# Dynamic Allocation in Clinical Trials: Past, Present, and Future


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## Introduction

**Motivated by Oncology Landscape**

- Crowded → encourages personalized medicine approach to identify characteristics of patients.
- Combination therapies → as a "backbone" treatment is established, the next wave of development includes add-on therapies.
- Emerging unmet medical need often in later lines of therapy which may have diverse earlier lines.

**Impact on Newer Trials**

- "Just add it as a stratification factor" is often suggested in discussions (e.g., biomarker status, prior response to backbone therapy, prior exposure to X, Y, or Z).
- There may already be existing clinical factors thought to influence treatment that warrant stratification
- Interest in balancing randomization across arms, but difficult to reduce to reasonable size.

## Motivating Example

Phase 2 trial of Nivolumab + Relatlimab vs. mono therapy of Nivolumab.
Stratification wanted on:

- Region (Asia/ Non-Asia)
- Biomarker Expression (Lag 3 +/-)
- Clinical factor (MVI +/-)

Primary endpoint is objective response rate (ORR).

→ 1:1 and 2:1 allocation was considered for 2 arm trial

→2:1:2 allocation ratio was considered for 3 arm trial

## Methods

### Simple Randomization

- Conceptually, it is the simplest and most robust method
- This method does not guarantee equal distribution of treatment assignment.

### Stratified Block Randomization

- Better control of Type 1 error for certain situations (e.g., adaptive allocation ratios, interactions between stratification variables)
- May lead predictability issue.
- Easier for recruitment and lower implementation cost
- Balances specified and unspecified covariates, including temporal effects

### Dynamic Allocation (Minimization)

- Minimization, a form of restricted randomization procedure.
- The minimization procedure maintains marginal balance for each stratum rather than attempting to achieve overall balance.
- Allow unequal allocation ratio (e.g., 2:1)
- Valid alternative for small-to-moderate sized trials with multiple significant prognostic factors having moderate to large treatment effects
- Makes treatment allocations unpredictable

### Hybrid Minimization Approaches

Two novel approaches were proposed based on Minimization method.

- Approach 1: Alternating Minimization (Use Minimization + Simple randomization)
- Approach 2: Stratified Nested Minimization (Minimization + Permuted Block randomization)

Let $n_{ijk}$ be the number of patients already assigned to treatment group k where $k = 1,2,..K$ at strata level $j$ $(j = 1,2, ... J)$ of the covariate $i(i = 1,2,..C)$. (Kuznetsova and Tymofyeyev, 2012, Jin et al., 2019) Assume the next patients is ready to allocate.

- Calculate the number of participants on each level of the covariates $i(i = 1,2,..C-1)$ for the new patients $n_{ir_ik}$ is allocated to each treatment group k.
- Next, we will measure the resulting total imbalance by the range (RG):
- $G_{RG} = \sum_{i=1}^{C} RG\left[\frac{n_{ir_i1}}{a_1}, \frac{n_{ir_i2}}{a_2}, \dots \frac{n_{ir_ik}}{a_k}\right]$
- This new subject will hypothetically be assigned to the k^th treatment group with $G_k = \min(G_1, G_2, \dots G_k)$ with a high probability $p$ and equally distributed to any $k-1$ groups with probability $\frac{1-p}{k-1}$.
- Record the hypothetical treatment assignment for each participant using biased coin minimization approach and create a new stratifying variable (S) based on C-1 covariate and the hypothetical treatment assignment as mentioned in previous steps.
- For this new stratifying covariates (S and C), we will use stratified permuted block randomization with equal / unequal block sizes.
- For example, In case of two arm trial, we will have new stratifying variable based on $G_{RG} > 0\ vs.\ G_{RG} < 0\ vs.\ G_{RG} = 0$. If the $C^{th}$ have 2 factors, then the combined new strata will be 6.

