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ADAPTIVE RANDOMIZATION – MINIMIZATION METHOD

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Overview

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- Case Study
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Introduction

- Randomization is the process of assigning clinical trial participants to treatment groups.
- R.A Fisher first introduced the idea of randomization in a 1926 agricultural study.
- Randomization gives each participant a known (usually equal) chance of being assigned to any of the groups.
- Successful randomization requires that group assignment cannot be predicted in advance.

Common randomization methods

- The common types of randomization includes
  - Simple Randomization
  - Blocked Randomization
  - Stratified Randomization
  - Unequal Randomization

Adaptive Randomization

- Adaptive randomization refers to any scheme in which the probability of treatment assignment changes according to assigned treatments of patients already in the trial. i.e; allocation of patients is determined by the current balance of the treatment groups.

- There are many types of adaptive randomizations. The goal of each of these designs is to balance the treatment groups as much as possible by changing the way the next patient is assigned to a treatment group.

Covariate-adaptive randomization

- One commonly used adaptive randomization procedures is
  - Covariate-adaptive randomization

- Covariate randomization designs aim to balance the covariates across the treatment groups.

- This randomization assigns the next patient to the group that causes the smallest imbalance across the covariate groups.

Minimization

- The method of minimization is the most commonly used covariate adaptive randomization method.
- The procedure was described independently by Taves (1974) and Pocock and Simon (1975).
- Minimization is a good method to limit imbalance in relatively small randomized clinical trials with more important prognostic factors (covariates).

Minimization

- It called minimization because imbalance in the distribution of covariates are minimized.

- Minimization revises the probability of treatment assignment based on baseline characteristics of the participant and participants already randomized.

- Important covariates are identified before the start of the trial.

Advantages of Minimization over other Randomizations

Advantages

- Offers better balancing than standard randomization methods. Treatment arms are balanced with respect to predefined patient factors as well as for the number of patients in each group.

- It can incorporate a larger number of stratifying factors than stratified randomization methods.

Disadvantages of Minimization over other Randomizations

Disadvantages

- Allocating patients to treatment via minimization is more complex than using other standard randomization methods.
- Randomization lists cannot be generated in advance when minimization is used. Each time a patient enters a trial, a computer must run the minimization algorithm to assign the patient to the appropriate treatment.
- Programming errors may occur.

Study Design

- This is a Phase III randomized, double-blind, 2-arm, placebo-controlled, parallel group study of the efficacy and safety of XYZ Gel 1% applied q.i.d. for at least 48 hours and up to 7 days to treat acute blunt, soft tissue injuries/contusions of the limbs.

- Subjects should be randomized as soon as possible after the injury.

Study Design

- The randomization will be stratified by study site, site of injury (arm vs. leg) and the mean assessment of SPI (Spontaneous Pain Intensity Score) at baseline.

- 200 subjects will be randomized to one of 2 arms

  A : XYZ Gel 1 percent four times a day

  B : Placebo four times a day

  in the ratio 1:1

Stratification Factors

- Stratification factors and levels are given below

Strata	Clinical Site		Grouped Spontaneous Pain Intensity Score		Site of Injury	
	1		1		1	
	R1	R1Text	R2	R2Text	R3	R3Text
	1	Site 1	1	Pain Score 5-6	1	Arm
	2	Site 2	2	Pain Score 7-8	2	Leg
	3	Site 3	3	Pain Score 9-10		
	4	Site 4				
	5	Site 5				
	6	Site 6				
	7	Site 7				
	8	Site 8				
	9	Site 9				
	10	Site 10				
	11	Site 11				
	12	Site 12				

Random Number Schedule

- A single set of 200 random numbers will be generated in SAS using RANUNI function with a random seed.

Randno = RANUNI (seed)

Sequence	Randno
1	0.7663
2	0.2608
3	0.4511
4	0.2368
5	0.4932
6	0.9861
...	
...	
...	
200	0.3311

Minimization Algorithm

- Assignment of subjects to treatments in this study follows a Pocock and Simon minimization method applied using a probabilities as follows:
  - If both treatment groups are tied for smallest minimum difference, then allocation to the two treatment groups will be performed with probability $p = 0.50$.
  - If there is one clear treatment group with smallest minimum difference then allocation to that treatment group will be performed with probability $p = 0.80$.

