Assessment of randomization procedures with respect to multiple objectives

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Challenges in small population group trials

- Total number of eligible patients may be very limited, which impacts the choice of **study design** and the statistical methodology (see O'Connor and Hemmings, 2014)
- Choice of a randomization procedure does not follow scientific arguments up to now.
- Unequal performance of randomization procedures in the presence of
  - Selection bias
  - Chronological bias
- Treatment comparisons should involve consideration of the potential contribution of bias to the *p*-value (ICH E9, 1998).

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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:

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

- 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 $\epsilon_i \underset{iid}{\sim} \mathcal{N}(0, 1)$.

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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

$$W := \sqrt{\frac{N_E\, N_C}{N_E + N_C}}\, \frac{\bar{y}_E - \bar{y}_C}{S_{\text{pooled}}} \sim t_{N-2,\delta,\lambda}$$

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

where N_E and N_C are the final numbers of patients assigned to the corresponding treatment group.

Types of bias

For **chronological bias** according to Tamm and Hilgers (2014) b_i is assumed to be increasing/decreasing in N. For a linear time trend we define:

$$b_i = \frac{(i-1)\,\vartheta}{N} \quad \text{with } \vartheta \in \mathbb{R} \text{ and } i \in \{1, 2, \ldots, N\}\ .$$

In the situation of **selection bias** b_i is dependent on the patients assigned to the corresponding treatment groups (Proschan, 1994):

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

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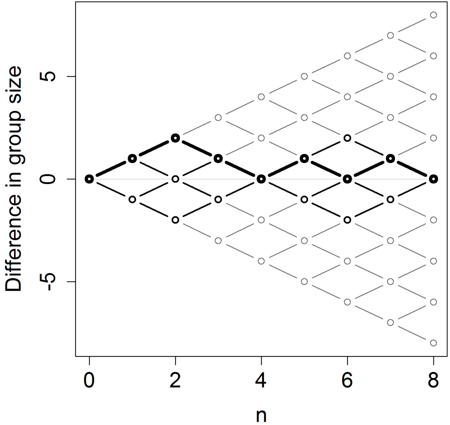
Permuted Block Randomization



- At the end of each block there is no difference in patient numbers.
- All sequences are equiprobable.

PBR(4): Permuted Block Randomization with block length 4

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Properties of PBR(4) with $N = 4$

Investigated settings for selection bias:

- $\alpha = 0.05$
- $\eta = 1.42$ (one quarter of the effect size)
- $\alpha_{SB}(\mathbf{T}_j) :=$ Type-I-error probability in case of selection bias

j	$\mathbf{T}_j$	$P(\mathbf{T}_j)$	$\alpha_{SB}(\mathbf{T}_j)$	$\alpha_{TT}(\mathbf{T}_j)$	$1-\beta_{TT}(\mathbf{T}_j)$	overall
1	CCEE	$1/6$	0.047			
2	CECE	$1/6$	0.138			
3	ECCE	$1/6$	0.060			
4	CEEC	$1/6$	0.060			
5	ECEC	$1/6$	0.138			
6	EECC	$1/6$	0.047			
	average value:		0.081			

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Properties of PBR(4) with $N = 4$

Investigated settings for chronological bias:

- $\alpha = 0.05$, $(1-\beta) = 0.8$, $\mu_E - \mu_C = 5.65$
- $\vartheta = 1$
- $\alpha_{TT}(\mathbf{T}_j)$:= Type-I-error probability in case of a linear time trend
- $1-\beta_{TT}(\mathbf{T}_j)$:= Power in case of a linear time trend

j	$\mathbf{T}_j$	$P(\mathbf{T}_j)$	$\alpha_{SB}(\mathbf{T}_j)$	$\alpha_{TT}(\mathbf{T}_j)$	$1-\beta_{TT}(\mathbf{T}_j)$	overall
1	CCEE	$1/6$	0.047	0.060	0.842	
2	CECE	$1/6$	0.138	0.047	0.792	
3	ECCE	$1/6$	0.060	0.043	0.755	
4	CEEC	$1/6$	0.060	0.043	0.755	
5	ECEC	$1/6$	0.138	0.047	0.734	
6	EECC	$1/6$	0.047	0.060	0.730	
	average value:		0.081	0.050	0.768	

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Properties of PBR(4) with $N = 4$

- No linked assessment score available
  $\Rightarrow$ How is the performance of PBR(4) in comparison to other randomization procedures?

j	$\mathbf{T}'_j$	$P(\mathbf{T}_j)$	$\alpha_{SB}(\mathbf{T}_j)$	$\alpha_{TT}(\mathbf{T}_j)$	$1-\beta_{TT}(\mathbf{T}_j)$	overall
1	CCEE	$1/6$	0.047	0.060	0.842	?
2	CECE	$1/6$	0.138	0.047	0.792	?
3	ECCE	$1/6$	0.060	0.043	0.755	?
4	CEEC	$1/6$	0.060	0.043	0.755	?
5	ECEC	$1/6$	0.138	0.047	0.734	?
6	EECC	$1/6$	0.047	0.060	0.730	?
	average value:		0.081	0.050	0.768	?

