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Optimal Designs and Adaptive Randomization Techniques in Clinical Trials

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Outline

1. Clinical Trials
2. Adaptive Designs
3. Adaptive Randomization
4. Optimal Allocation
5. Randomization procedures used to target optimal allocation
   - Allocation-Adaptive Randomization (AAR)
   - Response-Adaptive Randomization (RAR)
   - Covariate-Adaptive Randomization (CAR)
   - Covariate-Adjusted Response-Adaptive Randomization (CARA)

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Outline

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Clinical Trials

Clinical trials are prospective biomedical or behavioural research studies on ***human subjects*** *that are designed to answer specific questions about biomedical or behavioural interventions*:

- novel vaccines,
- drugs,
- treatments,
- functional foods,
- dietary supplements,
- devices,
- new ways of using known interventions

generating ***safety*** and ***efficacy*** data.

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Clinical Trials

- Typically randomized, double-blind, placebo and/or active controlled study designs.
- The most common objective of a randomized clinical trial is to test the hypothesis that a new treatment is better than the standard fo care in the population with the disease.

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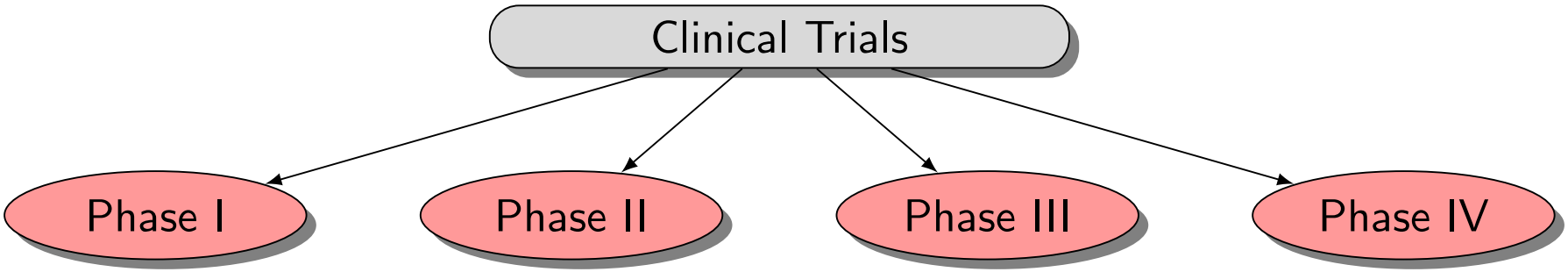
Clinical Drug Development



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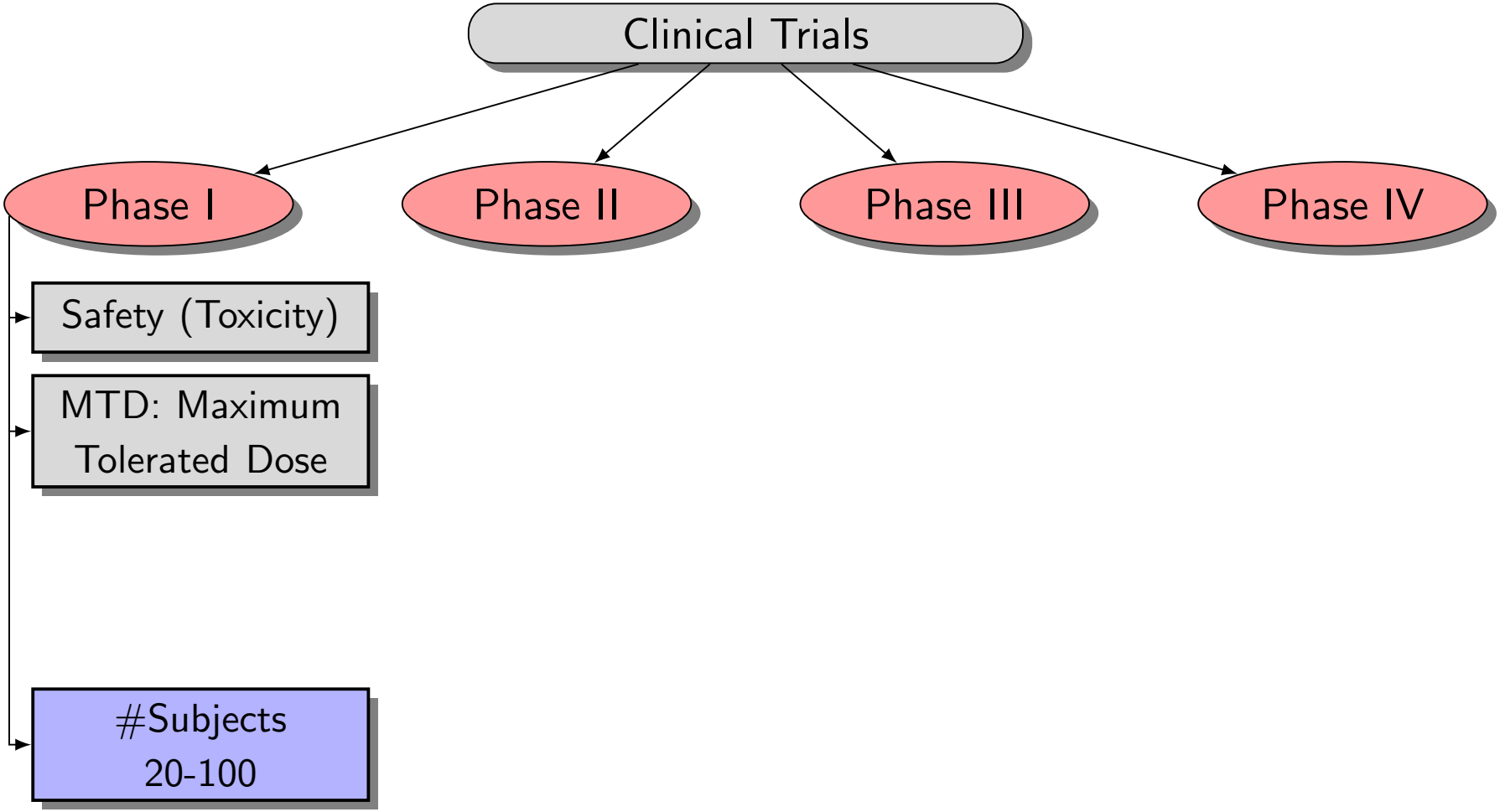

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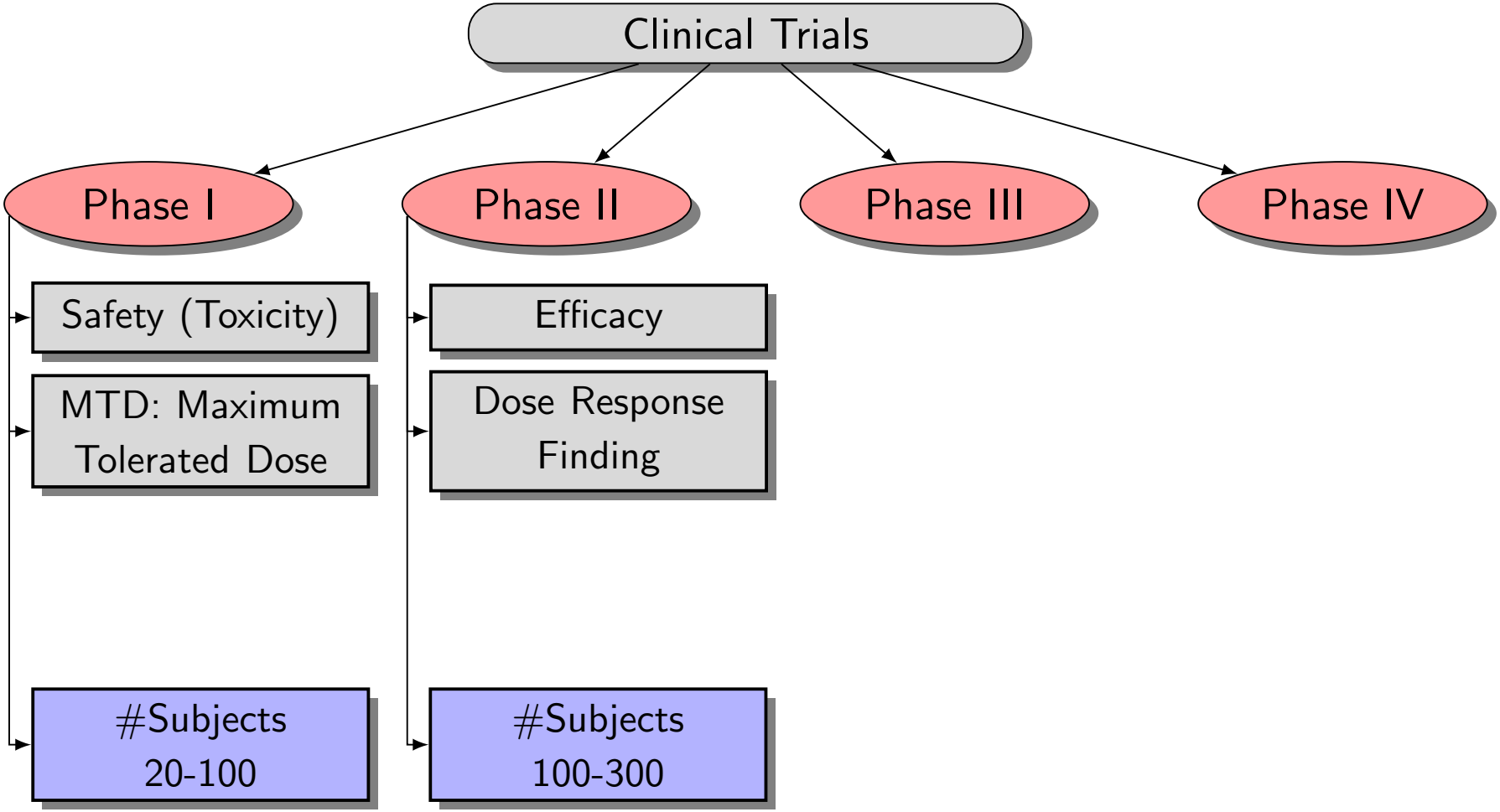

