EFSPI Discussion Session Proposal: Randomization in Clinical Trials

Diane Uschner (Roche, Basel, Switzerland), Olga Kuznetsova (Merck & Co., Inc., Rahway, NJ, USA), Johannes Krisam (Boehringer Ingelheim, Germany), Kerstine Carter (Boehringer Ingelheim, USA), Alex Sverdlov (Novartis, USA), on behalf of the Randomization SIG*

rwg

*diane.uschner@roche.com

Consideration 1:
Current State of Randomization in Clinical Research

Permuted Block Randomization

- Dominant clinical trial design due to ease of implementation and historical agency acceptance
- Controls treatment imbalance and mitigates time trends
- Averages a high rate of deterministic allocations, at a proportion of 2/(B+2) (e.g., 33% for block of length B=4)

Alternative randomization methods

- Include the Big Stick design, Wei's Urn design, or the Maximal Procedure
- Control imbalance equally well while minimizing deterministic allocations to reduce predictability (critical for open-label trials)
- Adoption is hindered by fears of regulatory pushback and prolonged discussion timelines

randomization working group
rwg

Consideration 2:
Scientific Progress & Statistical Validity

- **Major advances regarding the validity of statistical tests** following **Covariate-Adaptive Randomization** (CAR), such as minimization (Pocock and Simon version with a random component) or stratified randomization
- Recent evidence shows: **no Type I error inflation** of the log-rank test following minimization with a random component. These results extend to linear models (publication drafted).
- These **findings challenge the historical preference** by regulatory agencies for randomization-based tests as the primary analysis following randomization by minimization

randomization working group
rwg

Questions for the Regulatory Panel

1) **Alternative Procedures:**
   What is the current regulatory position on utilizing alternative randomization procedures with lower predictability, such as the Big Stick design, Wei's Urn design, or Maximal Procedure, in confirmatory trials?

2) **Inference Requirements:**
   What is the current regulatory position on statistical approaches for inference following covariate adaptive randomization?

3) **Path to Adoption:**
   Is there regulatory willingness to consider new randomization guidance?
   How can we foster the dialogue to adopt novel allocation procedures beyond permuted block designs?