## Simulation Design

Table 1: Randomization designs selected for the simulation study

| Design | Tuning Parameter | Method | Total No of Design |
|---|---|---|---|
| Simple randomization | N/A | N/A | 1 |
| Permuted Block Randomization | Block size = 4 (1:1), 3(2:1) 5(2:1:2) | N/A | 1 |
| Minimization Approach | P = 0.80,0.90 | Range/SD | 4 |
| Alternating Minimization | P = 0.80,0.90 | Range/SD | 4 |
| Stratified nested Minimization | P = 0.80,0.90 | Range/SD | 4 |

**Design Parameter:**

- 2 arm with 1:1 or 2:1 allocation ratio (N=200)
- 3 arm trial with 2:1:2 allocation ratio (N=250)
- To evaluate the type I error and power of randomization procedure, we apply stratified Cochran-Mantel-Haenszel (CMH) test.
- For two arm trial, type I error rate was calculated with the proportion of response is same in both arms i.e., $p_1 = p_2 = 0.3$ and the power was calculated with $p_1 = 0.50, p_2 = 0.30$.
- For Minimization based approach, re-randomization test was implemented and recommended.

## Results

Table: Compare the balancing property n (%) at each level of covariates using the **Stratified Nested minimization method** for different allocation ratios and p = 0.90 and Range Method is considered.

| Allocation ratio | Method | Range | | | SD | | |
|---|---|---|---|---|---|---|---|
| | | Treatment | | | Treatment | | |
| | | Arm A | Arm B | Arm C | Arm A | Arm B | Arm C |
| 1:1 | Lag3+ | 49.99 | 50.03 | | 49.94 | 50.03 | |
| | Lag3- | 50.01 | 49.97 | | 50.06 | 49.96 | |
| | Region(A) | 49.96 | 49.96 | | 50.08 | 49.99 | |
| | Region (N- A) | 50.05 | 50.04 | | 49.92 | 50.01 | |
| | MVI (Y) | 49.88 | 49.97 | | 50.04 | 49.93 | |
| | MVI (N) | 50.13 | 50.02 | | 49.97 | 50.06 | |
| 2:1 | Lag3+ | 66.68 | 33.37 | | 66.65 | 33.28 | |
| | Lag3- | 66.59 | 33.32 | | 66.69 | 33.38 | |
| | Region(A) | 66.67 | 33.32 | | 66.68 | 33.34 | |
| | Region (N- A) | 66.64 | 33.37 | | 66.66 | 33.33 | |
| | MVI (Y) | 66.63 | 33.38 | | 66.65 | 33.30 | |
| | MVI (N) | 66.68 | 33.31 | | 66.66 | 33.36 | |
| 2:1:2 | Lag3+ | 49.99 | 24.99 | 50.01 | 49.97 | 25.07 | 49.97 |
| | Lag3- | 49.99 | 25.01 | 50.01 | 50.06 | 25.05 | 49.91 |
| | Region(A) | 49.98 | 24.95 | 50.01 | 49.95 | 25.07 | 49.95 |
| | Region (N- A) | 50.01 | 25.06 | 50.00 | 50.04 | 25.05 | 49.93 |
| | MVI (Y) | 49.93 | 24.99 | 50.01 | 50.04 | 25.05 | 49.94 |
| | MVI (N) | 50.06 | 25.01 | 49.96 | 49.96 | 25.08 | 49.94 |

Table: Simulation of the overall relative imbalance and Type I error and Power for different randomization procedures using the stratified CMH test

