Evaluation of Randomization Procedures for Clinical Trial Design Optimization with various clinical trial layouts

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Randomization in Practice

- What the theory tells us:
  - no randomization procedure performs best with all criteria, Rosenberger (2016), Atkinson (2014)
- What applied scientist mostly feel:
  - scepticism to randomization
  - do not well understood randomization principle
  - is just allocation and think unequal group size is a major problem
  - think that randomization is for balancing covariates but does mostly not work
  - select a procedure by opinion or software availability
- What the literature mirrors:
  - no training in randomization
  - no recommendation to give scientific arguments for the choice of randomization procedure, neither ICH Guidelines nor CONSORT Statement

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Introduction - Objective

Propose a tool for assessing the impact of selection bias as well as chronological bias on the type one error probability for a given randomization sequence (procedure) and thus enabling a scientific discussion of the appropriate choice of the randomization procedure

clinical trial design

- continuous normal endpoint to prove a superiority hypothesis
- multicenter, 2-arm parallel group design with intended 1:1 allocation ratio
- no interim analysis and no adaptation in the randomization process

Notation

Model for two arm parallel group multicenter trial involving K centers

allocation sequence notation of the statistical model assuming no treatment by center interaction by

$$y_{ji} = \mu_E Z_{ji} + \mu_C(1 - Z_{ji}) + \tau_{ji} + \epsilon_{ji} \quad (1)$$

1. E, C: treatment indicator
2. j: index for center $j, 1 \leq j \leq K$
3. i: index for patient number $i, 1 \leq i \leq n_j = n_{jE} + n_{jC}$ in Center j
4. μ_ℓ expected response under treatment $\ell = E, C$
5. τ_{ji} denotes the fixed unobserved "bias" effect acting on the response of patient i in center j
6. errors ϵ_{ji} iid $N(0, \sigma^2)$
7. allocation $Z_{ji} = \begin{cases} 1 & \text{if patient } i \text{ in center } j \text{ is allocated to } E \\ 0 & \text{if patient } i \text{ in center } j \text{ is allocated to } C \end{cases}$

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Setting -Test Statistic (Fleiss, 1986)

Aim $H_0 : \mu_E = \mu_C$ vs. $H_1 : \mu_E \neq \mu_C$

use t-Test $$t = \frac{\sum_{j=1}^{K} w_j D_j}{s_p \sqrt{\sum_{j=1}^{K} w_j^2 / w_j^*}}$$

Notations:

- weights w_j and $w_j^* = \frac{n_{jE} \times n_{jC}}{n_{jE} + n_{jC}}$, $n_j = n_{jE} + n_{jC}$
- $D_j = \tilde{y}_{jE} - \tilde{y}_{jC}$ is the mean treatment difference is center j
- $\tilde{y}_{jE} = \frac{1}{n_{jE}} \sum_{i=1}^{n_j} y_{ji} Z_{ji}$ and $\tilde{y}_{jC} = \frac{1}{n_{jC}} \sum_{i=1}^{n_j} y_{ji}(1 - Z_{ji})$
- $s_p^2 = \left(\sum_{j=1}^{K} \sum_{\ell=E,C} (n_{j\ell} - 1) s_{j\ell}^2 \right) \Big/ \left(\sum_{j=1}^{K} \sum_{\ell=E,C} (n_{j\ell} - 1) \right)$

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Setting - Theorem (I)

Theorem: Under $H_0 : \mu_E = \mu_C$ the type 1 error probability in (1) (under misspecification) for the allocation sequence $\mathbf{Z} = (Z_1, \ldots, Z_n)$ is

$$P\left(|T| > t_{df}(1 - \tfrac{\alpha}{2}) \middle| \mathbf{Z}\right)$$
$$= F_{df,\delta(\mathbf{Z}),\lambda(\mathbf{Z})}\left(t_{df}(1 - \tfrac{\alpha}{2})\right) + F_{df,-\delta(\mathbf{Z}),\lambda(\mathbf{Z})}\left(t_{df}(\tfrac{\alpha}{2})\right).$$