Minimization Algorithm: Randomization Factors

Factor	Levels
Clinical Site (SITE)	$SITE_{(i=1)}$ = Site1 $SITE_{(i=2)}$ = Site2 $SITE_{(i=3)}$ = Site3 $SITE_{(i=4)}$ = Site4 $SITE_{(i=5)}$ = Site5 $SITE_{(i=6)}$ = Site6 $SITE_{(i=7)}$ = Site7 $SITE_{(i=8)}$ = Site8 $SITE_{(i=9)}$ = Site9 $SITE_{(i=10)}$ = Site10 $SITE_{(i=11)}$ = Site11 $SITE_{(i=12)}$ = Site12
Grouped Spontaneous Pain Intensity Score (SPIS)	$SPIS_{(j=1)}$ = 5-6 $SPIS_{(j=2)}$ = 7-8 $SPIS_{(j=3)}$ = 9-10
Site of Injury (INJRY)	$INJRY_{(k=1)}$ = Arm $INJRY_{(k=2)}$ = Leg

Minimization Algorithm

Step 0

- Initialize all randomization counters within the adaptive randomization algorithm to zero at the beginning of the study.

Step 1

- Identify the subject's stratification factors.

Step 2

- Calculate the existing treatment allocations before assigning the new subject's treatment group.

Minimization Algorithm: Step 2
Site Imbalance

- Count the number of subjects randomized to each treatment group corresponding to the current subject **SITE**
  - Number of subjects randomized to treatment group **A** within the same strata [$\mathbf{SITE_{(i)A}}$]
  - Number of subjects randomized to treatment group **B** within the same strata [$\mathbf{SITE_{(i)B}}$]

- Calculate the absolute difference

$$\mathbf{SITE_{(i)}}\ \text{absolute difference} = |(\mathbf{SITE_{(i)A}}) - (\mathbf{SITE_{(i)B}})|$$

Minimization Algorithm: Step 2
SPIS Imbalance and Injury Imbalance

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- Similarly, calculate SPIS imbalance and Injury imbalance.

- $\mathbf{SPIS_{(j)}}$ absolute difference $= |(\mathbf{SPIS_{(j)A}}) - (\mathbf{SPIS_{(j)B}})|$

- $\mathbf{INJRY_{(k)}}$ absolute difference $= |(\mathbf{INJRY_{(k)A}}) - (\mathbf{INJRY_{(k)B}})|$

Minimization Algorithm: Step 3

- Compute the hypothetical differences by alternately assigning the next subject to be randomized to each of the two treatment groups

Minimization Algorithm: Step 3

- Compute the difference in Clinical Site (SITE) with the subject currently being randomized
  - hypothetically assigned to Treatment group A

$$\mathbf{SITE}_{\mathbf{(i)}}\ \text{absolute difference/}\mathbf{A} = |(\mathbf{SITE}_{\mathbf{(i)A}} + 1) - (\mathbf{SITE}_{\mathbf{(i)B}})|$$

  - hypothetically assigned to treatment group B

$$\mathbf{SITE}_{\mathbf{(i)}}\ \text{absolute difference/}\mathbf{B} = |(\mathbf{SITE}_{\mathbf{(i)A}}) - (\mathbf{SITE}_{\mathbf{(i)B}} + 1)|$$

- Similarly calculate for other two factors SPIS and Injury.

Minimization Algorithm: Step 4

- Compute the Difference with the subject currently being randomized hypothetically assigned to Treatment group A

  $\mathbf{Diff_A = SITE_{(i)}}$ absolute difference/**A** $\mathbf{+ SPIS_{(j)}}$ absolute difference/**A** $\mathbf{+ INJRY_{(k)}}$ absolute difference/**A**

- Compute the Difference with the subject currently being randomized hypothetically assigned to Treatment group B

  $\mathbf{Diff_B = SITE_{(i)}}$ absolute difference/**B** $\mathbf{+ SPIS_{(j)}}$ absolute difference/**B** $\mathbf{+ INJRY_{(k)}}$ absolute difference/**B**

Minimization Algorithm: Step 5a

If $\mathbf{Diff_A} = \mathbf{Diff_B}$

- The system selects the treatment group using the next available sequential random number from the random number schedule as follows:

A for $0.0000 \leq$ random numbers < 0.5000

B for $0.5000 \leq$ random numbers < 1.0000

End of randomization: The procedure will stop here.

Minimization Algorithm: Step 5b

If $\mathbf{Diff_A < Diff_B}$

- The system selects the treatment group using the next available sequential random number from the random number schedule as follows:

A for $0.0000 \leq$ random numbers < 0.8000

B for $0.8000 \leq$ random numbers < 1.0000

End of randomization: The procedure will stop here.