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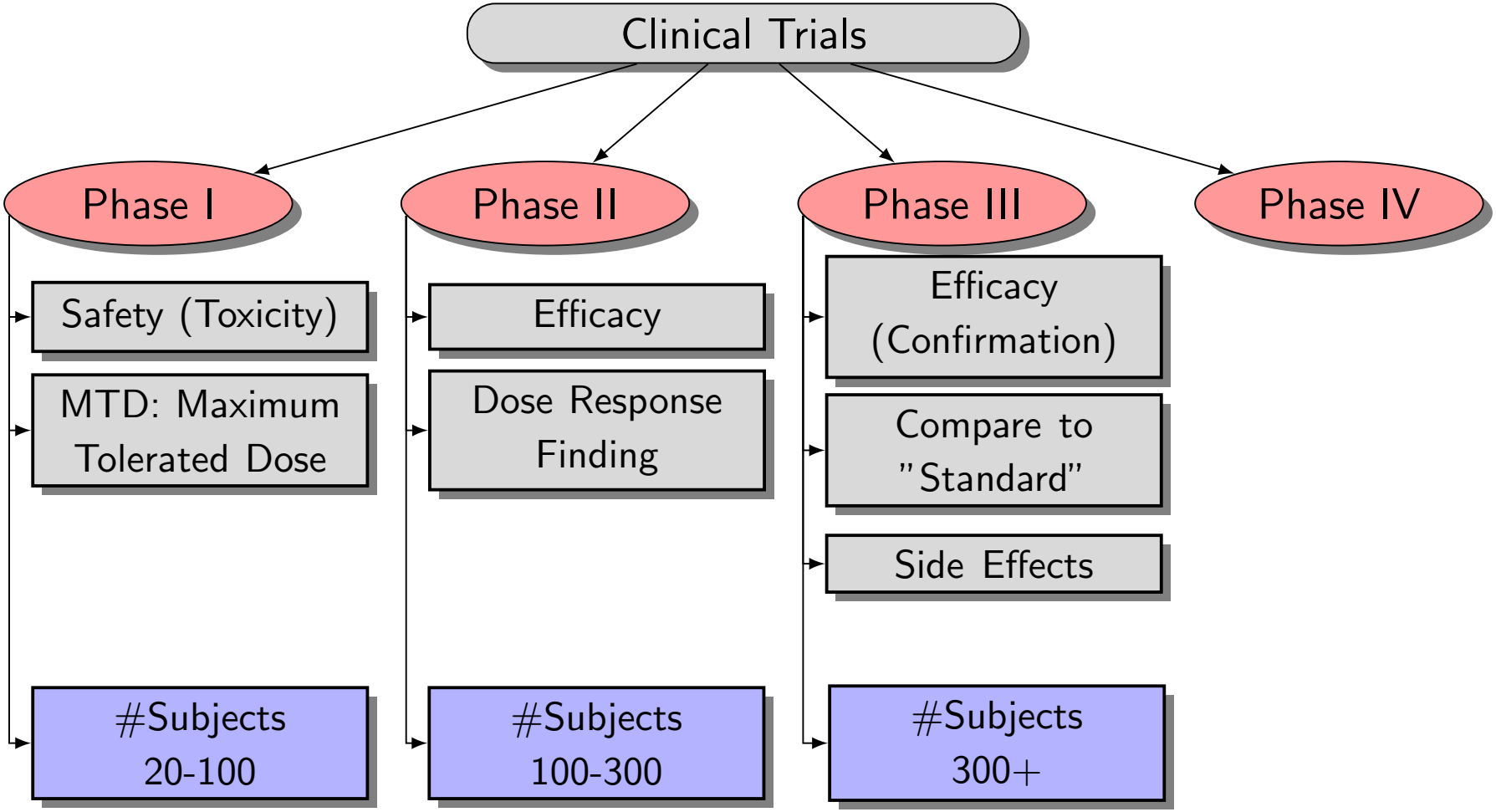

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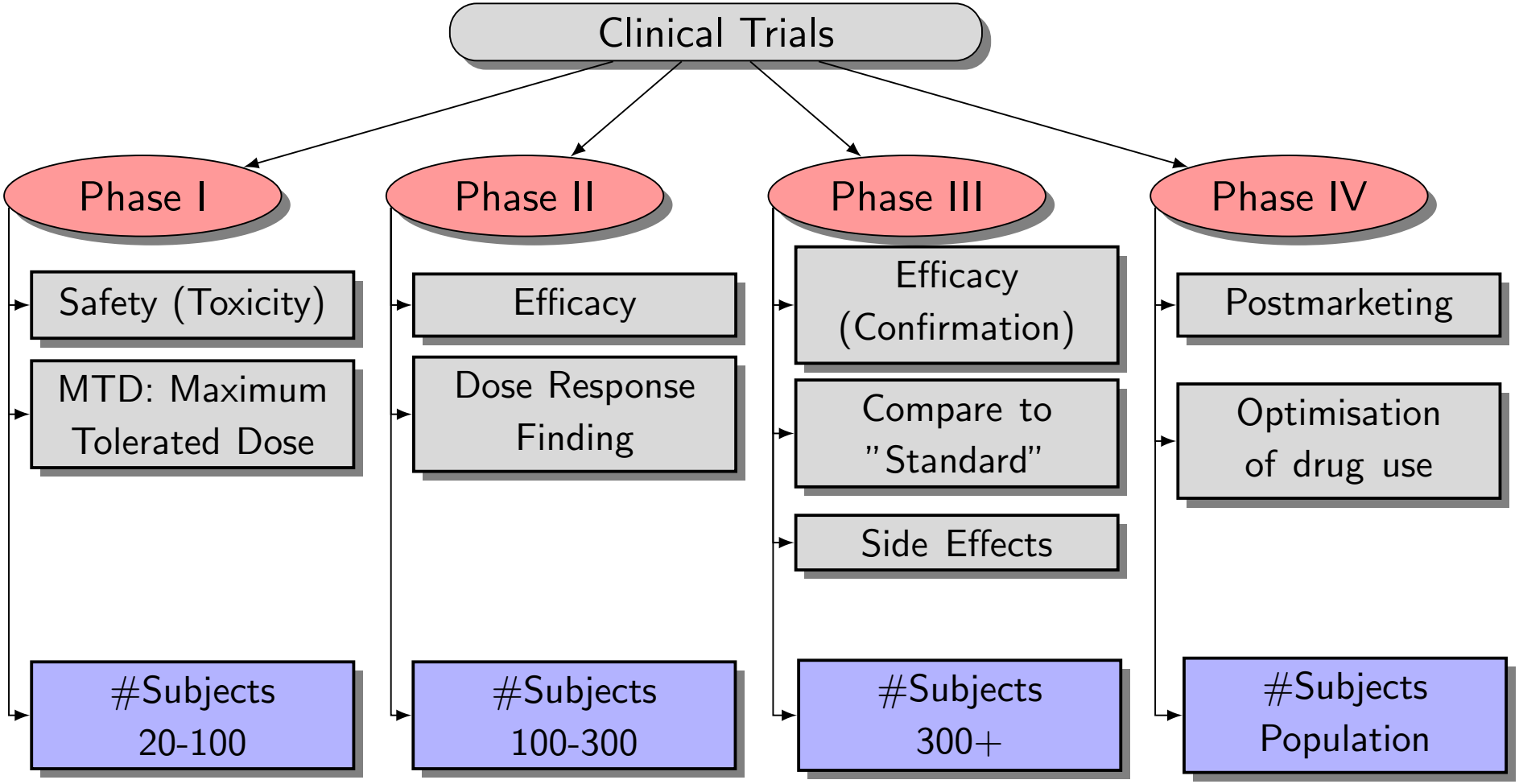

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Very Expensive (!) Process

It costs ~***$2.56B*** to bring a New Medicine to a Market!!![1]

March 10, 2016

Tufts CSDD Assessment of Cost to Develop and Win Marketing Approval for a New Drug Now Published

BOSTON – March 10, 2016 – The most recent analysis by the Tufts Center for the Study of Drug Development of the average cost to develop and gain marketing approval for a new drug—pegged at $2.558 billion—has been published in the *Journal of Health Economics*, it was announced today.

[1] The Tufts Center for the Study of Drug Development (independent, academic, non-profit research group at Tufts University in Boston, Massachusetts).

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Call for Innovation

Recognizing the challenges for modern drug development, the ***FDA*** released the ***Critical Path Initiative*** to encourage use of innovative tools to streamline drug development:

- Biomarkers
- Innovative trial designs
- Pharmacometrics
- Bioinformatics

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Outline

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Adaptive Designs: Motivation

The commonly used way of conducting a clinical trial:

- n subjects are involved in a study.
- $K \geq 2$ treatment arms are investigated (selected).
- Subjects are allocated to treatments according given proportions (***equal in many cases***).
- Given subjects' responses (***efficacy variables***), statistical inference on drug(s) properties is performed.

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Adaptive Designs: Motivation

- At the planning stage of a trial, various assumptions (treatment effect, variance, dropout rate) must be made. ***Inaccurate assumptions increase risk of trial failure***.
- Having an option to modify trial design adaptively, based on interim results ***can help reduced uncertainty and improve decision-making***.
- Adaptation is a design feature, not a remedy for poor planning

Adaptive Designs: Motivation

Analogy Between Adaptive Designs and Swiss Army Knife[2]

(a) Simple scissor

- Optimal tool for a specific task.

(b) Swiss Army knife

- Versatile tool that combines several individual functions in a single unit.

Giant Swiss Army knife

- Functions for every perceivable need.
- Looks impressive.
- Highly impracticable.
- Very expensive.