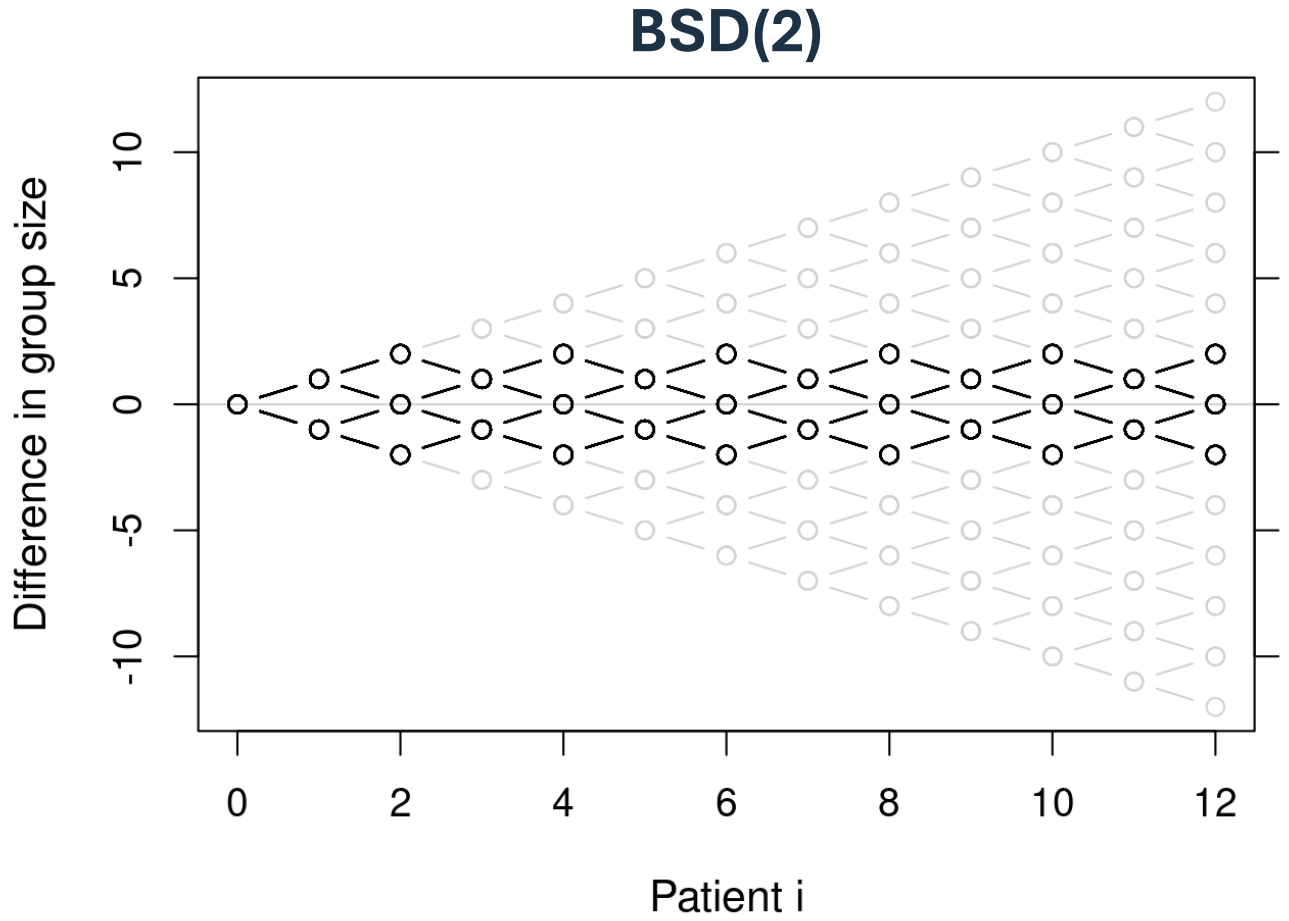
randomization working group
rwg

Appendix

Big Stick Design

The Big Stick Design proposed by Soares and Wu (1983) uses complete randomization whenever the imbalance is strictly below a prespecified maximum tolerated imbalance (MTI) **b** and forces a deterministic corrective assignment whenever the boundary is reached:

$$P(T_{j+1} = A \mid D_j) = \begin{cases} 1, & D_j = -b, \\ \frac{1}{2}, & |D_j| < b, \\ 0, & D_j = +b, \end{cases}$$



Set of all randomization sequences for Big Stick Design with b=2

Soares, J. F., & Jeff Wu, C. F. (1983). Some Restricted randomization rules in sequential designs. Communications in Statistics - Theory and Methods, 12(17), 2017–2034. https://doi.org/10.1080/03610928308828586