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Right-sided Derringer-Suich desirability function

Definition (Derringer and Suich (1980)):

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

TV: Target Value USL: Upper Specification Limit

i	Criterion$_i$ (c_i)	TV$_i$	USL$_i$
1	$\alpha_{SB}(\mathbf{T})$	0.05	0.10
2	$\alpha_{TT}(\mathbf{T})$	0.05	0.10
3	$\beta_{TT}(\mathbf{T})$	0.20	0.40

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Multi-objective combination criterion

- Desirability scores are in the interval $[0, 1]$.
- Desirability scores can be combined with the geometric mean:

$$\bar{d}(\mathbf{T}) := \prod_{i=1}^{3} d(\mathbf{T})^{\omega_i} \text{ with } \sum_{i=1}^{3} \omega_i = 1.$$

- The geometric mean is a multi-objective combination criterion.

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- The geometric mean is a multi-objective combination criterion.
- Weights should be chosen dependent on the planned trial.
- To give an example:
  Distribute the weight uniformly on selection bias and chronological bias

  $\Rightarrow \omega_1 = {}^1\!/_2$ and $\omega_2 = \omega_3 = {}^1\!/_4$

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

j	$\mathbf{T}'_j$	$P(\mathbf{T}_j)$	$\alpha_{SB}(\mathbf{T}_j)$	$d_1(\mathbf{T}_j)$	$\alpha_{TT}(\mathbf{T}_j)$	$d_2(\mathbf{T}_j)$	$1-\beta_{TT}(\mathbf{T}_j)$	$d_3(\mathbf{T}_j)$	$\bar{d}(\mathbf{T}_j)$
1	EECC	$1/6$	0.047	1.000					
2	ECEC	$1/6$	0.138	0.000					
3	CEEC	$1/6$	0.060	0.809					
4	ECCE	$1/6$	0.060	0.809					
5	CECE	$1/6$	0.138	0.000					
6	CCEE	$1/6$	0.047	1.000					
	average value:		0.081	0.603					

$$d_1(\mathbf{T}_1) = d(\alpha_{SB}(\mathbf{T}_1)) = 1, \text{because } 0.047 < 0.05$$

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

j	$\mathbf{T}'_j$	$P(\mathbf{T}_j)$	$\alpha_{SB}(\mathbf{T}_j)$	$d_1(\mathbf{T}_j)$	$\alpha_{TT}(\mathbf{T}_j)$	$d_2(\mathbf{T}_j)$	$1-\beta_{TT}(\mathbf{T}_j)$	$d_3(\mathbf{T}_j)$	$\bar{d}(\mathbf{T}_j)$
1	EECC	$1/6$	0.047	1.000	0.060	0.804	0.842	1.000	0.947
2	ECEC	$1/6$	0.138	0.000	0.047	1.000	0.792	0.961	0.000
3	CEEC	$1/6$	0.060	0.809	0.043	1.000	0.755	0.776	0.844
4	ECCE	$1/6$	0.060	0.809	0.043	1.000	0.755	0.776	0.844
5	CECE	$1/6$	0.138	0.000	0.047	1.000	0.734	0.668	0.000
6	CCEE	$1/6$	0.047	1.000	0.060	0.804	0.730	0.649	0.850
	average value:		0.081	0.603	0.050	0.935	0.768	0.805	0.581

$$
\begin{aligned}
\bar{d}(\mathbf{T}_1) &= \sqrt{d_1(\mathbf{T}_1)} \cdot \sqrt[4]{d_2(\mathbf{T}_1)} \cdot \sqrt[4]{d_3(\mathbf{T}_1)} \\
&= \sqrt{1} \cdot \sqrt[4]{0.804} \cdot \sqrt[4]{d_3(1)} \\
&= 0.947
\end{aligned}
$$

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

j	$\mathbf{T}'_j$	$P(\mathbf{T}_j)$	$\alpha_{SB}(\mathbf{T}_j)$	$d_1(\mathbf{T}_j)$	$\alpha_{TT}(\mathbf{T}_j)$	$d_2(\mathbf{T}_j)$	$1-\beta_{TT}(\mathbf{T}_j)$	$d_3(\mathbf{T}_j)$	$\bar{d}(\mathbf{T}_j)$
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	average value:		0.081	0.603	0.050	0.935	0.768	0.805	0.581

$$\varnothing \bar{d}(\mathbf{T}) = 1/6\,(0.947 + 0 + 0.844 + 0.844 + 0 + 0.850)$$
$$= 0.581$$