[2] Bretz F, Gallo P, Maurer W (2017) *The Swiss Army knife among clinical trial designs?* Clinical Trials 14(5), 417-424

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Types of Adaptation Available

- ***Adaptive allocation rule*** – change in the randomization procedure to modify the allocation proportion or the number of treatment arms
- ***Adaptive sampling rule*** – change in the number of study subjects
- ***Adaptive stopping rule*** – early stopping due to efficacy, futility, or safety
- ***Adaptive decision rule*** – change in the way decisions will be made about the trial (e.g., change of endpoint, change of test statistics, etc.)

In practice, combinations of adaptive rules are used.

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Adaptive Randomization

Let us consider a clinical trial with n subjects involved.

Let

- $T_1, T_2, \ldots, T_n, \quad T_j = k \quad (j = 1, 2, \ldots, n; \quad k = 1, 2, \ldots, K)$ be a ***sequence of treatment assignments***;
- $X_1, X_2, \ldots, X_n, \quad X_j = x_k \quad (j = 1, 2, \ldots, n; \quad k = 1, 2, \ldots, K)$ be a ***sequence of responses***;
- $\boldsymbol{Z}_1, \boldsymbol{Z}_2, \ldots, \boldsymbol{Z}_n, \quad \boldsymbol{Z}_j = \left(z_j^{(1)}, z_j^{(2)}, \ldots, z_j^{(r)}\right)' \quad (j = 1, 2, \ldots, n)$ be a ***sequence of subjects' covariates***;

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Adaptive Randomization

- ***Allocation-Adaptive Randomization (AAR)***

$$P_k(j) = \Pr\left(T_j = k | T_1, \ldots, T_{j-1}\right).$$

- ***Response-Adaptive Randomization (RAR)***

$$P_k(j) = \Pr\left(T_j = k | T_1, \ldots, T_{j-1}, X_1, \ldots, X_{j-1}\right)$$

- ***Covariate-Adaptive Randomization (CAR)***

$$P_k(j) = \Pr\left(T_j = k | T_1, \ldots, T_{j-1}, \boldsymbol{Z}_1, \ldots, \boldsymbol{Z}_{j-1}, \boldsymbol{Z}_j\right)$$

- ***Covariate-Adjusted Response-Adaptive Randomization (CARA)***

$$P_k(j) = \Pr\left(T_j = k | T_1, \ldots, T_{j-1}, X_1, \ldots, X_{j-1}, \boldsymbol{Z}_1, \ldots, \boldsymbol{Z}_{j-1}, \boldsymbol{Z}_j\right)$$

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Three Steps to Develop an Optimal Randomization Procedure

- Derive an ***optimal allocation*** to satisfy selected experimental objectives.
- Choose ***randomization procedure(s)*** to implement the desired optimal allocation.
- Evaluate ***operating characteristics*** of the optimal randomization procedures under a variety of standard to worst-case scenarios

Select one that has best performance for use in practice

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Outline

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Optimal Allocation

Consider a clinical trial with $K \geq 2$ treatment arms for which we want to find an ***optimal design***. Then, one has to perform the following steps:

1. Study objectives are formulated as a mathematical problem (***usually as an optimization problem***).
2. ***Optimal allocation*** $\boldsymbol{\rho}^* = (\rho_1^*, \rho_2^*, \ldots, \rho_K^*)$ is found as a solution of the problem under constraints:
   - $0 \leq \rho_k^* \leq 1, \quad k = 1, 2, \ldots, K.$
   - $\sum_{k=1}^{K} \rho_k^* = 1.$
3. A ***randomization procedure*** has to be constructed:
   - it sequentially allocates subjects to treatments.
   - the allocation proportion vector

$$(n_1/n, n_2/n, \ldots, n_K/n) \approx (\rho_1^*, \rho_2^*, \ldots, \rho_K^*)\,.$$

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Optimal Allocation: Example #1

- Two treatment groups: 1 and 2.
- $n = n_1 + n_2$ – total sample size (fixed).
- $\rho^* \in (0, 1)$ – optimal allocation proportion for treatment 1 (to be determined) such that $n_1 = n\rho^*$ and $n_2 = n(1 - \rho^*)$.
- $Y_{jk} \sim Normal(\mu_k, \sigma^2)$ – response of the jth $(j = 1, 2, \ldots, n)$ patient in group k $(k = 1, 2)$.
- ***Objective***: Maximize power of t-test for testing $H_0 : \mu_1 = \mu_2$.
- ***Solution***: $\rho^* = 0.5$ (equal number of patients should be assigned to treatments 1 and 2).

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Optimal Allocation: Example #2

- Two treatment groups: 1 and 2.
- $n = n_1 + n_2$ – total sample size (fixed).
- $Y_{jk} \sim Bernoulli(p_k)$ – binary response of the jth $(j = 1, 2, \ldots, n)$ patient in group k $(k = 1, 2)$. Here, $p_k = \Pr(Y_{jk} = 1)$ – probability of success.
- ***Objective 1***: Maximize power of Z-test for testing $H_0 : p_1 = p_2$.
  - ***Solution 1***: $\rho^* = \frac{\sqrt{p_1 q_1}}{\sqrt{p_1 q_1} + \sqrt{p_2 q_2}}$.
- ***Objective 2***: Minimize expected number of treatment failures subject to fixed power of Z-test under $H_0 : p_1 \neq p_2$.
  - ***Solution 2***: $\rho^* = \frac{\sqrt{p_1}}{\sqrt{p_1} + \sqrt{p_2}}$.

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Optimal Allocation: Example #2

- Two treatment groups: 1 and 2.
- $n = n_1 + n_2$ – total sample size (fixed).
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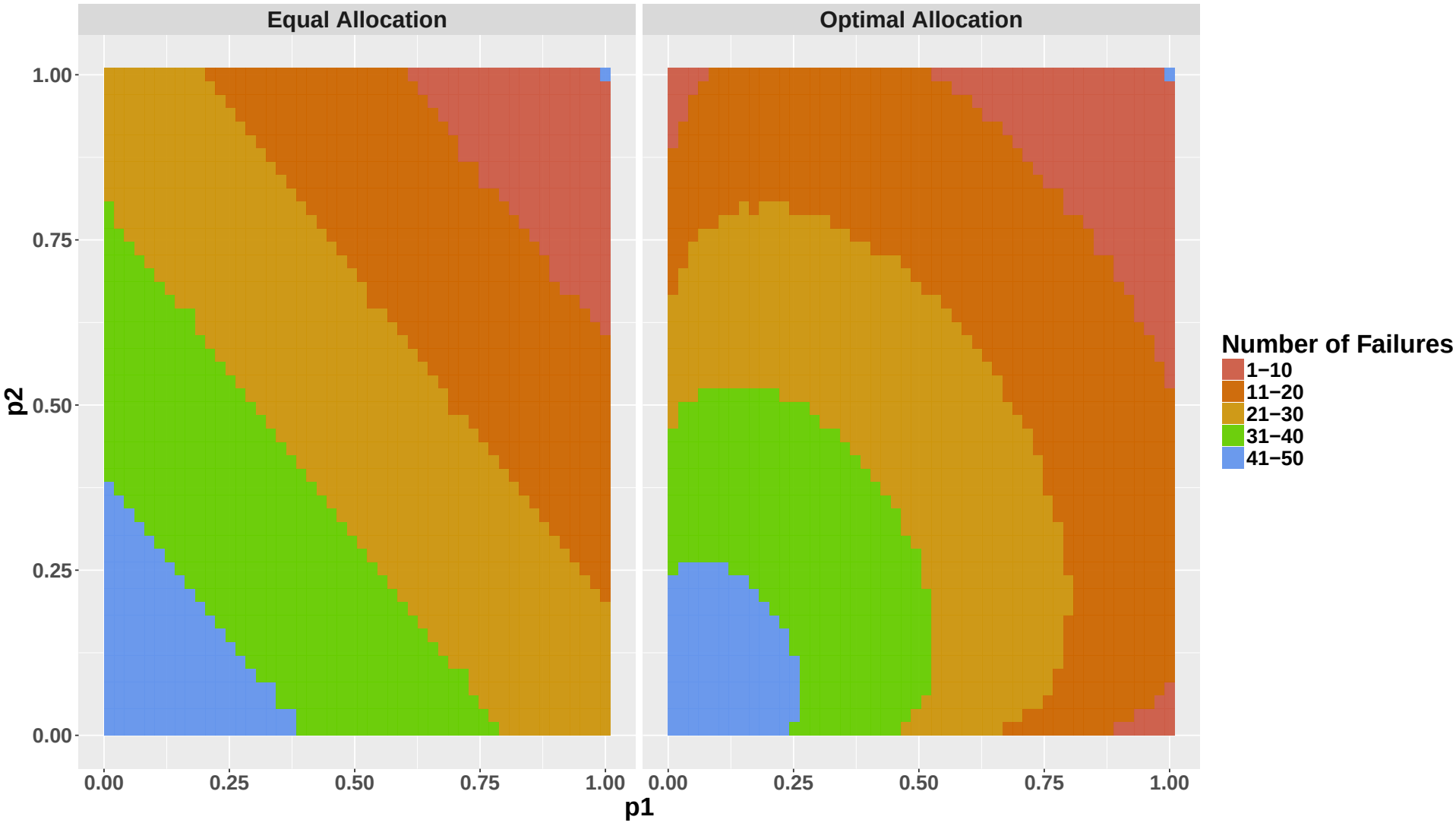

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Optimal Allocation: Example #3

