Chapter 880

Randomization Lists

Introduction

This module is used to create a randomization list for assigning subjects to one of up to 25 treatment groups. The list can be stratified by up to 25 centers (strata) with an additional 2 stratification factors, each with up to 25 levels.

Seven randomization algorithms are available. Five of the algorithms (Block Randomization, Efron's biased coin randomization, Smith's randomization, Wei's urn randomization, and random sorting using maximum allowable % deviation) are designed to generate balanced random samples throughout the course of an experiment. The other two (complete randomization and random sorting) are less complex but have higher probabilities of imbalance. Technical details for each of these algorithms (except random sorting) as well as a discussion of randomization issues in general are given in Rosenberger and Lachin (2002), Pocock (1983), and Piantadosi (2005).

Why Randomize?

Random allocation has been an important part of scientific discovery since the time of R.A. Fisher. He and other scientists recognized the potential for bias in nonrandomized experiments that could compromise treatment comparisons. Randomization controls the influence of unknown factors, reducing potential bias in an experiment. Rosenberger and Lachin (2002) state on page 18 that "...the randomization of subjects between the treatment groups is the paramount statistical element that allows one to claim that a study is unbiased." The elimination of bias, however, is not the only reason for randomization. Pocock (1983) states on page 50 that randomization is used "to provide a basis for the standard methods of statistical analysis such as significance tests." Clearly, randomization is necessary in order to produce accurate and generalizable statistical conclusions.

Randomization in Clinical Trials

In non-clinical (or non-human) experiments, researchers often have tight control over the environment and conditions surrounding an experiment, so randomization can usually be implemented with minor difficulty. Clinical experiments, however, are quite different. Because human patients are used in clinical trials, various ethical issues must be addressed. These ethical considerations complicate the experimental design and often require adjustments in the way subjects are randomly assigned to treatments. Other factors that influence randomization in clinical trials are purely logistical. How can the investigators ensure that treatments are administered the same for all patients without the patient or the doctor knowing what treatment is being given? These and other design factors influence how randomization is administered in clinical trials.

One of the issues that arise in clinical experiments is treatment imbalance. Clinical trials are usually administered over time with patients enrolling at different time points throughout the study. It is often desirable to maintain balance in the number of patients assigned to each treatment throughout the course of the experiment. This is particularly true when time-dependent covariates influence the response or when

sequential testing will be used to analyze results. Several randomization algorithms have been developed to produce lists that balance the number of patients assigned to each treatment throughout the experiment while still maintaining the randomness of the assignments. These include block randomization, Efron's biased coin randomization, Smith's randomization, Wei's urn randomization, and random sorting using maximum allowable % deviation. Each of these algorithms will be discussed in detail in the section that follows.

Randomization Algorithms

Seven different randomization algorithms are available. These can be roughly divided into two categories: those that aim to produce balanced randomization lists and those that do not. The following table outlines the goal of each algorithm by the number of groups each algorithm will allow.

	Non-Balancing Algorithms	**Balancing Algorithms**
2 Groups	Complete Randomization†, Random Sorting	Block Randomization†, Efron's Biased Coin*†, Smith*†, Wei's Urn*†, Random Sorting using Maximum Allowable % Deviation
***k* Groups**	Complete Randomization†, Random Sorting	Block Randomization†, Wei's Urn*, Random Sorting using Maximum Allowable % Deviation

*These randomization algorithms have the additional restriction that unequal treatment allocation is not allowed, i.e. all groups must have the same target sample size.

†These randomization algorithms produce randomization lists in which the actual group sample size may not equal the target group sample size.

The discussion of each algorithm that follows will be based on the following scenario and notation. Suppose we have k treatments and that n_i subjects (not necessarily all equal) are to be assigned to each treatment, i = 1, 2, ..., k. The value n_i will be referred to in discussion as the "target" sample size for each group. Let the actual sample size for each group be a_i. For some algorithms, the actual group sample size may not always equal the target sample size for all groups. The total sample size is

$$N = \sum_{i=1}^{k} n_i = \sum_{i=1}^{k} a_i,$$

and the target allocation ratio for each group is

$$R_i = \frac{n_i}{N}.$$

Define the probability of assignment of subject j to treatment i as p_{ij}.

Define the number of subjects in each group after the j^{th} subject is assigned as $n_i[j]$.

When the list is stratified with centers and/or additional stratification factors, randomization is completed independently within each strata combination. This is, for s = 1, 2, …, S strata, the total sample size (N in the notation above) within a given stratum is equal to N_s. The individual strata may have different sample sizes. All discussions that follow refer to randomization within a single stratum, but the results can be generalized to stratified randomization lists.