Minimization Algorithm: Step 5c

If $\mathbf{Diff_A > Diff_B}$

- The system selects the treatment group using the next available sequential random number from the random number schedule as follows:

A for $0.0000 \leq$ random numbers < 0.2000

B for $0.2000 \leq$ random numbers < 1.0000

End of randomization: The procedure will stop here.

Step 6

- Reset all factor counts to zero and repeat from Step 1 for next subject.

Requirements

Population proportions

- Sponsor has to provide the expected population proportions.
  - For 'Clinical Site (SITE)' the following population proportions provided by sponsor

Site	Number of Subjects
1	30 subjects (15.0%)
2	20 subjects (10.0%)
3	25 subjects (12.5%)
4	30 subjects (15.0%)
5	15 subjects (7.5 %)
6	10 subjects (5.0%)
7	25 subjects (12.5%)
8	20 subjects (10.0%)
9	15 subjects (7.5%)
10	10 subjects (5.0%)
11	0 subjects (0.0%)
12	0 subjects (0.0%)

Population proportions

- For 'Grouped Spontaneous Intensity Pain Score (SPIS)' the following population proportions provided by sponsor.

SPIS	Number of Subjetcs
5-6	**120 (60.0%)** (60 subjects each with SPIS score 5 and 6)
7-8	**60 (30.0%)** (40 subjects with SPIS score 7 and 20 subjects with SPIS score 8)
9-10	**20 (10.0%)** (15 subjects with SPIS score 9 and 5 subjects with SPIS score 10)

Population proportions

- Site of Injury (INJRY) the following population proportions provided by sponsor.

INJRY	Number of Subjetcs
Arm	**100 (50.0%)**
Leg	**100 (50.0%)**

Simulation Datasets

- Based on the above population proportions, we will create 4 simulation lists containing 200 subjects.
- Each of these 4 simulations lists will have different set of subjects matching this population requirement by using different seeds to generate stratification factors.
- Simulations 1-3 will use the same test random number and simulation 4 will use a different random number list.

Simulation Datasets

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Set I

Sequence	Randno	R1	R1Text	R2	R2Text	R3	R3Text	SPIS Score
1	0.7663	7	Site 7	1	Spontaneous Pain Intensity Score (5-6)	2	Site of Injury (Leg)	5
2	0.2608	3	Site 3	1	Spontaneous Pain Intensity Score (5-6)	2	Site of Injury (Leg)	6
3	0.4511	4	Site 4	1	Spontaneous Pain Intensity Score (5-6)	1	Site of Injury (Arm)	6
4	0.2368	4	Site 4	3	Spontaneous Pain Intensity Score (9-10)	1	Site of Injury (Arm)	9
5	0.4932	1	Site 1	2	Spontaneous Pain Intensity Score (7-8)	2	Site of Injury (Leg)	8
...	...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...	...
200	0.3311	7	Site 7	2	Spontaneous Pain Intensity Score (7-8)	2	Site of Injury (Leg)	8

Set II

Sequence	Randno	R1	R1Text	R2	R2Text	R3	R3Text	SPIS Score
1	0.7663	9	Site 9	1	Spontaneous Pain Intensity Score (5-6)	1	Site of Injury (Arm)	6
2	0.2608	3	Site 3	1	Spontaneous Pain Intensity Score (5-6)	1	Site of Injury (Arm)	6
3	0.4511	1	Site 1	1	Spontaneous Pain Intensity Score (5-6)	2	Site of Injury (Leg)	5
4	0.2368	3	Site 3	1	Spontaneous Pain Intensity Score (5-6)	2	Site of Injury (Leg)	5
5	0.4932	10	Site 10	1	Spontaneous Pain Intensity Score (5-6)	2	Site of Injury (Leg)	6
...	...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...	...
200	0.3311	2	Site 2	3	Spontaneous Pain Intensity Score (9-10)	2	Site of Injury (Leg)	9

Simulation Datasets

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Set III

Sequence	Randno	R1	R1Text	R2	R2Text	R3	R3Text	SPIS Score
1	0.7663	1	Site 1	2	Spontaneous Pain Intensity Score (7-8)	1	Site of Injury (Arm)	7
2	0.2608	4	Site 4	1	Spontaneous Pain Intensity Score (5-6)	2	Site of Injury (Leg)	5
3	0.4511	3	Site 3	1	Spontaneous Pain Intensity Score (5-6)	1	Site of Injury (Arm)	5
4	0.2368	6	Site 6	1	Spontaneous Pain Intensity Score (5-6)	2	Site of Injury (Leg)	5
5	0.4932	3	Site 3	2	Spontaneous Pain Intensity Score (7-8)	2	Site of Injury (Leg)	7
...	...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...	...
200	0.3311	4	Site 4	1	Spontaneous Pain Intensity Score (5-6)	1	Site of Injury (Arm)	6