D-optimal design for dose-finding studies with TTE outcomes

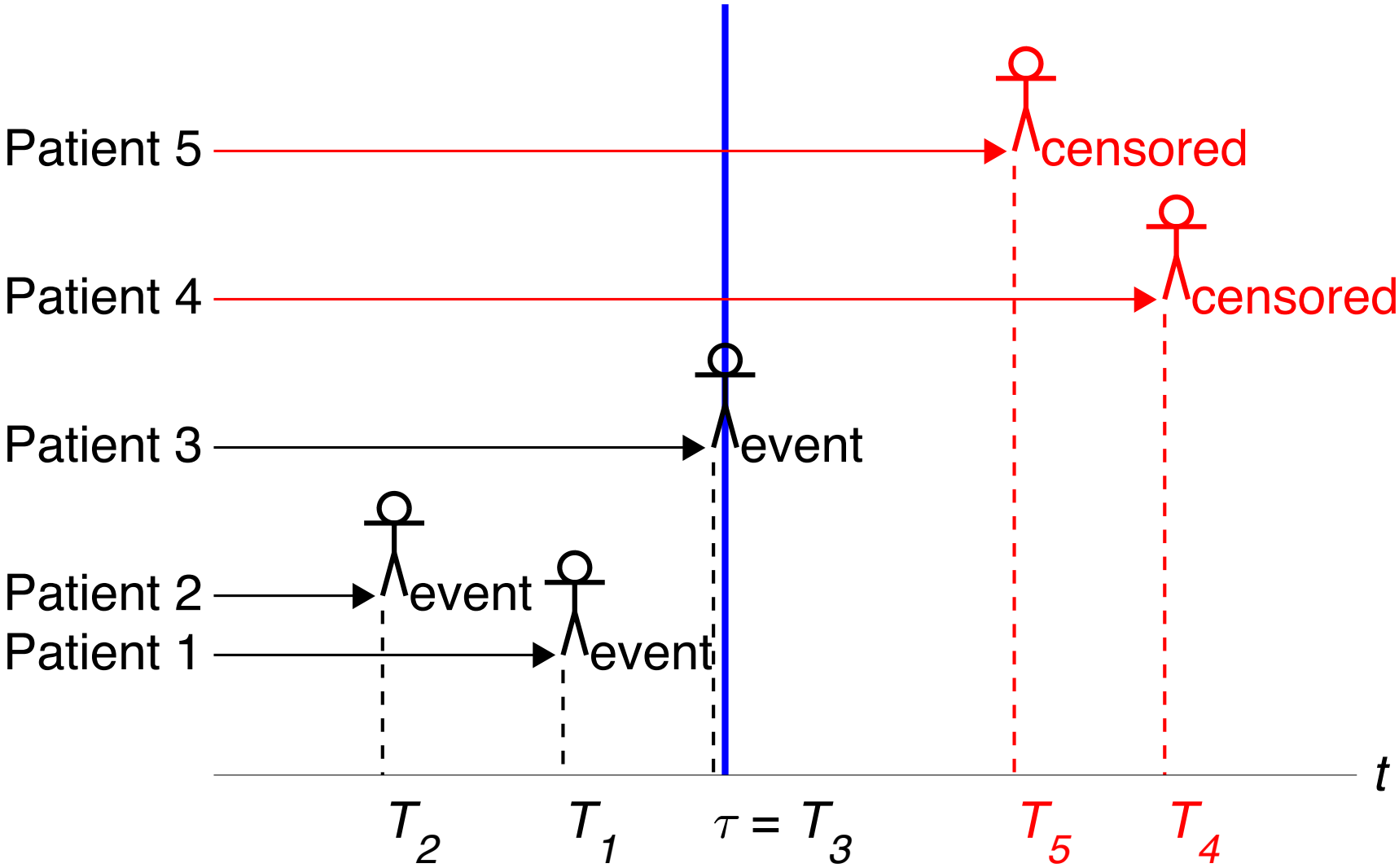
- $T \sim Weibull(\lambda, k), \quad f_T(t) = \frac{k}{\lambda}\left(\frac{t}{\lambda}\right)^{k-1} \exp\left(-\left(\frac{t}{\lambda}\right)^k\right)$
- ***Accelerated Failure Time (AFT) model***:

$$\begin{aligned} \log(T) &= \beta_0 + \beta_1 x + \beta_2 x^2 + b\varepsilon \\ \lambda &= \exp\left(\beta_0 + \beta_1 x + \beta_2 x^2\right), \quad b = k^{-1} \\ \varepsilon \sim f_\varepsilon(u) &= \exp(-\exp(-u)) - \underline{\text{extreme value distribution}} \\ x \in \mathcal{X} &= [0,1] \text{ is a treatment dose} \end{aligned}$$

- The aim is to define a dose-response curve (***Median TTE***)

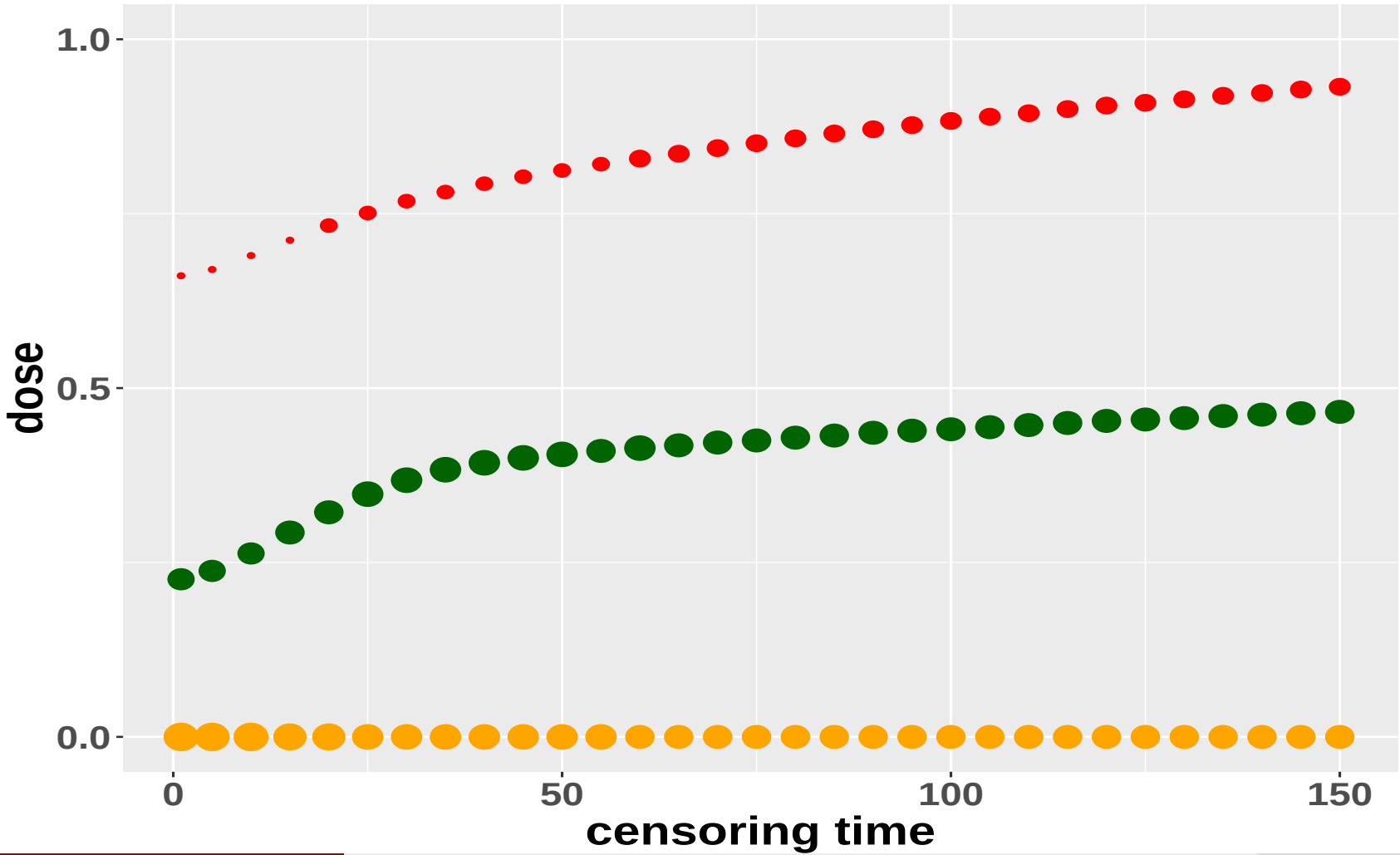
$$Median(T|x) = \exp\left(\beta_0 + \beta_1 x + \beta_2 x^2\right) \log^b(2)$$