$F_{df,\delta(\mathbf{Z}),\lambda(\mathbf{Z})}$ denotes the distribution function of the doubly non-central t-distribution with $df = \sum_{j=1}^{K} \sum_{\ell=E,C} (n_{j\ell} - 1)$ degrees of freedom

$$\mathbf{Z}^t = (\mathbf{Z_1}^t, \ldots, \mathbf{Z_K}^t) = (Z_{11}, \ldots, Z_{1n_1}, \ldots, Z_{K1}, \ldots, Z_{Kn_K})$$

Setting - Theorem (II)

non-centrality parameters:

$$\delta(\mathbf{Z}) = \left(\sigma \sqrt{\sum_{j=1}^{K} w_j^2 / w_j^*} \right)^{-1} \left((\mu_E - \mu_C) \sum_{j=1}^{K} w_j + \sum_{j=1}^{K} w_j \left(\tilde{\tau}_{jE} - \tilde{\tau}_{jC} \right) \right)$$

$$\lambda(\mathbf{Z}) = \frac{1}{\sigma^2} \left(\sum_{j=1}^{K} \sum_{i=1}^{n_j} \tau_{ji}^2 - \sum_{j=1}^{K} n_{jE} \tilde{\tau}_{jE}^2 - \sum_{j=1}^{K} n_{jC} \tilde{\tau}_{jC}^2 \right)$$

$$\text{where } \tilde{\tau}_E = \frac{1}{n_E} \sum_{i=1}^{n} \tau_i Z_i \; ; \quad \tilde{\tau}_C = \frac{1}{n_C} \sum_{i=1}^{n} \tau_i (1 - Z_i)$$

Proof - 1st Argument: Distribution of nominator

$$\frac{\sum_{j=1}^{K} w_j D_j}{\sigma\sqrt{\sum_{j=1}^{K} w_j^2/w_j^*}} \sim \mathcal{N}(\delta, 1)$$

$$E(\sum w_j D_j) = E\left(\sum_{j=1}^{K} w_j \left(\frac{1}{n_{jE}}\sum_{i=1}^{n_j} y_{ji} Z_{ji} - \frac{1}{n_{jC}}\sum_{i=1}^{n_j} y_{ji}(1 - Z_{ji})\right)\right)$$

$$= \left((\mu_E - \mu_C)\sum_{j=1}^{K} w_j + \sum_{j=1}^{K} w_j\left(\tilde{\tau}_{jE} - \tilde{\tau}_{jC}\right)\right) := \delta\left(\sigma\sqrt{\sum_{j=1}^{K} w_j^2/w_j^*}\right)$$

$$Var(\sum w_j D_j) = \sum_{j=1}^{K} w_j^2\left(\frac{1}{n_{jE}^2}\sum_{i=1}^{n_j} Var\left(y_{ji}\right) Z_{ji} + \frac{1}{n_{jC}^2}\sum_{i=1}^{n_j} Var\left(y_{ji}\right)(1 - Z_{ji})\right)$$

$$= \sigma\sqrt{\sum_{j=1}^{K} w_j^2/w_j^*}$$

Proof - 2nd Argument: Distribution of denominator

$$\frac{s_p^2}{\sigma^2} \sim \chi^2_{\sum_{j=1}^{K}(n_{jE}+n_{jC}-2)} \left(\frac{1}{\sigma^2} \left(\sum_{j=1}^{K} \sum_{i=1}^{n_j} \tau_{ji}^2 - \sum_{j=1}^{K} n_{jE} \tilde{\tau}_{jE}^2 - \sum_{j=1}^{K} n_{jC} \tilde{\tau}_{jC}^2 \right) \right)$$