randomization working group
rwg

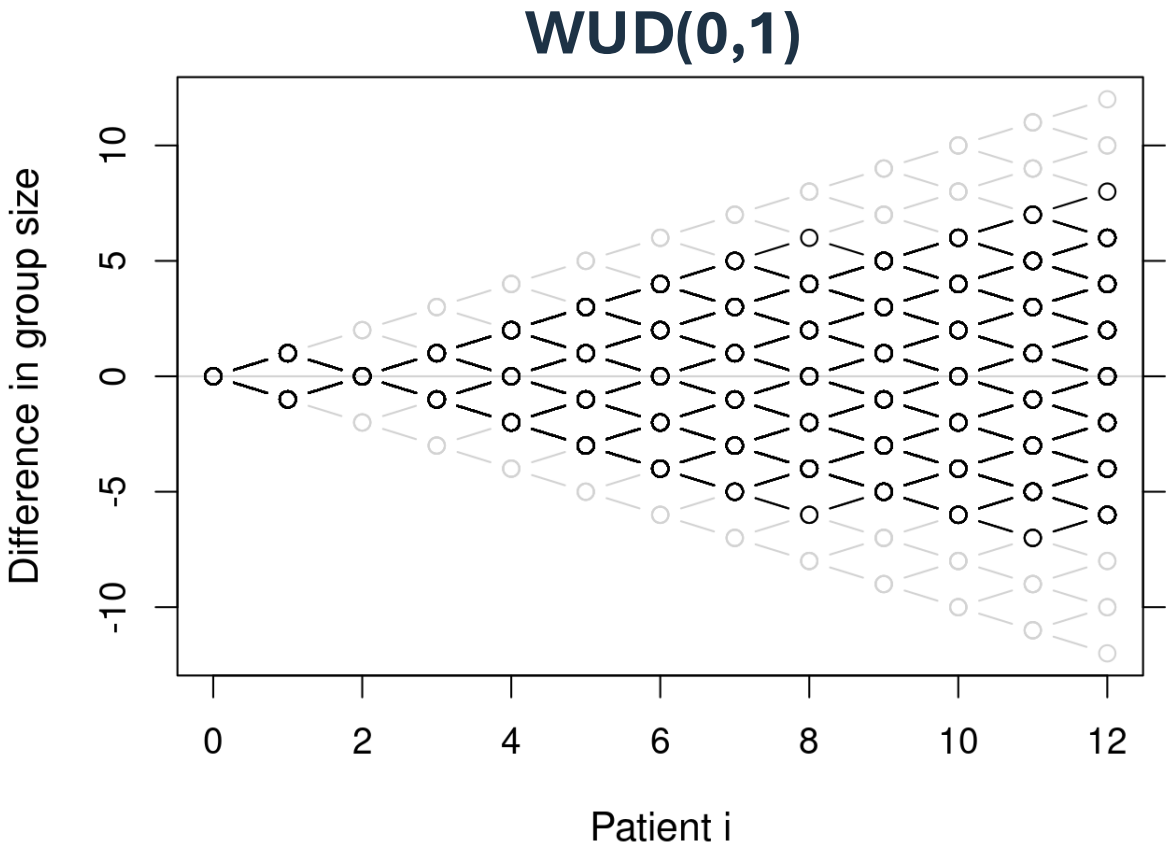
Wei's Urn Design

Wei's Urn Design starts with an urn containing α balls of type A and α balls of type B. At step j + 1 a ball is drawn at random; the corresponding treatment is assigned, the ball is replaced, and β additional balls of the opposite type are added to the urn. The conditional allocation probability is

$$P(T_{j+1} = A \mid \mathcal{H}_j) = \frac{\alpha + \beta\, N_B(j)}{2\alpha + \beta\, j}.$$

Setting α = 0 and β = 1 leaves the urn empty at the start; by convention the first assignment is made with probability 1/2, and for j ≥1

$$P(T_{j+1} = A \mid \mathcal{H}_j) = \frac{N_B(j)}{j} = \frac{1}{2}\left(1 - \frac{D_j}{j}\right).$$



Set of all randomization sequences for Wei's Urn Design with α = 0 and β = 1

Wei, L.J. (1977). A class of designs for sequential clinical trials. Journal of the American Statistical Association, 72(358), 382–386.