Optimal Allocation: Example #3



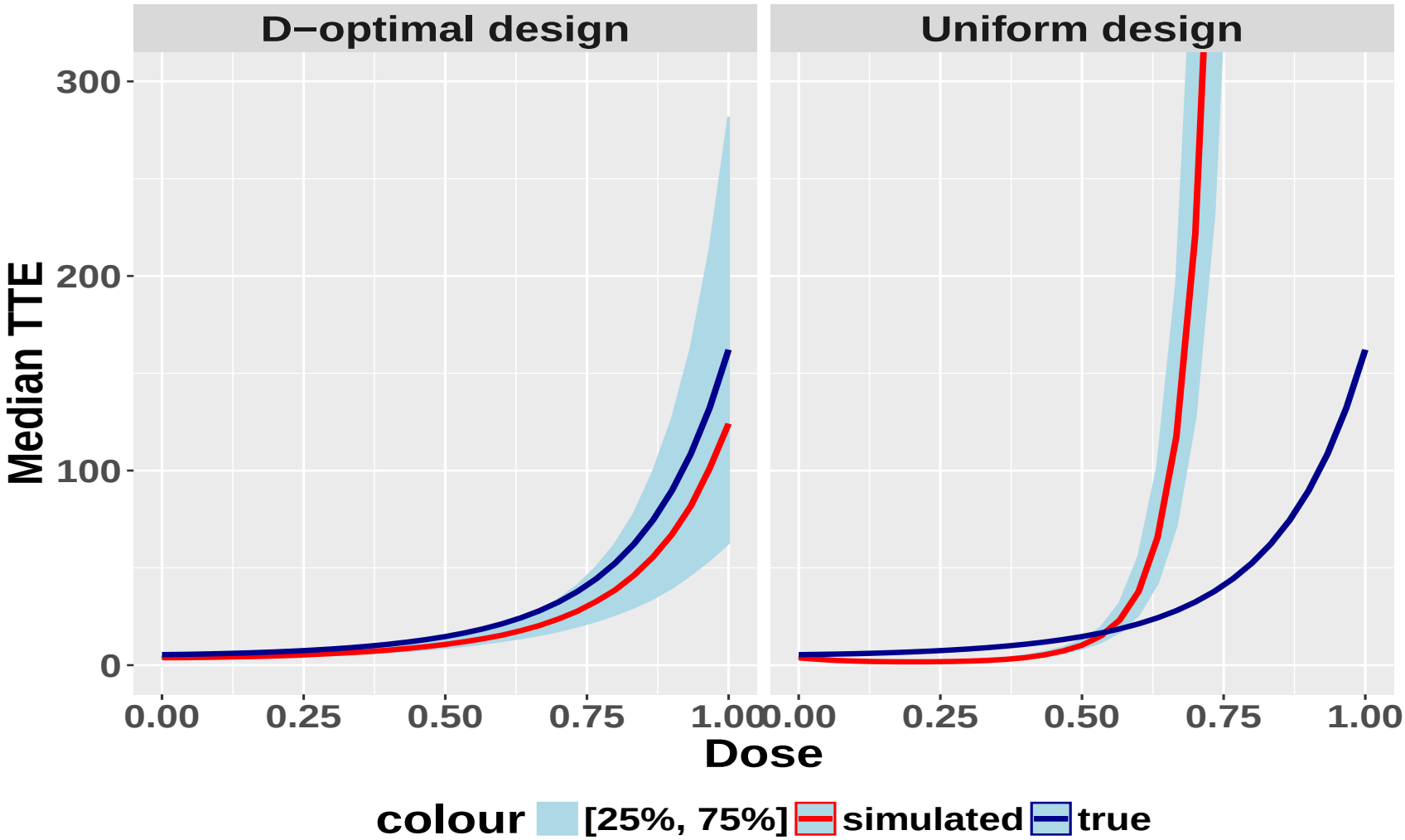
Optimal Allocation: Example #3

Optimal design vs. censoring time: $(\beta_0 = 1.9, \beta_1 = 0.6, \beta_2 = 2.8, b = 0.57721)$



Optimal Allocation: Example #3

Dose-response fit, response rate = 50%: $(\beta_0 = 1.9, \beta_1 = 0.6, \beta_2 = 2.8, b = \gamma)$



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Optimal Allocation: Summary

- Choice of the target allocation ratio stems from the study objectives.
- ***Unequal allocation designs may be preferred*** over equal allocation designs for statistical (e.g. power/efficiency) and ethical reasons.
- Practical implementation of the chosen target allocation requires a ***careful choice of randomization*** (which can promote selected study objectives while ***protecting study from experimental bias***)

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Outline

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AAR

The following randomization procedures target allocation ratio

$$w = (w_1 : w_2 : \ldots : w_K)\,, \quad w_k \in \mathbb{N}, \quad GCD(w_1, w_2, \ldots, w_K) = 1,$$

$$\boldsymbol{\rho}^* = (\rho_1, \rho_2, \ldots, \rho_K)\,, \quad \rho_k = \frac{w_k}{\sum_{i=1}^{K} w_k}.$$

- Permuted Block Design (PBD)
- Block Urn Design (BUD)
- Mass Weighted Urn Design ($MWUD$)
- Drop-the-Loser Urn Design ($DLUD$)
- Doubly-Adaptive Biased Coin Design ($DBCD$)
- Maximum Entropy Constraint Balance Randomization ($MaxEnt$)

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- Maximum Entropy Constraint Balance Randomization ($MaxEnt$)

All the designs depend on a tweak parameter the choice of which is an open question!

Charachteristics of randomization procedure:

- ***Imbalance***

$$Imb(n) = \frac{1}{n}\sum_{j=1}^{n}\sqrt{\sum_{k=1}^{K}\left(N_k(j) - j\rho_k\right)^2}$$

- ***Forcing Index***

$$FI(n) = \frac{1}{n}\sum_{j=1}^{n}\left(\sum_{k=1}^{K}\left(P_k(j) - \rho_k\right)^2\right)$$

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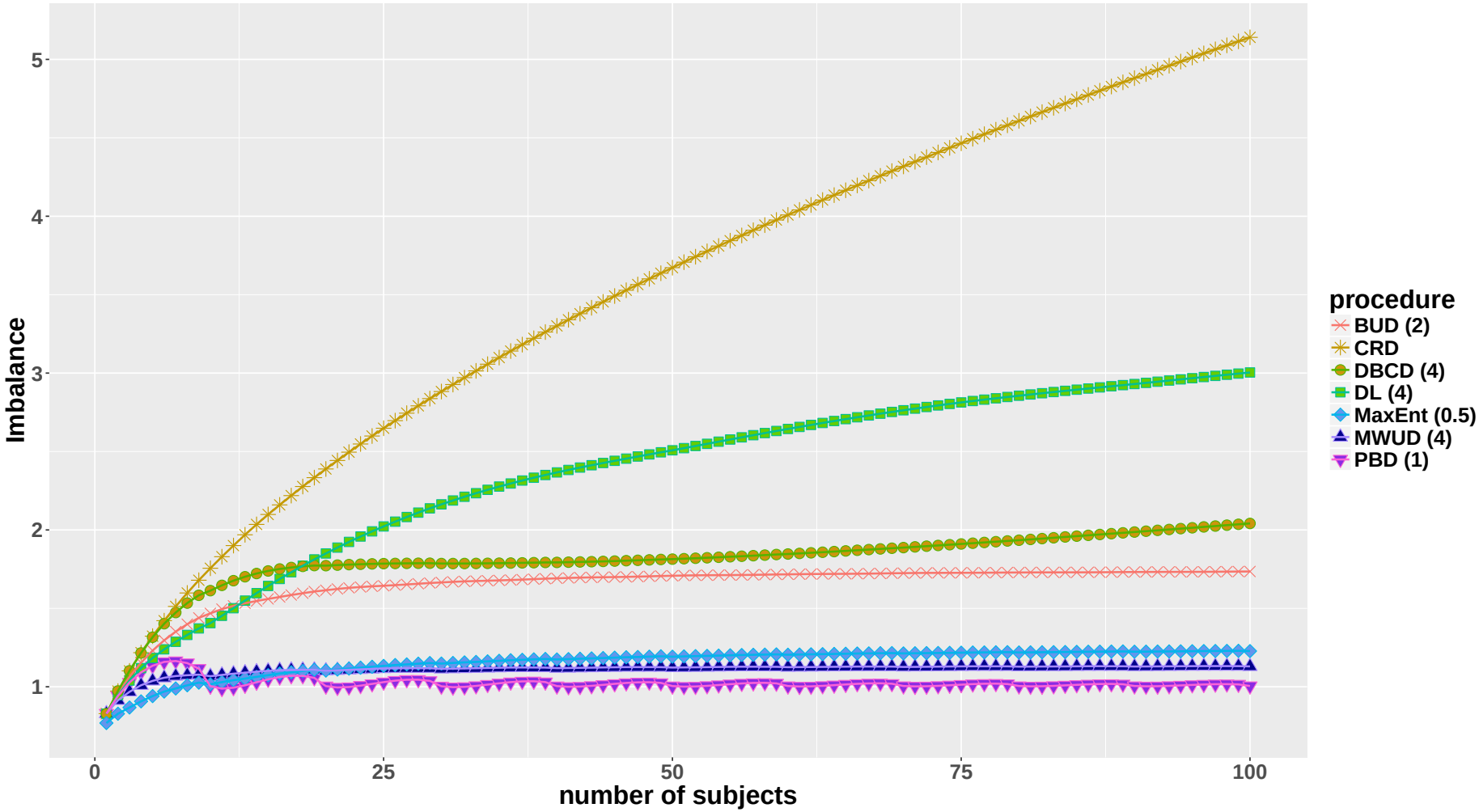
AAR

Imbalance plot



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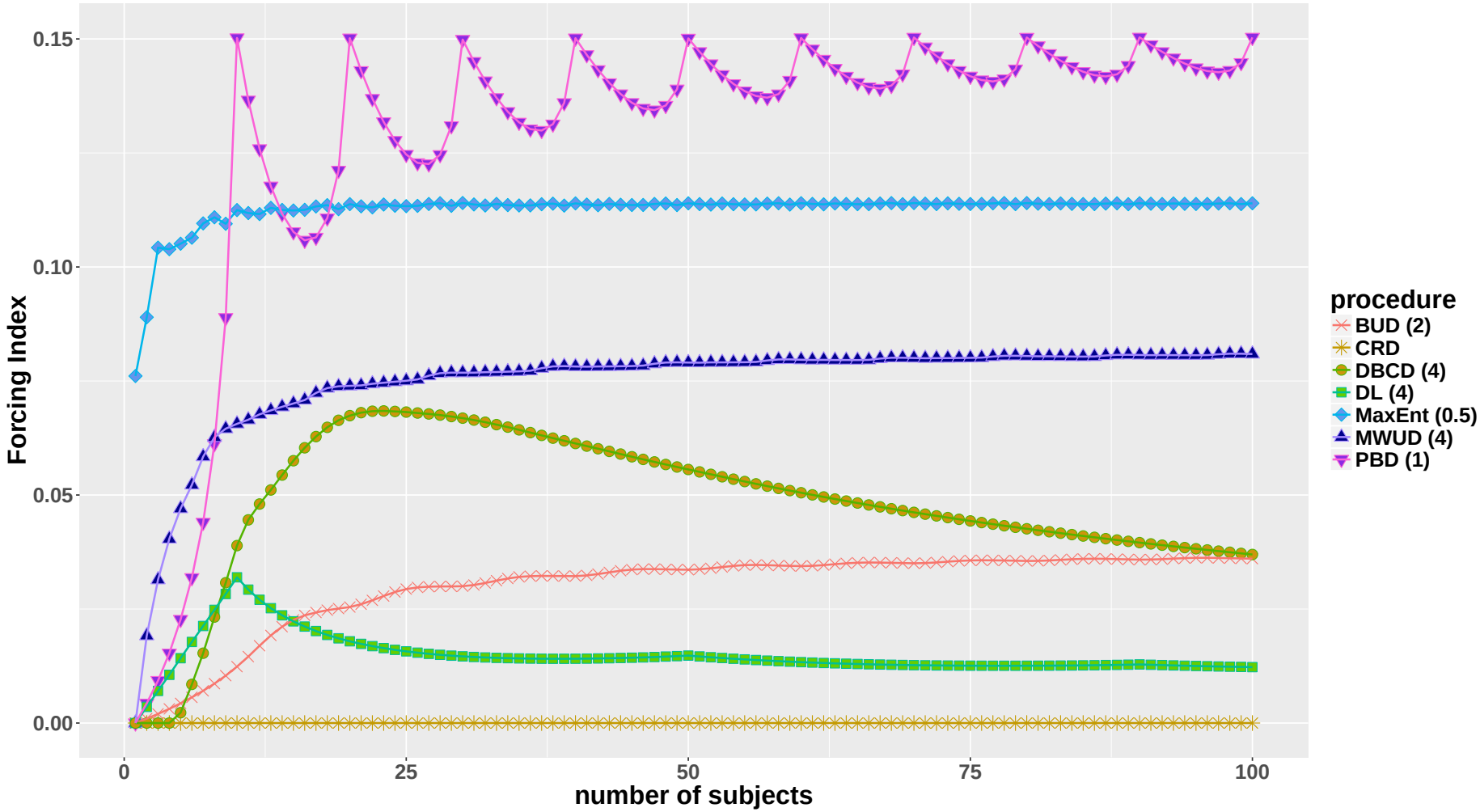
Forcing index plot