Using Johnson & Kotz (1970) page 130 the distribution of $\frac{s_p^2}{\sigma^2}$ results from

$$\sum_{i=1}^{n_j} Z_{ji}(y_{ji} - \tilde{y}_{jE})^2/\sigma^2 \sim \chi^2_{n_{jE}-1} \left(\sum_{i=1}^{n_j} \frac{Z_{ji}}{\sigma^2}(\tau_{ji} - \tilde{\tau}_{jE})^2 \right)$$

$$\sum_{i=1}^{n_j}(1 - Z_{ji})(y_{ji} - \tilde{y}_{jC})^2/\sigma^2 \sim \chi^2_{n_{jC}-1} \left(\sum_{i=1}^{n_j} \frac{(1 - Z_{ji})}{\sigma^2}(\tau_{ji} - \tilde{\tau}_{jC})^2 \right)$$

Proof - 3rd Argument: Independence

show the independence of the nominator and the denominator statistic Searle (1971): If $\mathbf{x} \sim N(\mu, \mathbf{V})$, then $\mathbf{x}^t\mathbf{A}\mathbf{x}$ and $\mathbf{B}\mathbf{x}$ are independent if and only if $\mathbf{BVA} = 0$. Use matrix notation

$$\mathbf{B}_j = w_j\left(\frac{1}{n_{jE}}\mathbb{1}^t_{n_{jE}}, -\frac{1}{n_{jC}}\mathbb{1}^t_{n_{jC}}\right)^t$$

and with $\mathbf{H}_{ij} = \mathbf{I}_{n_{ij}} - \frac{1}{n_{ij}}\mathbb{1}_{n_{ij}\times n_{ij}}$

$$\mathbf{A}_j = (\mathbf{H}_{n_{jE}}, \mathbf{H}_{n_{jC}}) = \left(\mathbf{I}_{n_{jE}} - \frac{1}{n_{jE}}\mathbb{1}_{n_{jE}\times n_{jE}}, \mathbf{I}_{n_{jC}} - \frac{1}{n_{jC}}\mathbb{1}_{n_{jC}\times n_{jC}}\right)$$

Assessment - Stratified Randomization Procedures

Randomization Procedure within center $P(\mathbf{Z}_j = \mathbf{z}_j | \mathbf{z}_j \in \{0,1\}^{n_j})$

Stratified Randomization Procedure $\prod_{j=1}^{K} P(\mathbf{Z}_j = \mathbf{z}_j | \mathbf{z}_j \in \{0,1\}^{n_j})$

Randomization Procedures

- CR — Complete randomization: probability that patient i will receive treatment 1 is always $\frac{1}{2}$
- BSD(a) — (Big Stick design) CR allow for imbalance within a limit a
- RAR — Randomize so that half of the N patients receive E
- PBR(m_s) — (Permuted Block Randomization) Implementation of RAR within k Blocks of size $m_s, 1 \leq s \leq k$
- MP(a) — (Maximal Procedure) allow for imbalance within a limit (a) but force terminal balance at the end, resulting sequences are set to be equiprobable

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Joint Bias Model

Joint additive linear bias model

$$\tau_{ji} = \underbrace{\theta_j \frac{i}{n_{jE} + n_{jC}}}_{\textit{linear time trend}} + \underbrace{\eta_j \, \text{sign}(n_{jE}(i-1) - n_{jC}(i-1))}_{\textit{selection bias with } q=0.5}$$

1. θ_j of the linear time trend varying between centers
2. formulate θ_j as fraction of the variance σ^2
3. different shape of time trend can be incorporated
4. weights via definition of θ_j and η_j
5. $\eta_j \geq 0$ selection bias effect depend on the center
6. relaxed version of selection bias possible
7. Joint multiplicative linear bias model could also be done

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Metric: Preserve type-I-error probability

ICH E9: The interpretation of statistical measures of uncertainty of the treatment effect and treatment comparisons should involve consideration of the potential contribution of bias to the p-value, confidence interval, or inference.