Non-Balancing Algorithms

Complete Randomization

The complete randomization algorithm is commonly referred to as a "coin flip". For the case to two treatments, a coin is flipped each time a subject is to be randomized, determining the assignment. The probability of assignment to either treatment is 0.5 for all subjects.

The algorithm generalizes to more than two groups and allows for unequal allocation. The probability of assignment of subject j to group i is

$$p_{ij} = R_i$$

for all j. If the target sample size is the same for all k groups, then

$$p_{ij} = 1/k$$

The complete randomization algorithm proceeds by randomly assigning subjects to treatments using the above assignment probabilities. The algorithm may result in imbalances between groups even when the target group sample sizes are equal, i.e., the actual sample sizes may not always equal the target sample sizes for all groups. This algorithm is not recommended when balance is important throughout the course of an experiment.

Random Sorting

The random sorting algorithm can be used for any number of treatment groups and any allocation ratios. The random sorting algorithm always results in randomized assignment lists in which the actual group sample sizes match the target group sample sizes, i.e., $a_i = n_i$ for all i. The algorithm begins by creating a virtual database containing group names. Each row corresponds to one group, and the i^{th} group is represented by n_i rows. For example, if we were randomly assigning three groups (A, B, and C) with ten subjects in each group, then the database would consist of ten rows containing A's, followed by ten rows containing B's and ten rows containing C's, for a total of 30 rows. Next, a random number is assigned to each row in the database, and then the database is sorted based on the column of random numbers to place the group names in random order. The first subject is then assigned to the group in row one of the randomly sorted database, the second subject is assigned to the group in row two, and so forth. Although this algorithm always results in groups containing the target sample sizes, longitudinal imbalances among groups may still occur, therefore, this algorithm is not recommended when balance is important throughout the course of an experiment.

Balancing Algorithms

Block Randomization

This algorithm is designed to randomize subjects to two or more treatments and achieves balance across treatment groups over time. Predetermined blocks of set sizes containing each treatment assignment are individually randomized to keep the number of subjects assigned to each group in balance as enrollment progresses.

Block randomization is completed as follows:

For randomization of *k* groups, define r_i as an integer allocation ratio value for group *i*. For a study with 3 treatments with equal sample sizes in each group (i.e., allocation ratio = 1:1:1), $r_i = 1$ for all *k*. If the allocation ratio were 1:2:2, then $r_1 = 1$, $r_2 = 2$, and $r_3 = 2$. The minimum block size is equal to

$$B_{Min} = \sum_{i=1}^{k} r_i.$$

Thus, for a study with 3 groups, $B_{Min} = 3$ for the case of equal group sizes, and $B_{Min} = 5$ for 1:2:2 allocation.

The actual block sizes used in randomization are computed as multiples of B_{Min}, using block size multipliers, M_b (*b* = 1, 2, ... # of block sizes) entered by the user

$$B_b = M_b \times B_{Min}$$

If multipliers M_b = 1, 2, and 3 were used, then for equal allocation the block sizes would be 3, 6, and 9, with treatments allocated within each block according to the given ratio. For 1:2:2 allocation, the block sizes would be 5, 10, and 15. In general, the multipliers should be chosen so that the block sizes are relatively small to maintain balance, and at least two different block sizes should be selected to avoid the possibility of administrators or subjects being able to guess their treatment in a blinded study by the assignment of previous subjects. When multiple block sizes are randomly assigned, the current treatment cannot usually be guessed based solely on the previous assignments, because the block sizes are not constant.

After the block sizes have been determined, all possible permuted combinations of assignment sequences within each block must be calculated. For 3 groups (A, B, C) and a block size of 3, the possible block sequences are

ABC, ACB, BAC, BCA, CAB, CBA

Block sizes and sequences are chosen and randomly ordered to determine subject assignment into the treatment groups. The user can specify whether the block sizes are chosen completely at random or according to a custom block-subject allocation. The random block selection terminates when the number of subjects assigned in blocks reaches or surpasses the required sample size. It is possible for the final sample size to be larger than the target unless the block sizes are constrained to a set where the overall target sample size is achieved.

Efron's Biased Coin Randomization

This algorithm may only be used for random assignment of subjects to two treatments. The target sample sizes must also be the same for both groups. In order to achieve longitudinal balance between groups, the algorithm dynamically changes the group assignment probabilities. The algorithm is outlined in Efron (1971).

