(\boldsymbol{T}) = 0)$
CR	0.5131 (0.388)	0.3534
RPBR(8)	0.6088 (0.081)	0.0011
PBR(8)	0.6759 (0.07)	0.0001
PBR(50)	0.7797 (0.181)	0.0408
BSD(4)	0.8400 (0.084)	0.0024

- BSD(4) has low probability of generating undesired randomization sequences.
- BSD(4) seems to be the best compromise between handling a time trend, the proportion of correct guesses, and the loss in power.

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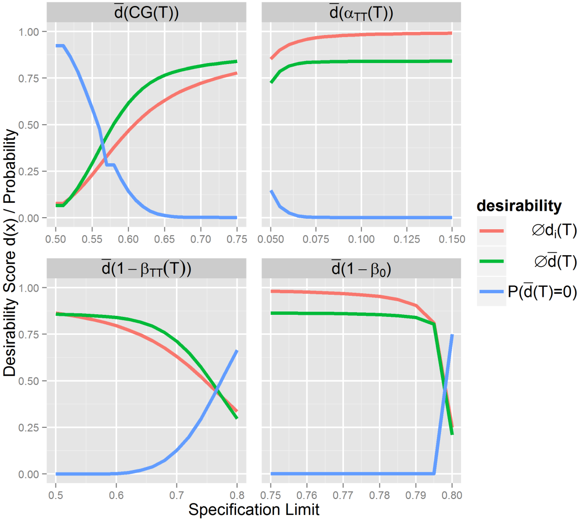
Analysis of the used USLs for BSD(4)



- Change of the desirability scores, when a specification limit convergences against the TV_i.

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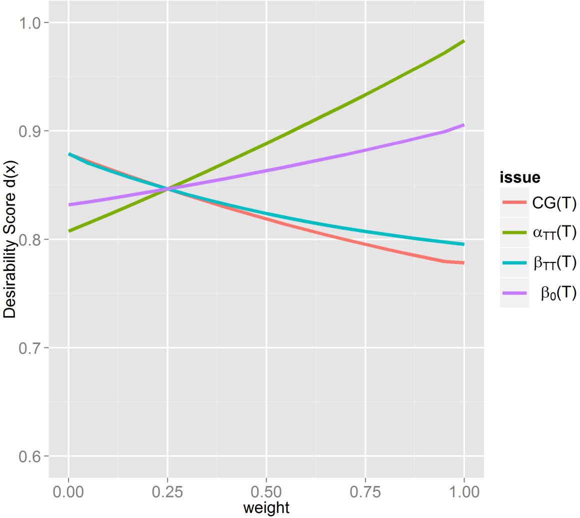
Analysis of the used weights for BSD(4)



- Change of the weight of an fixed issue. The other weights are splitted equally.

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Conclusions

- Presented a framework for the scientific evaluation of randomization procedures dependent on arising demands.
- Evaluation should be part of the statistical trial and analysis plan.
- Other TVs, USLs, and weights for the investigated issues lead to different recommendations.
- Other randomization procedures can be implemented easily.
- Include other issues for measuring (further) demands.

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References

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

Derringer, G. and R. Suich (1980). Simultaneous optimization of several response variables. *Journal of Quality Technology 12*, 214–219.

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

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

Schindler, D. and D. Uschner (2015). *randomizeR: Randomization for clinical trials*. R package version 1.0.

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.

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