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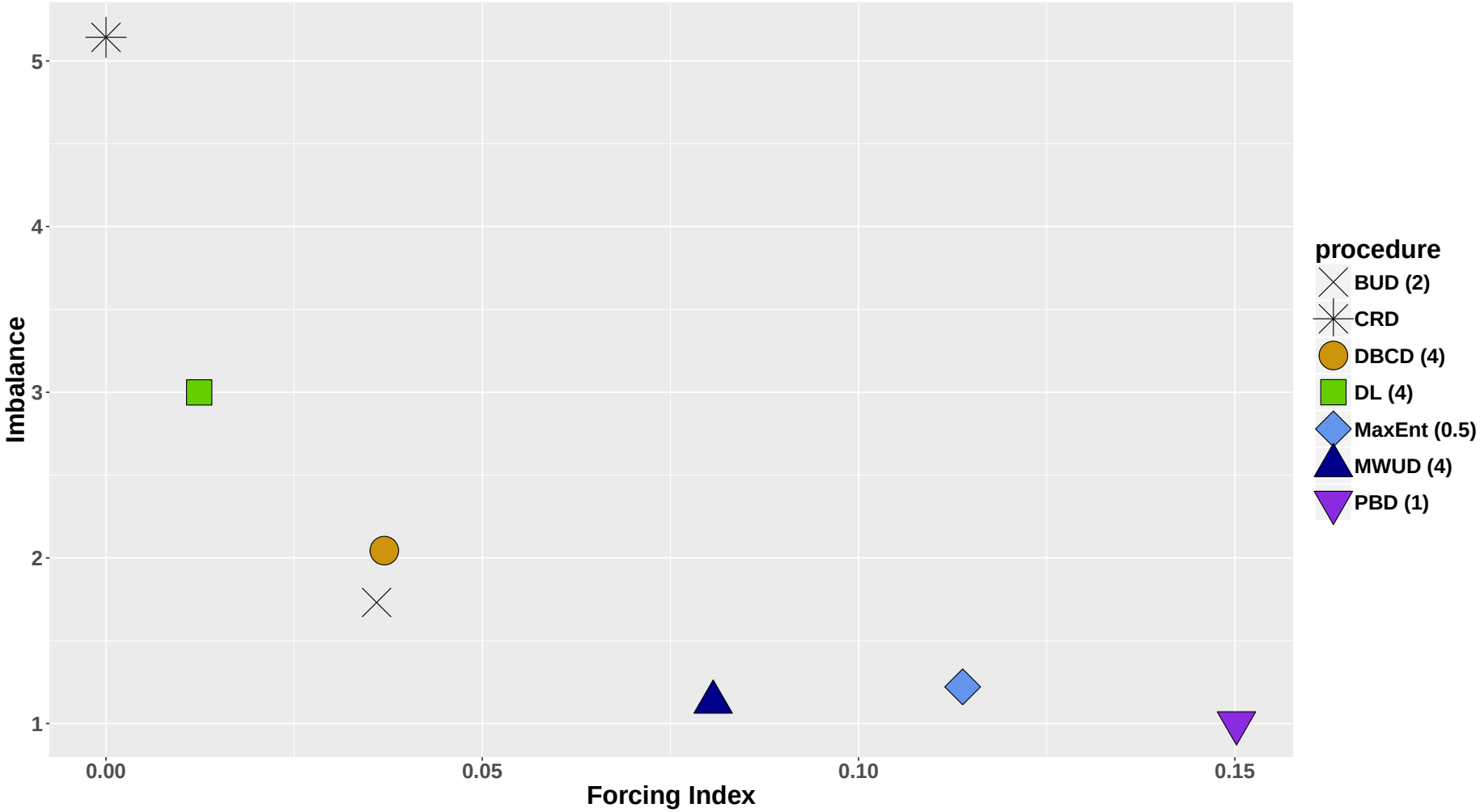
Imbalance vs. Forcing index



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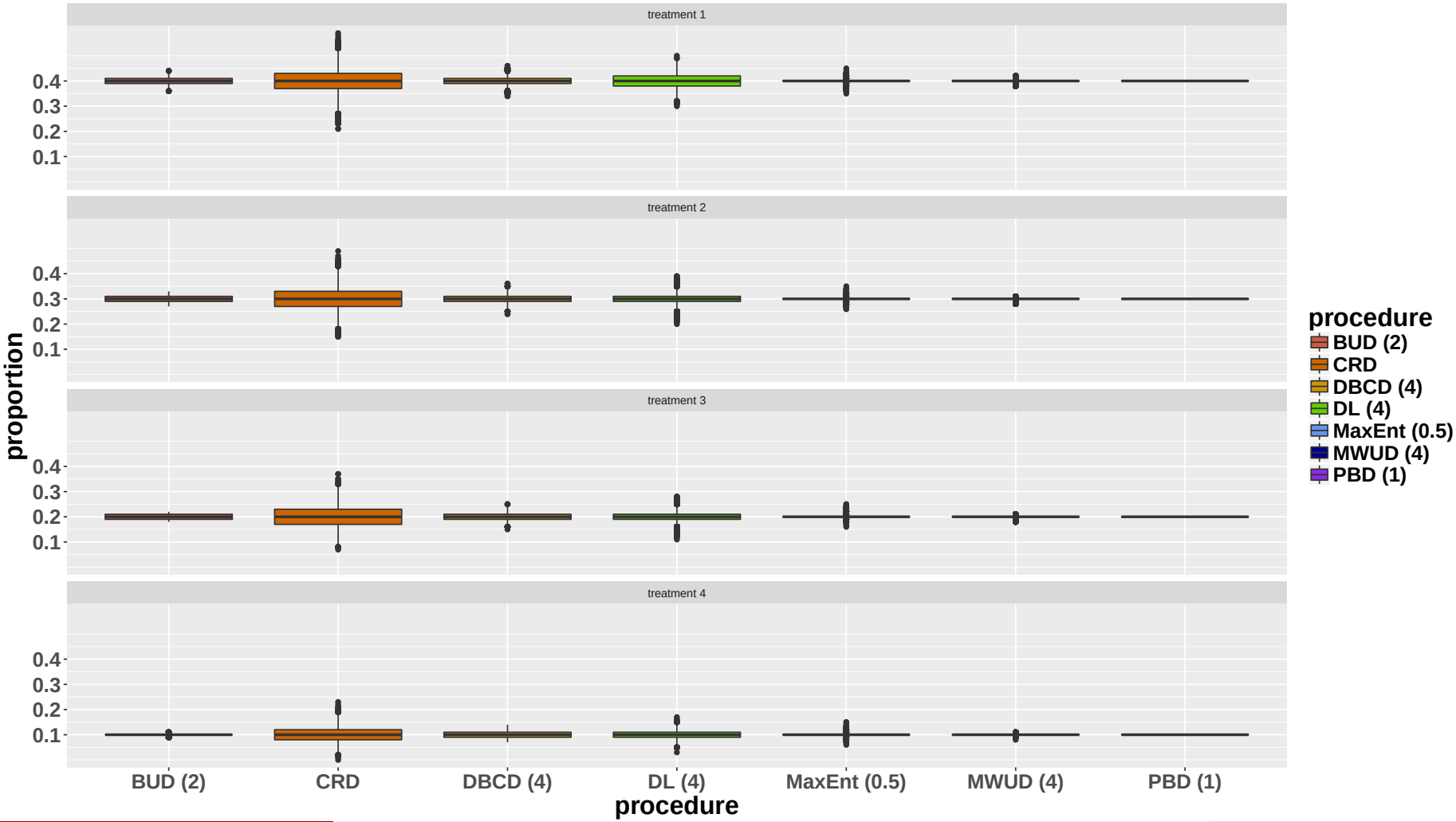
Distributions of final allocation proportions