Set IV

Sequence	Randno	R1	R1Text	R2	R2Text	R3	R3Text	SPIS Score
1	0.3304	7	Site 7	1	Spontaneous Pain Intensity Score (5-6)	1	Site of Injury (Arm)	5
2	0.8125	1	Site 1	2	Spontaneous Pain Intensity Score (7-8)	2	Site of Injury (Leg)	7
3	0.6136	9	Site 9	1	Spontaneous Pain Intensity Score (5-6)	1	Site of Injury (Arm)	6
4	0.3208	8	Site 8	3	Spontaneous Pain Intensity Score (9-10)	2	Site of Injury (Leg)	9
5	0.4637	4	Site 4	3	Spontaneous Pain Intensity Score (9-10)	2	Site of Injury (Leg)	9
...	...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...	...
200	0.6769	4	Site 4	1	Spontaneous Pain Intensity Score (5-6)	1	Site of Injury (Arm)	5

Simulation Datasets

- We use this 4 simulation data sets to illustrate the extent to which the system randomizes subjects to both treatment groups in a 1:1 ratio.

- Based on the result of these simulation, we will take a decision on the level of deterministic factor.

Execution of minimization algorithm: Step 0

- Initialize all randomization counters within the adaptive randomization algorithm to zero at the beginning of the study.

	Value	
Clinical Site ($SITE_{(i)}$) =	0	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12
Grouped Spontaneous Pain Intensity Score ($SPIS_{(j)}$) =	0	1, 2 or 3
Site of Injury ($INJRY_{(k)}$) =	0	1 or 2

Step 1

- Assume that first subject in the study is with prognostic (stratification) factors
  - Site - Site 7 (R1=7)
  - SPIS - Pain Score 5-6 (R2=1)
  - INJRY – Leg (R3=2)

Step 2

- Calculate the existing allocations before assigning the new subject's treatment group

	A	B	Absolute difference
$SITE_{(7)}$ =	0	0	0
$SPIS_{(1)}$ =	0	0	0
$INJRY_{(2)}$ =	0	0	0

- Hypothetically assigned to treatment group A

	A	B	Diff
$SITE_{(7)}$ =	1	0	1
$SPIS_{(1)}$ =	1	0	1
$INJRY_{(2)}$ =	1	0	1
		$Diff_A$ =	3

- Hypothetically assigned to treatment group B

	A	B	Diff
$SITE_{(7)}$ =	0	1	1
$SPIS_{(1)}$ =	0	1	1
$INJRY_{(2)}$ =	0	1	1
		$Diff_B$ =	3

Step 5

- Assign the Treatment based on comparison of DIFFs and the random number value
  - Here the DIFF condition is **$Diff_A = Diff_B$**
  - So the rule is

A for $0.0000 \leq$ random number < 0.5000

B for $0.5000 \leq$ random numbers < 1.0000

  - And the first random number is 0.7663

- So treatment group **B** is assigned to first subject based on above rule.

Result

- So the first subject is assigned to treatment group B.

Sequence	Random no	R1	R1Text	R2	R2Text	R3	R3Text	Raw_SPIS	rule	randl	randH	Treatment
1	0.7663	7	Site 7	1	Spontaneous Pain Intensity Score (5-6)	2	Site of Injury (Leg)	5	5a	0.5000	0.9999	B

- Similarly we are repeating the steps for next subjects and the treatment groups are assigned.

- For example, the second subject is with factor values

Sequence	Random no	R1	R1Text	R2	R2Text	R3	R3Text	Raw_SPIS	rule	randl	randH	Treatment
1	0.7663	7	Site 7	1	Spontaneous Pain Intensity Score (5-6)	2	Site of Injury (Leg)	5	5a	0.5000	0.9999	B
2	0.2608	3	Site 3	1	Spontaneous Pain Intensity Score (5-6)	2	Site of Injury (Leg)	6				

Step 6

- Initialize all randomization counters within the adaptive randomization algorithm to zero prior to each subject randomization.