First, we define a constant probability *p* (called "Efron's p"), where $0.5 < p \leq 1$. A common value for *p* is 2/3. Also define a difference function $D_j = n_1[j] - n_2[j]$. The probability of assignment of subject *j* to group 1 is

$$p_{1j} = \begin{cases} 1/2 & \text{if} \quad D_{j-1} = 0 \\ p & \text{if} \quad D_{j-1} < 0 \\ 1-p & \text{if} \quad D_{j-1} > 0 \end{cases}$$

Efron's biased coin randomization proceeds by randomly assigning subjects to treatments using the above assignment probabilities. When group 1 has more subjects assigned than group 2, the assignment probability changes to make group 2 more probable for assignment. When group 2 has more, then group 1 becomes more probable. The algorithm may result in final imbalances between groups, but the degree of imbalance throughout the randomization process is greatly reduced.

Smith's Randomization

This algorithm may only be used for random assignment of subjects to two treatments. The target sample sizes must also be the same for both groups. Like Efron's biased coin randomization, Smith's algorithm dynamically changes the group assignment probabilities based on the degree of imbalance to achieve longitudinal balance between groups. The algorithm is outlined in Smith (1984).

We define a positive exponent parameter ρ (called "Smith's Exponent"). The probability of assignment of subject *j* to group 1 is

$$p_{1j} = \frac{n_2[j-1]^\rho}{n_1[j-1]^\rho + n_2[j-1]^\rho}$$

Smith's randomization proceeds by randomly assigning subjects to treatments using the above assignment probabilities. When group 1 has more subjects assigned than group 2, the assignment probability changes to make group 2 more probable for assignment. When group 2 has more, then group 1 becomes more probable. The algorithm may result in final imbalances between groups, but the degree of imbalance throughout the randomization process is greatly reduced.

Wei's Urn Randomization

This algorithm may be used for random assignment of subjects to two or more treatments. The target sample sizes must also be the same for all groups. Like Smith's randomization, Wei's urn randomization algorithm dynamically changes the group assignment probabilities based on the degree of imbalance to achieve longitudinal balance between groups. Urn randomization is reviewed in Wei and Lachin (1988).

Define positive parameters *A* and *B* (called "Wei's A" and "Wei's B", respectively). We start the algorithm by placing *A* balls representing each group in an urn. A single ball is then randomly chosen from the urn, recorded, and *replaced*, and then *B* new balls corresponding to each of the other groups are added to the urn. Therefore, when a ball from one group is chosen, the probability shifts to make the other groups more

probable on the next draw. The probability of the first assignment is 1/*k*. After that, the probability of assignment of subject *j* to group *i* is

$$p_{ij} = \frac{A + B(j-1) - Bn_i[j-1]}{kA + B(j-1)(k-1)}.$$

The algorithm continues until all subjects have been assigned to one of the groups. The algorithm may result in final imbalances between groups, but the degree of imbalance throughout the randomization process is diminished due to the shifting of probabilities toward the underrepresented groups.

Random Sorting using Maximum Allowable % Deviation

This algorithm is equivalent to the random sorting algorithm described earlier except that a search is conducted to find a randomization list that satisfies the Maximum Allowable % Deviation criterion. The % Deviation for group *i* after subject *j* has been assigned is defined as

$$\%Deviation_{ij} = \left|\frac{n_i[j] - E(n_i[j])}{n_i}\right| \times 100$$

$$= \left|\frac{n_i[j] - jR_i}{n_i}\right| \times 100$$

The % Deviation measures how far the actual sample size for group *i* is from the expected sample size after subject *j* is randomly assigned. The Maximum Allowable % Deviation represents the upper bound for this measure. The search is conducted by creating an assignment list based on random sorting and then running through the assignments and calculating the maximum % Deviation for all groups after each assignment. If the maximum % Deviation is greater than the Maximum Allowable % Deviation value specified, then the list is rejected, the number of iterations is incremented, and the random sorting algorithm is started again with a new set of random numbers. The search continues until a randomization list is generated for which the criterion is satisfied for all individual assignments. Conducting a search in this manner assures a degree of balance throughout the course of the experiment.