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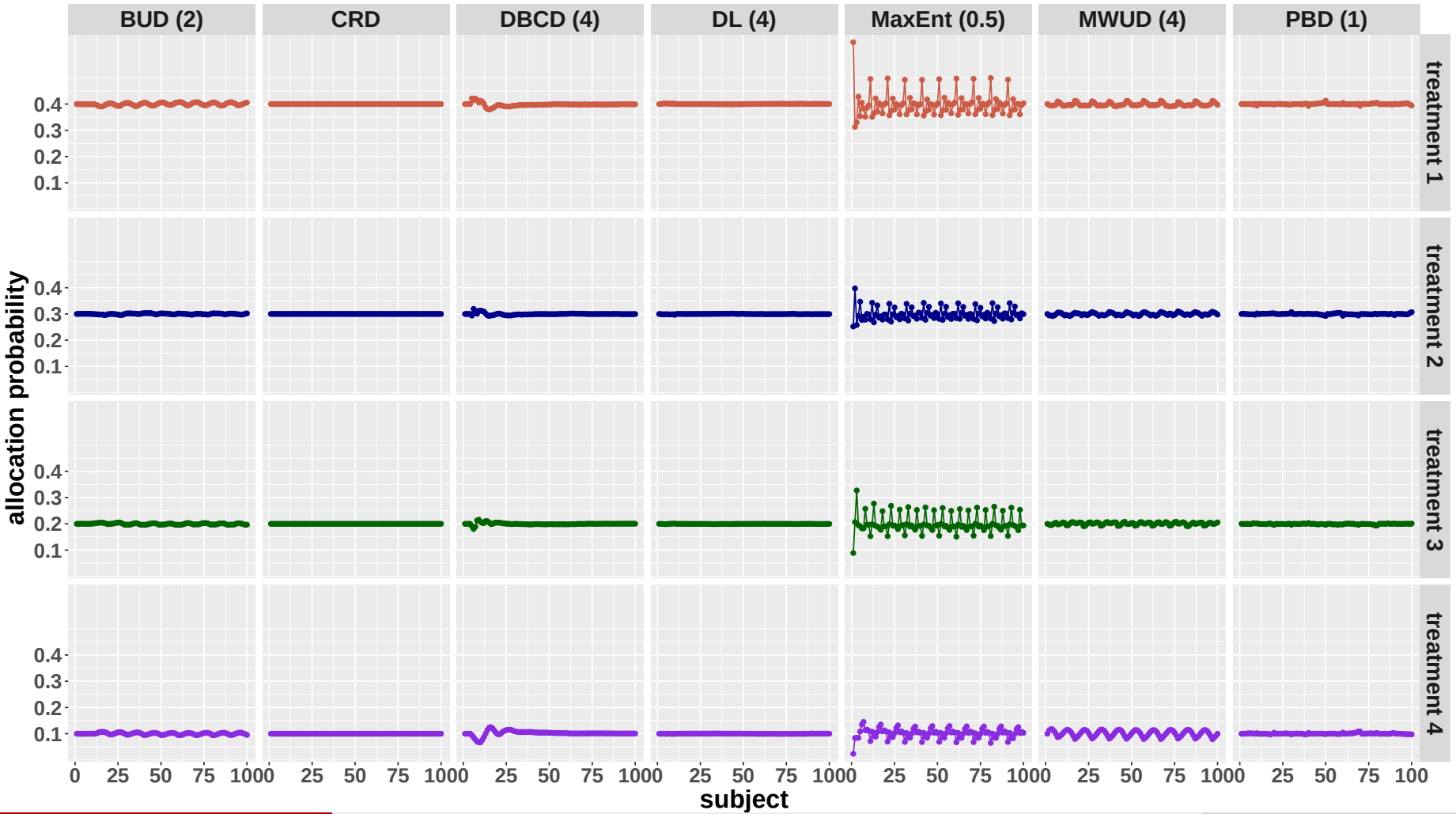
AAR

Allocation ratio preserving (ARP) property



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Outline

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RAR

Let us consider a ***dose-finding trial with time-to-event outcomes*** and n subjects involved.

$$Median(T|x) = \exp\left(\beta_0 + \beta_1 x + \beta_2 x^2\right) \log^b(2)$$

A D-optimal optimal allocation as well as optimal treatments (doses) are found as a solution of the following optimization problem

$$(\boldsymbol{x}^*, \boldsymbol{\rho}^*) = \arg\max_{(\boldsymbol{x},\boldsymbol{\rho})} \det|\boldsymbol{FIM}(\boldsymbol{x}, \boldsymbol{\rho}, \boldsymbol{\theta})|, \quad \boldsymbol{\theta} = (\beta_0, \beta_1, \beta_2, b)$$

$$x_k \in [d_{min}, d_{max}], \quad k = 1, 2 \ldots, K$$

$$\text{s.t.} \quad \rho_k \in [0, 1], \quad k = 1, 2 \ldots, K$$

$$\sum_{k=1}^{K} \rho_k = 1$$

"Ideal" case

- All subjects are available.
- They are just splitted into two groups

$$n_1 \approx n\rho_1^*, \quad n_2 \approx n\rho_2^*, \quad n_3 \approx n\rho_3^*.$$

(we assume that n_1, n_2 and n_3 are rounded up to integers, if necessary)

RAR

However, there are potential problems with this approach:

- All n subjects are unavailable at the beginning of the trial.
- Model parameters $\boldsymbol{\theta} = (\beta_0, \beta_1, \beta_2, b)$ are unknown at the beginning of the trial. Basically, the trial itself is conducted to estimate $\boldsymbol{\theta}$ (and perform other statistical analysis, such as, for example, hypothesis testing of $H_0 : \beta_1 = \beta_2 = 0$)
- Subjects cannot be just "split" into groups. They must be randomized in order to avoid selection bias.

Randomization is an essential component of any comparative experiment.

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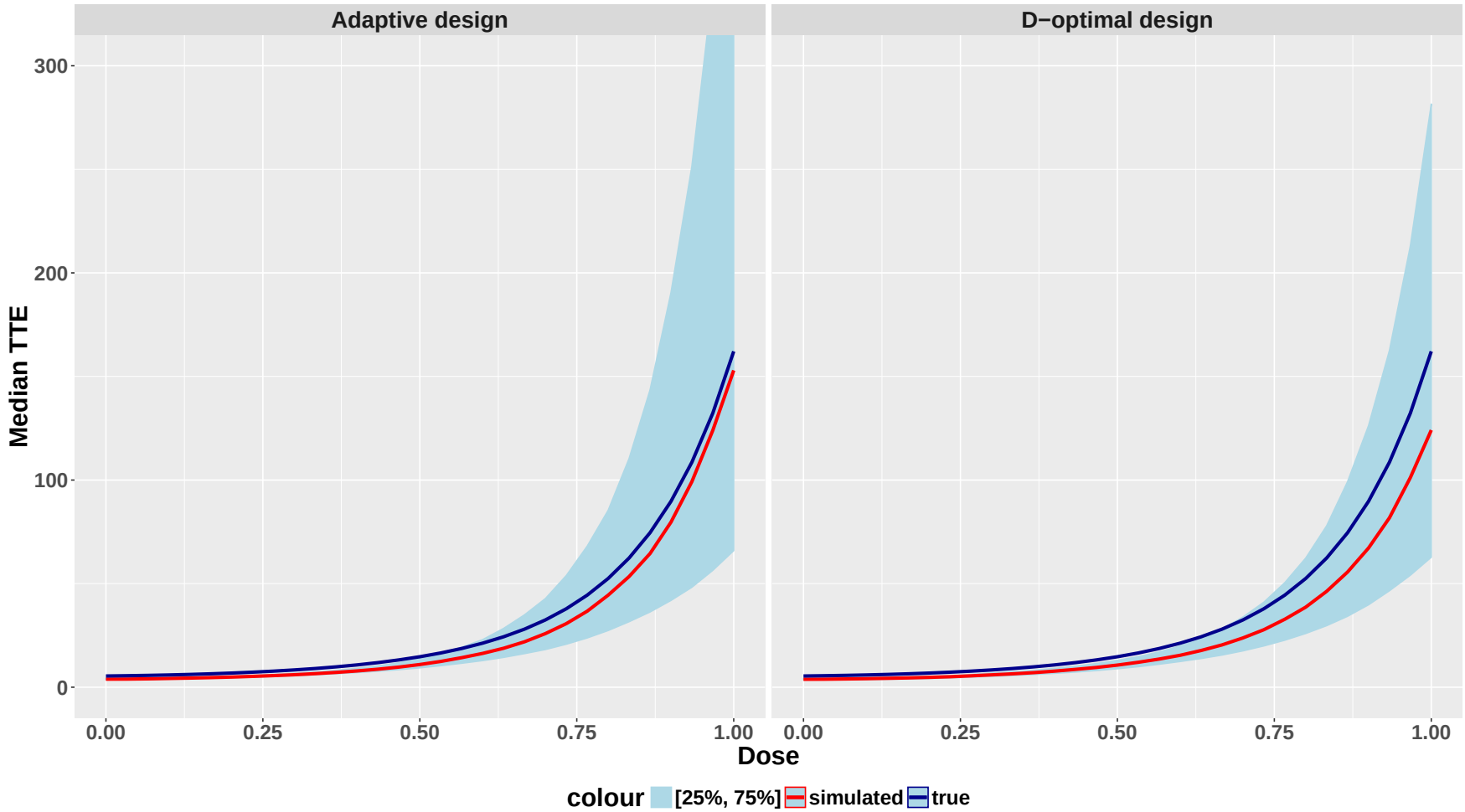
RAR

- In practice, the n subjects enter the trial sequentially and must be immediately randomized to one of K $(= 3)$ treatments.
- The enrolled subjects generate data, and these data can be used to sequentially estimate the model parameters $\boldsymbol{\theta} = (\beta_0, \beta_1, \beta_2, b)$.
- Thus, we construct ***response-adaptive randomization*** procedures which converges to the desired optimal allocations.

Dose-finding studies for TTE outcomes



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Outline

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CAR

- In most randomized phase III clinical trials patients are heterogeneous.
- ***Linear regression model with constant variance*** for the primary outcome – the most efficient allocation is one for which treatment numbers are balanced, both overall and across selected covariates.
- ***Heteroscedastic or nonlinear model*** for the primary outcome – the concept of balance is different from the linear model case.
  - Covariate-balanced response-adaptive design.