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

j	$\mathbf{T}'_j$	$P(\mathbf{T}_j)$	$\alpha_{SB}(\mathbf{T}_j)$	$d_1(\mathbf{T}_j)$	$\alpha_{TT}(\mathbf{T}_j)$	$d_2(\mathbf{T}_j)$	$1-\beta_{TT}(\mathbf{T}_j)$	$d_3(\mathbf{T}_j)$	$\bar{d}(\mathbf{T}_j)$
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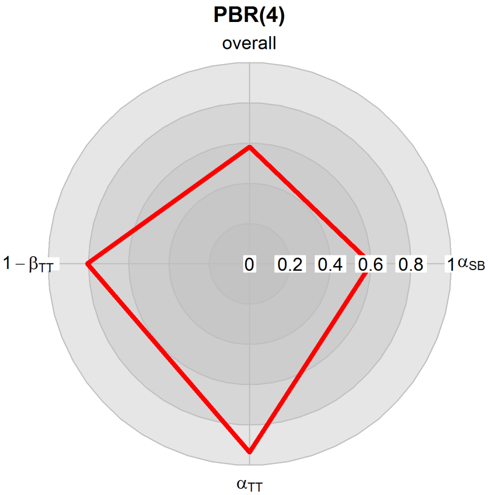
	average value:		0.081	0.603	0.050	0.935	0.768	0.805	0.581

- Average desirability scores can be visualized in a radar plot, which is available in the `randomizeR` package (Schindler et al., 2015).

Radar plot



- PBR(4) seems to be good in handling the assumed linear time trend.
- PBR(4) seems to be susceptible to the convergence strategy.

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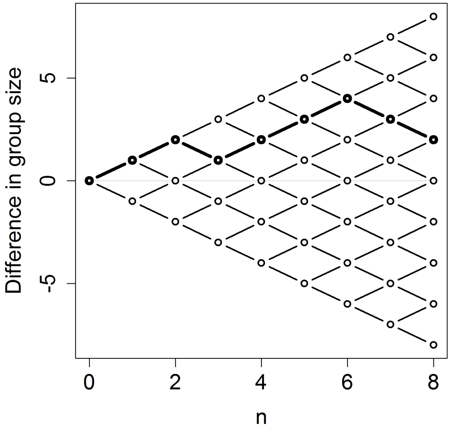
Complete Randomization



- Fair coin toss for each patient allocation.

CR: Complete Randomization

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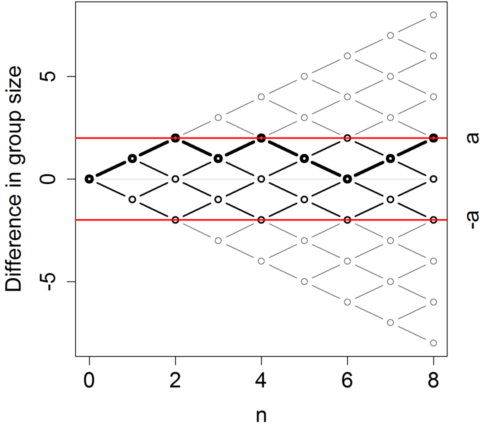
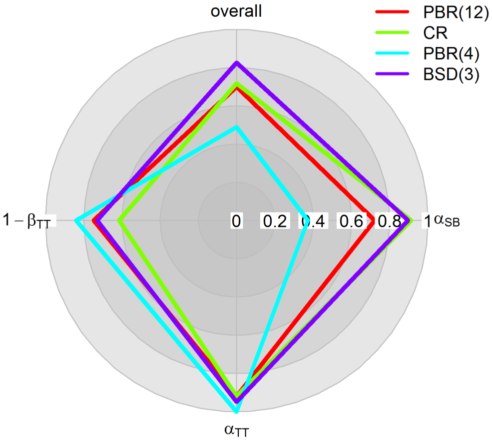
Big Stick Design (Soares and Wu, 1983)



- Fair toin toss with imbalance boundary a.

BSD(2): Big Stick Design with imbalance boundary $a = 2$

Comparison for $N = 12$



- PBR(4) seems to be very susceptible to selection bias.
- BSD(3) manages the investigated criteria the best.

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Conclusion

- Randomization procedures differ in terms of their susceptibility to selection bias and chronological bias.
- The linked assessment criterion makes a fair comparison of different randomization procedures possible.
- The radar plot compares the behavior of randomization procedures at a glance.
- We developed `randomizeR` (Schindler et al., 2015) for making fair comparisons of randomization procedures concerning different types of bias and their balancing behavior.

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Flexibility of the approach

- The linked assessment criterion summarizes all imaginable criteria to one unified score and takes their importance into account.
- Other suggested criteria in the literature are:
  - Correct Guesses (Blackwell and Hodges Jr., 1957)
  - Loss in treatment estimation (Atkinson, 2001)
- Other randomization procedures can be easily assessed such as:
  - Efron's Biased Coin Design
  - Truncated Binomial Design
  - Randomized Permuted Block Randomization
  - Maximal Procedure

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Comparison for $N = 12$

RP	$\bar{d}(1-\beta_{TT}(\mathbf{T}_j))$	$\bar{d}(\alpha_{TT}(\mathbf{T}_j))$	$\bar{d}(\alpha_{SB}(\mathbf{T}_j))$	$\varnothing\bar{d}(\mathbf{T}_j)$
PBR(4)	0.840	1.000	0.371	0.489
PBR(12)	0.747	0.919	0.721	0.699
CR	0.615	0.919	0.911	0.717
BSD(3)	0.729	0.947	0.895	0.825

- PBR(4) seems to be very susceptible to selection bias.
- BSD(3) manages the investigated criteria the best.

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