For example, for 40 subjects to be assigned to two groups A and B with equal allocation ratios (0.5), suppose that there are 7 assigned A's and 3 assigned B's after 10 random assignments and the Maximum Allowable % Deviation is 10%. With the allocation ratio at 0.5, we would expect to have 5 A's and 5 B's (10 × 0.5 = 5) after 10 assignments. Therefore, the % Deviation for group A is |7 – 5|/20 = 10% and the % Deviation for group B is |3 – 5|/20 = 10%. Both of these are equal to the Maximum Allowable % Deviation so the next assignment would be tested. If the next assignment were to group A then the randomization list would be rejected because the % Deviation for group A is |8 – 5|/20 = 15% > 10%. A new randomization list based on random sorting would be generated and the search would continue.

Comparison of Balancing Properties

Rosenberger and Lachin (2002) provides a simulation comparison of the balancing properties of complete randomization, Efron's biased coin (*p* = 2/3), Wei's Urn (*A* = 0, *B* = 1), and Smith (exponent = 5). The simulation was carried out for two treatment groups with target sample sizes of 25 in each group. They found that complete randomization did not balance as well as the other three "restricted randomization" procedures. Efron's biased coin and Smith's randomization algorithms were very close in terms of bias and variability. Wei's urn was found to be slightly more variable.

Example 1 – Block Randomization with Equal Allocation Ratios

A clinical researcher wishes to randomly assign 60 subjects to three treatment groups (Low, Medium, High) using block randomization with 1:1:1 allocation and block sizes of 3 and 6. The list will include sequence numbers, subject ID's, block identifiers, abbreviated treatment codes, and randomization codes.

For reproducibility, we'll use a random seed of 60502.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 1** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Randomization Tab	
Randomization Algorithm	**Block Randomization**
Random Seed	**60502**
Block Size Multiplier(s)	**1 2**
Block-Subject Allocation	**Random**
Constrain the actual block allocation…	**Unchecked**
Search for a randomization list…	**Unchecked**
Maximum Search Iterations	**1000**
Sample Size Entry Type	**Enter the Overall Total Sample Size for the Study**
Overall Total Sample Size	**60**
Number of Treatment Groups	**3**
Title or Name	**Treatment**
Assign Equal Sample Sizes to All Treatment Groups	**Checked**
Treatment Group 1 Label	**Low**
Treatment Group 2 Label	**Medium**
Treatment Group 3 Label	**High**

Centers (Strata) Tab	
Number of Centers (Strata)	**1 (Not Stratified)**
Number of Additional Factors	**0**

List Options Tab	
Include a Column of Sequence Numbers	**Checked**
Include a Column of Subject ID's	**Checked**
Subject ID Prefix	**{Set}**
Include a Column of Block Identifiers	**Checked**
Include a Column of Combined Stratification Codes	**Unchecked**
Include a Column of Abbreviated Treatment Codes	**Checked**
Include a Column of Unique Randomization Codes	**Checked**

Storage Tab

Write Randomization List to Spreadsheet..... **Unchecked**

Reports Tab

Show Summary ..... **Checked**
Show Randomization List ..... **Checked**
Show Randomization List Details ..... **Checked**
Show References ..... **Checked**

Output

Click the Calculate button to perform the calculations and generate the following output.

Randomization List Summary

Randomization List Summary

Randomization Algorithm	Block Randomization
Random Seed	60502 (User-Entered)
Block Size Multiplier(s)	1 2
Block Size(s)	3 6
Total Number of Blocks	12
Overall Total Sample Size	60
Number of Treatment Groups	3

Treatment	Treatment Code	Sample Size	Allocation % Actual	Allocation % Target
Low	L	20	33.33%	33.33%
Medium	M	20	33.33%	33.33%
High	H	20	33.33%	33.33%

This report displays the summary of the randomization list, including block information.

Randomization Algorithm

States the algorithm used in randomization and any associated parameters (e.g., Block Size Multiplier(s), Block Size(s), Total Number of Blocks).

Random Seed

Indicates the random seed used in creating the randomization list. If the random seed was computer-generated, it will be indicated here.

Overall Total Sample Size

The actual sample size of the randomization list. If the sample size is different from the target, the target sample size will be indicated here.

Number of Treatment Groups

The treatment groups.

Treatment

The treatment groups.

Treatment Code

The abbreviated treatment group code.

Sample Size

The sample size for each treatment group.

Actual Allocation %

The actual allocation percentage achieved by each treatment group.

Target Allocation %

The target allocation percentage specified on the input. Note that the user input may have had integer values for the allocation ratios (e.g., 1:1:1), but they are converted to percentages in this report.