| | | 1:1 (N = 200) | | | 2:1 (N = 200) | | | 2:1:2 (N = 250) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Method | Prob. of assignment | Imbalance | Type I error | Power | Total Imbalance | Type I error | Power | Total Imbalance | Type I error | Power |
| SR | N/A | 0.239 | 0.050 | 0.821 | 0.170 | 0.047 | 0.772 | 0.166 | 0.048 | 0.732 |
| Block Rand | N/A | 0.170 | 0.049 | 0.824 | 0.122 | 0.048 | 0.777 | 0.117 | 0.049 | 0.730 |
| Minimization | 0.90 (RN) | 0.170 | 0.049 | 0.828 | 0.122 | 0.045 | 0.783 | 0.118 | 0.052 | 0.736 |
| Alternating | 0.90 (RN) | 0.235 | 0.053 | 0.822 | 0.165 | 0.050 | 0.778 | 0.164 | 0.048 | 0.742 |
| Stratified Nested | 0.90 (RN) | 0.170 | 0.045 | 0.831 | 0.121 | 0.051 | 0.774 | 0.118 | 0.052 | 0.730 |
| Minimization | 0.80 (RN) | 0.171 | 0.047 | 0.833 | 0.123 | 0.051 | 0.783 | 0.119 | 0.050 | 0.737 |
| Alternating | 0.80 (RN) | 0.237 | 0.056 | 0.807 | 0.169 | 0.050 | 0.779 | 0.163 | 0.046 | 0.741 |
| Stratified Nested | 0.80 (RN) | 0.170 | 0.062 | 0.826 | 0.121 | 0.051 | 0.783 | 0.118 | 0.052 | 0.738 |
| Minimization | 0.90 (SD) | 0.171 | 0.055 | 0.835 | 0.121 | 0.052 | 0.776 | 0.118 | 0.048 | 0.745 |
| Alternating | 0.90 (SD) | 0.237 | 0.052 | 0.824 | 0.166 | 0.050 | 0.775 | 0.162 | 0.051 | 0.740 |
| Stratified Nested | 0.90 (SD) | 0.172 | 0.052 | 0.819 | 0.121 | 0.047 | 0.784 | 0.119 | 0.054 | 0.746 |
| Minimization | 0.80 (SD) | 0.172 | 0.052 | 0.829 | 0.124 | 0.046 | 0.786 | 0.118 | 0.049 | 0.740 |
| Alternating | 0.80 (SD) | 0.238 | 0.046 | 0.826 | 0.167 | 0.049 | 0.772 | 0.162 | 0.047 | 0.738 |
| Stratified Nested | 0.80 (SD) | 0.171 | 0.049 | 0.830 | 0.121 | 0.052 | 0.774 | 0.119 | 0.046 | 0.748 |

All the simulation ran for 10,000 times; Type I error calculated using the p1 = p2 = 0.30; Power was calculated using the P1 = 0.50, p2 = 0.30; For 3 arms, Power was calculated using the P1 = 0.50, p2 = 0.40, p3 = 0.30; RN indicate Range and SD indicate Standard Deviation was considered

### Re-randomization test

- Compute the test statistics of the CMH test for the observed responses using the randomization approach for treatment assignment.
- Reallocate the treatment assignment in accordance with the given randomization procedure.
- Reobtain the test statistics $T$ for this reallocation and obtain reference test statistics.
- Repeat steps 2 and 3 for $R$ repeated number of times.
- The P-value of the re-randomization test can be estimated by the Monte-Carlo method.

| | 1:1 (N = 200) | | 2:1 (N = 200) | | 2:1:2 (N = 250) | |
|---|---|---|---|---|---|---|
| Method | Type I error | Power | Type I error | Power | Type I error | Power |
| SR | 0.054 | 0.819 | 0.048 | 0.769 | 0.051 | 0.734 |
| Block Rand | 0.049 | 0.822 | 0.051 | 0.776 | 0.046 | 0.738 |
| Minimization | 0.051 | 0.824 | 0.051 | 0.770 | 0.050 | 0.743 |
| Alternating Minimization | 0.051 | 0.817 | 0.049 | 0.774 | 0.049 | 0.738 |
| Stratified Nested Minimization | 0.049 | 0.821 | 0.051 | 0.773 | 0.050 | 0.735 |

All the simulation ran for 10,00 times with R = 1000 repetitions; Type I error calculated using the p1 = p2 = 0.30; And Power was calculated using the P1 = 0.50 p2 = 0.30; For 3 arms, Power was calculated using the P1 = 0.50, p2 = 0.40, p3 = 0.30

SR = Simple Randomization

## Conclusions

- Provide a brief summary of various randomization approach
- Propose a novel hybrid approaches that combines the strength of each existing methods without their drawbacks
- Hybrid approaches enables balance of additional stratification variables while maintaining balance.
- Stratified Nested Minimization method offer an alternative method which allow prioritization of the Cth variable for marginal balancing while minimizing the imbalance on the remaining C-1 variables.

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