CAR

Why is it important to force balance over known covariates?
Let us consider a model where responses follow a linear regression model with constant varince

$$\boldsymbol{Y} = \mu + \alpha \boldsymbol{t} + \beta \boldsymbol{z}_1 + \varepsilon,$$

where

- μ is the overall mean.
- α is the treatment effect.
- β is the covariate effect.
- $\boldsymbol{t}$ is an n-vector of treatment assignments (whose elements are 1 or -1).
- $\boldsymbol{z}_1$ is an n-vector of covariate values.
- $\varepsilon \sim N(0, \sigma^2 \boldsymbol{I})$.

CAR

Why is it important to force balance over known covariates?

Let

- $\boldsymbol{\theta} = (\mu, \alpha, \beta)$ be a vector of unknown parameters;
- $\boldsymbol{X} = [\mathbf{1}, \boldsymbol{t}, z_1]$ be a design matrix (for simplicity, assume that $\boldsymbol{z}_1$ is centred and scaled, that is, $\mathbf{1}\boldsymbol{z}_1' = 0$, and $\boldsymbol{z}_1\boldsymbol{z}_1' = 1$);
- $\widehat{\boldsymbol{\theta}} = (\boldsymbol{X}'\boldsymbol{X})^{-1}\boldsymbol{X}'\boldsymbol{Y}$. be the least square estimator of $\boldsymbol{\theta}$;

The variance-covariance matrix of $\widehat{\boldsymbol{\theta}}$ is given by

$$\text{Var}\left[\widehat{\boldsymbol{\theta}}\right] = \sigma^2(\boldsymbol{X}'\boldsymbol{X})^{-1}.$$

CAR

Why is it important to force balance over known covariates?
Particularly,

$$\mathrm{Var}\left[\widehat{\alpha}\right] = \frac{\sigma^2}{n - (\boldsymbol{z}'\boldsymbol{t})^2 - (\mathbf{1}'\boldsymbol{t})^2/n}.$$

It is minimized when both

- $\boldsymbol{z}'\boldsymbol{t} = 0$ (balance over covariate).
- $\mathbf{1}'\boldsymbol{t} = 0$ (balanced treatment assignments).

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CAR procedures

- Pocock-Simon's "minimization" procedure (1975).
- Atkinson's biased coin design (1982).
- Covariate-balanced randomization design (Yuan and Huang, 2010)

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Outline

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CARA

Two main reasons to consider ***CARA***:

- ***Statistical***: For nonlinear and heteroscedastic models, optimal allocation may not be balanced across treatment arms.
- ***Ethical***: The degree and direction of treatment effect may differ for patient subgroups within a treatment $\Rightarrow$ increase probability of assigning the treatment that is most efficacious given the patient's covariate profile (***personalized treatment***).

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CARA

CARA Randomization for Survival Trials[3]

- n patients are enrolled sequentially and are randomized to treatments 1 and 2.
- For the j-th patient, survival time T_{jk}, conditional on covariates z_i is exponential with mean

$$\lambda_k(\boldsymbol{z}_j) = \exp\left(\boldsymbol{\theta}_k' \boldsymbol{z}_j\right), \quad k = 1, 2,$$

  where $\theta_k = (\theta_{k0}, \theta_{k1}, \ldots, \theta_{kp})'$ and $\boldsymbol{z}_j = (1, z_{1j}, \ldots, z_{pj})'$.
- T_{jk} is subject to independent right-censoring with $\tau_j > 0$.
  - $t_{jk} = \min(T_{jk}, \tau_j)$,
  - $\delta_{jk} = \mathbf{1}_{t_{jk}=T_{jk}}$,
  - (t_{jk}, δ_{jk}) are independent, $j = 1, \ldots, n_k, \quad k = 1, 2$

[3] Sverdlov O., Rosenberger W.F., Ryeznik Y. (2013) "Utility of covariate-adjusted response-adaptive randomization in survival trials" *Statistics in Biopharmaceutical Research* 5(1), p. 38-53.

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CARA

Example: Redesigning a Survival Trial[3] (cetuximab trial in advanced colorectal cancer)

- In a 21-month period, $n = 572$ eligible patients were randomized at a $1:1$ ratio among TRT 1 (cetuximab plus best supportive care) and TRT 2 (best supportive care alone).
- The primary endpoint was overall survival (OS).
- Effectiveness of cetuximab was significantly associated with ***K-ras mutation status***:
  - Patients with ***wild-type K-ras tumors*** benefited from cetuximab (median OS, 9.5 vs. 4.8 months; HR for death, 0.55).
  - Patients with a ***colorectal tumor bearing mutated K-ras*** did not benefit from cetuximab (median OS, 4.6 vs. 4.5 months; HR for death, 0.98).

[3] Karapetis, C. S., Khambata-Ford, S., Jonker, D. J., et al. (2008). "K-ras mutations and benefit from cetuximab in advanced colorectal cancer". *The New England Journal of Medicine*, 359, p. 17571765

Simulation Study Results (10,000 simulation runs)

$n = 572$	Pocock-Simon	CARA	RAR
N_A/n (S.D.)	0.500 (0.002)	0.588 (0.037)	0.583 (0.039)
$N_{A0}\|N_{B0}$ (S.D.)	169|169 (1)	211|127 (16)	197|141 (14)
$N_{A1}\|N_{B1}$ (S.D.)	117|117 (1)	125|109 (13)	137|97 (11)
Deaths (S.D.)	372 (11)	362 (12)	366 (12)
Total Time (S.D.)	3076 (106)	3155 (113)	3132 (112)
$\hat{\theta}_{A0}$ (S.D.)	2.62 (0.11)	2.62 (0.10)	2.62 (0.10)
$\hat{\theta}_{A1}$ (S.D.)	-0.68 (0.16)	-0.68 (0.15)	-0.68 (0.15)
$\hat{\theta}_{B0}$ (S.D.)	1.87 (0.09)	1.86 (0.11)	1.87 (0.10)
$\hat{\theta}_{B1}$ (S.D.)	0.02 (0.14)	0.03 (0.16)	0.02 (0.16)

- Because of treatment-covariate interaction, CARA resulted in greater skewing to A in the wild-type *K-ras* subgroup than in the mutated *K-ras* subgroup, whereas RAR had similar degree of skewing in the subgroups.
- CARA and RAR had, on average, 10 and 6 fewer deaths and greater total survival time than the Pocock-Simon design.
- All three procedures had the same power and very similar M.L.E.'s.

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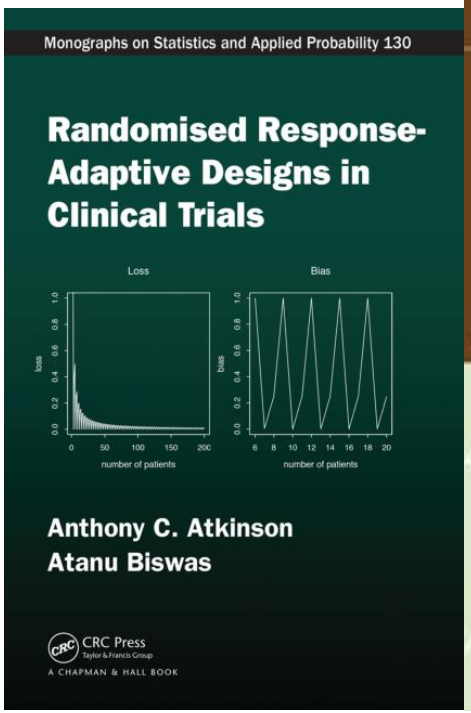
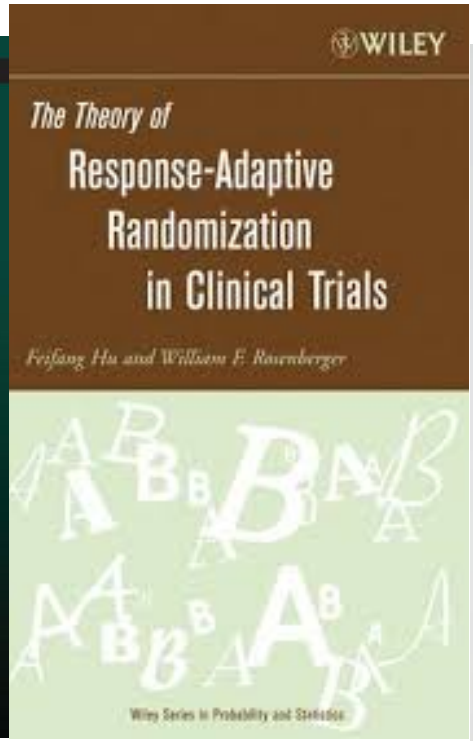
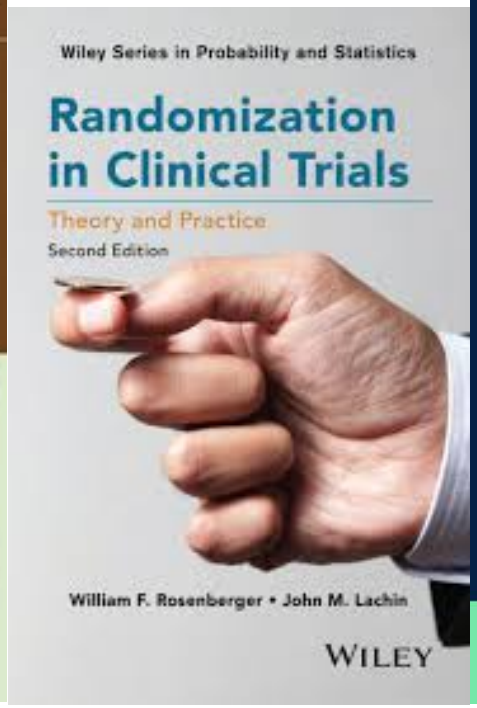
Books







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CIM Course for Master/PhD students (Period IV 2018)

1. Introduction to clinical trials, adaptive designs, optimal adaptive randomization procedures.
2. Choice of a target allocation for a multi-arm clinical trial.
3. Adaptive randomization designs to implement optimal allocation:
   - Allocation-adaptive randomization
   - Covariate-adaptive randomization
   - Response-adaptive randomization
   - Covariate-adjusted response-adaptive randomization
4. Case studies (with examples in R) and practical aspects of implementing adaptive randomization