randomization working group
rwg

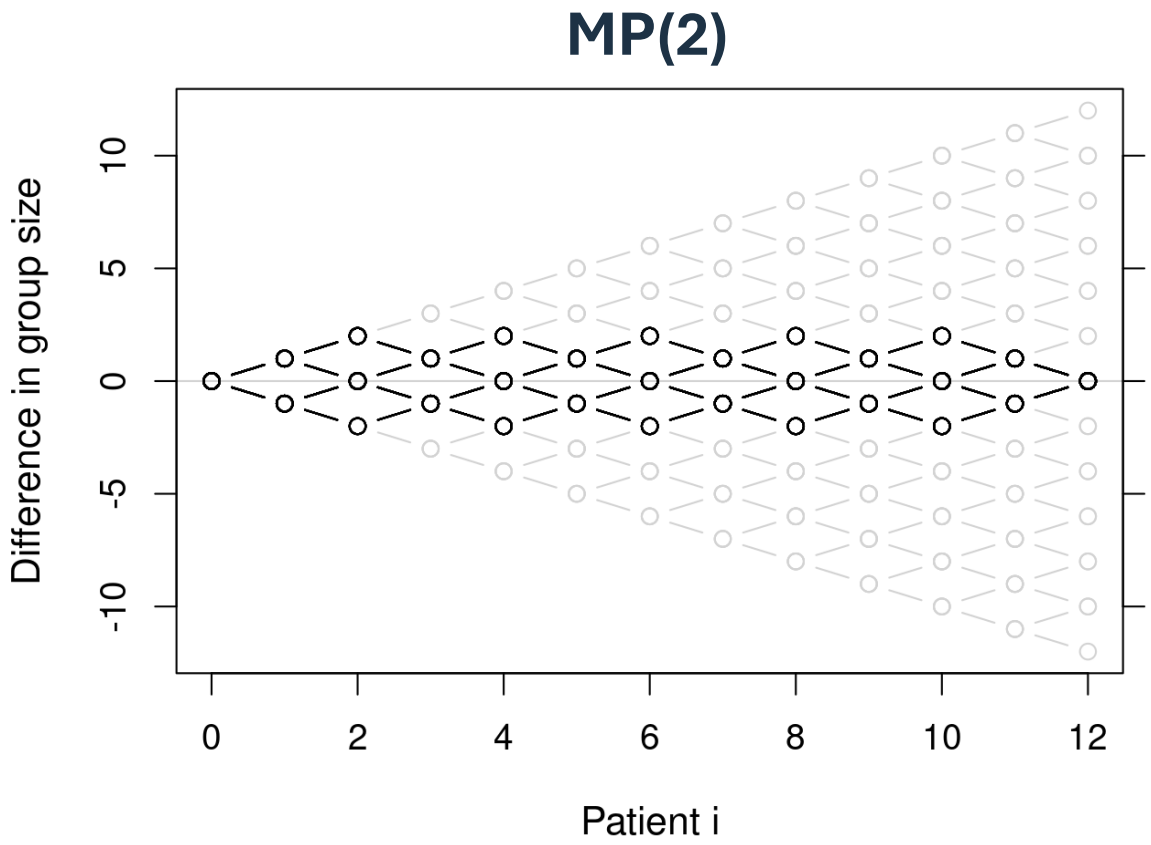
Maximal Procedure

The Maximal Procedure of Berger, Ivanova and Knoll (2003) is defined by uniform sampling from the set of all sequences of length N hat (i) achieve exact final balance ($N_A(N) = N_B(N) = N/2$) and (ii) never exceed the MTI b at any intermediate step

$$\Omega_b = \left\{ (t_1, \ldots, t_N) : \max_{1 \le j \le N} |d_j| \le b, \;\; d_N = 0 \right\},$$

where d_j is the imbalance induced by $(t_1,\ldots,t_j)$. The design places a uniform distribution over Ω_b, i.e. for every admissible sequence $t = (t_1,\ldots,t_N) \in \Omega_b$,

$$P(T = t) = \frac{1}{|\Omega_b|}, \qquad b = 2.$$



Set of all randomization sequences for Maximal Procedure with b=2

Berger VW, Ivanova A, Knoll MD. Minimizing predictability while retaining balance through the use of less restrictive randomization procedures. Stat Med. 2003 Oct 15;22(19):3017-28. doi: 10.1002/sim.1538. PMID: 12973784.

randomization working group
rwg

Minimization

- Largely deterministic version by Taves (1974) – treatment that leads to the smallest imbalance across the set of baseline covariates is assigned to the next subject. Only when the two treatments lead to the same imbalance, an assignment is selected by a toss of a fair coin
  - Taves, D. (1974). Minimization: a new method of assigning subjects to treatment and control groups. Clinical Pharmacology and Therapeutics 15, 443–453.
- Pocock and Simon version uses a biased coin (typically with bias of 0.8 or 0.9) to assign the preferred treatment with high probability, but not deterministically. Recommended over the version without a random element; well studied
  - Pocock, S. J. and Simon, R. (1975). Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 31, 103–115.

Type I error control under Pocock and Simon minimization

- Inferential properties following covariate-adaptive randomization (stratification or dynamic balancing) depend on the asymptotic properties of the covariance matrix of the normalized within-stratum imbalances
  - Shao, J. (2021). Inference after covariate-adaptive randomisation: aspects of methodology and theory. Statistical Theory and Related Fields 5(3), 172–186.
  - Ye, T. and Shao, J. (2020). Robust tests for treatment effect in survival analysis under covariate adaptive randomization. Journal of the Royal Statistical Society, Series B, Statistical Methodology 82(5), 1301–1323.
- The explicit form of the asymptotic covariance matrix has been recently established
  - Kuznetsova, O. M., Johnson, V. P., Gekhtman, M. Explicit form of the asymptotic covariance matrix of the normalized within-stratum imbalances following minimization with independent factors with application to the log-rank test. Statistica Sinica, 2026, DOI: 10.5705/ss.202025.0213 http://www3.stat.sinica.edu.tw/ss_newpaper/SS-2025-0213_na.pdf
- Pocock and Simon minimization with high enough bias (≥0.8) belongs to a class of allocation procedures for which the Type I error of the log-rank test or score test for time-to-event endpoints as well as t-test for continuous endpoints is not inflated
  - Johnson, V. P., Gekhtman, M. and Kuznetsova O.M. (2024). Validity of Tests for Time-to-Event Endpoints in Studies with the Pocock and Simon Covariate-Adaptive Randomization. Statistics in Biopharmaceutical Research 16(4), 468–482.
  - Kuznetsova et al., 2026

randomization working group
rwg