Randomization List

Randomization List

Randomization Algorithm	Block Randomization (Block Sizes = 3 6)
Random Seed	60502 (User-Entered)

Sequence	Subject ID	Block	Treatment	Treatment Code	Randomization Code
1	101	1	High	H	MW0
2	102	1	Low	L	RN7
3	103	1	Low	L	GI8
4	104	1	Medium	M	DX0
5	105	1	Medium	M	TD6
6	106	1	High	H	RN2
7	107	2	Low	L	LF5
8	108	2	Low	L	QD8
9	109	2	High	H	CZ9
10	110	2	High	H	PL6
.	.	.	.	.	.
.	.	.	.	.	.
.	.	.	.	.	.

This report shows the complete randomization list

Sequence

The sequence identifier.

Subject ID

The text identification value of the subject.

Block

The randomization block to which each subject belongs.

Treatment

The treatment group to which the subject was randomly assigned.

Treatment Code

An abbreviated treatment code corresponding to the treatment group.

Randomization Code

Unique, random, computer-generated code for each subject. This information can be used to blind the study.

Randomization List Details

Randomization List Details

Randomization Algorithm	Block Randomization (Block Sizes = 3 6)
Number of Blocks	12
Sample Size	60
Number of Treatment Groups	3

Block-Subject Allocation

Block Size	Number of Blocks	Subjects Assigned	Allocation %	
			Actual	Target
3	4	12	20%	Random
6	8	48	80%	Random

This report displays a more detailed summary of the randomization list, including block information in the Block-Subject Allocation section.

Block Size

The block sizes used to create the randomization list.

Number of Blocks

The number of blocks of each size.

Subjects Assigned

The number of subjects assigned to the list by blocks of the corresponding size.

Actual Allocation %

The actual allocation percentage achieved by each block size.

Target Allocation %

The target allocation percentage specified on the input. Note that the user input may have had integer values for the allocation ratios (e.g., 1:1:1), but they are converted to percentages in this report.

Treatment Groups

Treatment	Treatment Code	Sample Size	Allocation %	
			Actual	Target
Low	L	20	33.33%	33.33%
Medium	M	20	33.33%	33.33%
High	H	20	33.33%	33.33%

This section displays the same sample size information as is found in the Randomization List Summary report.

Cumulative Details

Sequence	Subject ID	Block	Treatment	Largest % Deviation from Target	Cumulative Sample Size (L, M, H)
1	101	1	High	3.33%	(0, 0, 1)
2	102	1	Low	3.33%	(1, 0, 1)
3	103	1	Low	5.00%	(2, 0, 1)
4	104	1	Medium	3.33%	(2, 1, 1)
5	105	1	Medium	3.33%	(2, 2, 1)
6	106	1	High	0.00%	(2, 2, 2)
7	107	2	Low	3.33%	(3, 2, 2)
8	108	2	Low	6.67%	(4, 2, 2)
9	109	2	High	5.00%	(4, 2, 3)
10	110	2	High	6.67%	(4, 2, 4)
.	.	.	.	.	.
.	.	.	.	.	.
.	.	.	.	.	.

This report shows more detailed summaries and cumulative randomization list details.

Sequence

The sequence identifier.

Subject ID

The text identification value of the subject.

Block

The randomization block to which each subject belongs.

Treatment

The treatment group to which the subject was randomly assigned.

Largest % Deviation from Target

The largest observed % deviation after the current assignment was made. This measures how far away the group sample sizes are from the expected sample size based on the targets. That is, this measures the degree of imbalance over time.

Cumulative Sample Size

The cumulative sample size total for each treatment group after the current assignment was made.

References

References

Piantadosi, S. 2005. Clinical Trials - A Methodological Perspective. John Wiley & Sons. New Jersey.
Pocock, S.J. 1983. Clinical Trials - A Practical Approach. John Wiley & Sons. New York.
Rosenberger, W.F., and Lachin, J.M. 2002. Randomization in Clinical Trials - Theory and Practice. John Wiley & Sons. New York.

This report displays the references associated with this procedure.

Example 2 – Block Randomization with Unequal Allocation Ratios and Centers

Continuing with Example 1, suppose the researcher wants now to create a randomization list with twice as many Low treatments as the other two (allocation = 2:1:1) at 4 different centers. Each center should have 80 subjects. They want to randomize with block sizes of 4, 8, and 12 with an equal number of subjects randomized by each block size. We'll also save the randomization list to the spreadsheet.