	Value	
Clinical Site ($SITE_{(i)}$) =	0	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12
Grouped Spontaneous Pain Intensity Score ($SPIS_{(j)}$) =	0	1, 2 or 3
Site of Injury ($INJRY_{(k)}$) =	0	1 or 2

Step 1

- Identify the prognostic (stratification) factors
  - Site - Site 3 (R1=3)
  - SPIS - Pain Score 5-6 (R2=1)
  - INJRY – Leg (R3=2)

Step 2

- Calculate the existing allocations before assigning the new subject's treatment group

	A	B	Absolute difference
$SITE_{(3)}$ =	0	0	0
$SPIS_{(1)}$ =	0	1	1
$INJRY_{(2)}$ =	0	1	1

Step 3, 4

- Hypothetically assigned to treatment group A

	A	B	Diff
$SITE_{(3)}$ =	1	0	1
$SPIS_{(1)}$ =	1	1	0
$INJRY_{(2)}$ =	1	1	0
		$Diff_A$ =	1

- Hypothetically assigned to treatment group B

	A	B	Diff
$SITE_{(3)}$ =	0	1	1
$SPIS_{(1)}$ =	0	2	2
$INJRY_{(2)}$ =	0	2	2
		$Diff_B$ =	5

Step 5

- Assign the Treatment based on comparison of DIFFs and the random number value
  - Here the DIFF condition is **$Diff_A < Diff_B$**
  - So the rule is

A for $0.0000 \leq$ random numbers < 0.8000

B for $0.8000 \leq$ random numbers < 1.0000

  - And the second random number is 0.2608

- So treatment group **A** is assigned to second subject based on above rule.

Result

- So the second subject is assigned to treatment group A.

Sequence	Random no	R1	R1Text	R2	R2Text	R3	R3Text	Raw_SPIS	rule	randl	randH	Treatment
1	0.7663	7	Site 7	1	Spontaneous Pain Inte	2	Site of Injury (Leg)	5	5a	0.5000	0.9999	B
2	0.2608	3	Site 3	1	Spontaneous Pain Inte	2	Site of Injury (Leg)	6	5b	0.0000	0.7999	A

- Similarly we are repeating the steps for next subjects and the treatment groups are assigned.

Results

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- Finally we get a data with treatment assigned for each subject as given below (for Simulation I)

Sequence	Random no	R1	R1Text	R2	R2Text	R3	R3Text	Raw_SPIS	Rule	RandL	RandH	Treatment
1	0.7663	7	Site 7	1	Spontaneous Pain Intensity Score (5-6)	2	Site of Injury (Leg)	5	5a	0.5000	0.9999	B
2	0.2608	3	Site 3	1	Spontaneous Pain Intensity Score (5-6)	2	Site of Injury (Leg)	6	5b	0.0000	0.7999	A
3	0.4511	4	Site 4	1	Spontaneous Pain Intensity Score (5-6)	1	Site of Injury (Arm)	6	5a	0.0000	0.4999	A
4	0.2368	4	Site 4	3	Spontaneous Pain Intensity Score (9-10)	1	Site of Injury (Arm)	9	5c	0.2000	0.9999	B
5	0.4932	1	Site 1	2	Spontaneous Pain Intensity Score (7-8)	2	Site of Injury (Leg)	8	5a	0.0000	0.4999	A
...	...	...	...	...	...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...	...	...	...	...	...

Results

- Summary of treatment counts by Stratification Factor is given below (for Simulation I)

Overall	
Trt A	Trt B
99	101

SITE	Treatment		Total
	A	B	
1	15	15	30
2	9	11	20
3	13	12	25
4	15	15	30
5	7	8	15
6	5	5	10
7	12	13	25
8	10	10	20
9	8	7	15
10	5	5	10
11	0	0	0
12	0	0	0

SPIS	Treatment		Total
	A	B	
1	59	61	120
2	30	30	60
3	10	10	20

INJRY	Treatment		Total
	A	B	
1	48	52	100
2	51	49	100

Results

- Balance between treatment groups are also observed in other 3 simulations.

- Finally we create a live random number schedule. And based on this random numbers, subjects are actually assigned into the study.

Conclusion

- Minimization method can be used in studies with small and moderate sample size and with large number of covariates.
- Computation process is complicated. SAS code needs to be develop for each study.
- Needs to perform thorough simulation testing on a random adaptive algorithm before implementation.
- It is highly recommended to incorporate the subject allocation procedure into the clinical trial protocol.

References

- Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics. 1975;31(1):103–115.
- DR Taves. Minimization: A new method of assigning patients to treatment and control groups. Clinical Pharmacology and Therapeutics 1974; 15(3): 443-453.
- Scott NW, McPherson GC, Ramsay CR, Campbell MK. The method of minimization for allocation to clinical trials: a review. Control ClinTrials. 2002;23(6):662–674.