Metric (empirical type-I-error rate)

$$P_{RP,\tau}(H_1|H_0) = P_{RP,\tau}\left(\mathbf{Z} \in \{0,1\}^N : |t_{df,\delta(\mathbf{Z}),\lambda(\mathbf{Z})}(1-\tfrac{\alpha}{2})| \geq |t_{df}(1-\tfrac{\alpha}{2})|\right)$$

- study the empirical type-I-error rate or empirical test size via simulation
- other metrics are implemented

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Evaluation scenarios

Table: Evaluation scenarios

Senario	Item	Center 1	Center 2
1	Sample size	40	40
	η	$0.2 \cdot \Delta$	$0.2 \cdot \Delta$
	θ	$0.1 \cdot \sigma$	$0.1 \cdot \sigma$
2	Sample size	40	40
	η	$0.1 \cdot \Delta$	$0.1 \cdot \Delta$
	θ	$0.05 \cdot \sigma$	$0.05 \cdot \sigma$

- Using Fleiss (1986) optimal weights $w_j = w_j^* = \frac{n_{jE} \times n_{jC}}{n_{jE} + n_{jC}}$
- 100 000 drawing of allocation sequences
- CR, EBC(2/3) , RAR, PBR (2), BSD(4), MP

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Simulation - Results

Table: $P_{RP,\tau}(H_1|H_0)$ for different tests two center, $n_1 = n_2 = 40$

Senario	Randomization Procedure	weighted stratified analysis	unstratified randomization
1	CR	0.34	0.50
1	EBC(2/3)	0.01	0.02
1	RAR	0.02	0.20
1	PBR(2)	0	0
1	BSD(4)	0.31	0.46
1	MP(4)	0.02	0.14
2	CR	0.33	0.50
2	EBC(2/3)	0.01	0.02
2	RAR	0.02	0.20
2	PBR(2)	0	0
2	BSD(4)	0.30	0.46
2	MP(4)	0.02	0.15

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Other Designs

Table: ERDO handled trial designs

Design parallel group	Endpoint	Hypothesis	Test	Selection Bias	Time Trend
2-arm single center	continuous *(Hilgers, 2017)*	$H_0 : \mu_E = \mu_C$	t-Test	yes, additiv	stepwise, linear, logarithmic
2-arm multicenter	continuous *(Hilgers, 2018)*	$H_0 : \mu_E = \mu_C$	t-Test	yes, additiv	stepwise, linear, logarithmic
2-arm single center	time to event *(Rückbeil, 2017)*	$H_0 : \lambda_E/\lambda_C = 1$ $(H_0 : S_E = S_C)$	F-Test *(logRank)*	yes, multiplicative	*stepwise, linear, logarithmic*
multi-arm single center	continuous *(Uschner, 2018)*	$H_0 : \mu = \mathbf{0}$	ANOVA	yes, additiv	
group sequential design	continuous *(Ventsch, 201x)*	$H_0 : \mu = \mathbf{0}$		yes, additiv	*stepwise, linear, logarithmic*
2-arm single center	continuous *(Hilgers, 201x)*	$H_0 : \beta_E = \beta_C$	LMEM	yes, additiv	*stepwise, linear, logarithmic*
2-arm single center	binary (stratified)	$H_0 : OR = 1$	χ^2 (stratified)	yes, multiplicative	*stepwise, linear, logarithmic*

Discussion

FDA, Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, 1998)

Any clinical trial may be subject to unanticipated, undetected, systematic biases. These biases may operate despite the best intentions of sponsors and investigators, and may lead to flawed conclusions.

- presented a framework for scientific evaluation of stratified randomization procedures in the presence of bias with multicenter trials
- work on LMEM
- start understanding the effect in clinical trials with dichotomous endpoint
- start understanding the effect in clinical trials with interim analysis

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