For reproducibility, we'll use a random seed of 102203.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 2** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Randomization Tab	
Randomization Algorithm	**Block Randomization**
Random Seed	**102203**
Block Size Multiplier(s)	**1 2 3**
Block-Subject Allocation	**Equal**
Constrain the actual block allocation…	**Unchecked**
Search for a randomization list…	**Unchecked**
Maximum Search Iterations	**1000**
Sample Size Entry Type	**Enter Individual Center (Stratum) Sample Sizes**
Number of Treatment Groups	**3**
Title or Name	**Treatment**
Assign Equal Sample Sizes to All Treatment Groups	**Unchecked**
Treatment Group 1 Label	**Low**
Treatment Group 1 Allocation Ratio	**2**
Treatment Group 2 Label	**Medium**
Treatment Group 2 Allocation Ratio	**1**
Treatment Group 3 Label	**High**
Treatment Group 3 Allocation Ratio	**1**

Centers (Strata) Tab	
Number of Centers (Strata)	**4**
Title or Name	**Center**
Assign Equal Sample Sizes to All Centers (Strata)	**Checked**
Center Sample Size	**80**
Center (Stratum) 1 Label	**Center 1**
Center (Stratum) 2 Label	**Center 2**
Center (Stratum) 3 Label	**Center 3**
Center (Stratum) 4 Label	**Center 4**
Number of Additional Factors	**0**

List Options Tab

Include a Column of Sequence Numbers	**Checked**
Include a Column of Subject ID's	**Checked**
Restart Numbering for each Center (Stratum)	**Checked**
Subject ID Prefix	**{Set}**
Include a Column of Block Identifiers	**Checked**
Include a Column of Combined Stratification Codes	**Unchecked**
Include a Column of Abbreviated Treatment Codes	**Checked**
Include a Column of Unique Randomization Codes	**Checked**

Storage Tab

Store Randomization List	**Checked**
Store Randomization List Data Starting In	**1**
Update Column Names	**Checked**

Reports Tab

Show Summary	**Checked**
Show Randomization List	**Checked**
Show Randomization List Details	**Checked**
Show References	**Checked**

Output

Click the Calculate button to perform the calculations and generate the following output.

Randomization List Summary

Randomization List Summary

Randomization Algorithm	Block Randomization
Random Seed	102203 (User-Entered)
Block Size Multiplier(s)	1 2 3
Block Size(s)	4 8 12
Total Number of Blocks	52
Overall Total Sample Size	320
Number of Treatment Groups	3
Number of Centers (Strata)	4

Treatments

Treatment	Treatment Code	Sample Size	Allocation % Actual	Allocation % Target
Low	L	160	50%	50%
Medium	M	80	25%	25%
High	H	80	25%	25%

Centers (Strata)

Center	First Subject ID	Blocks	Sample Size	Allocation % Actual	Allocation % Target
Center 1	1001	13	80	25%	25%
Center 2	2001	13	80	25%	25%
Center 3	3001	13	80	25%	25%
Center 4	4001	13	80	25%	25%

The summary indicates that 80 subjects are randomized within each center. Randomization occurs independently within each Center.

Randomization List

Randomization List

Randomization Algorithm	Block Randomization (Block Sizes = 4 8 12)
Random Seed	102203 (User-Entered)

Sequence	Subject ID	Center	Block	Treatment	Treatment Code	Randomization Code
1	1001	Center 1	1	Low	L	DNC3
2	1002	Center 1	1	Medium	M	VJF1
3	1003	Center 1	1	High	H	LCD5
4	1004	Center 1	1	Low	L	NBW1
5	1005	Center 1	2	High	H	WVE1
6	1006	Center 1	2	Low	L	LSC6
7	1007	Center 1	2	Medium	M	OWK0
8	1008	Center 1	2	Low	L	UCN3
9	1009	Center 1	3	Low	L	LUS2
10	1010	Center 1	3	Low	L	GFF7
.	.	.	.	.	.	.
.	.	.	.	.	.	.
.	.	.	.	.	.	.

The randomization list has a length of 320 subjects with 80 each in 4 different centers. This randomization list will also have been written to the spreadsheet.

Randomization List Details

Randomization List Details for Strata Combination 1 of 4

Strata Combination	Center = "Center 1"
Randomization Algorithm	Block Randomization (Block Sizes = 4 8 12)
Number of Blocks	13
Sample Size	80
Number of Treatment Groups	3

Block-Subject Allocation

Block Size	Number of Blocks	Subjects Assigned	Allocation %	
			Actual	Target
4	8	32	40%	33.33%
8	3	24	30%	33.33%
12	2	24	30%	33.33%

Treatment Groups

Treatment	Treatment Code	Sample Size	Allocation %	
			Actual	Target
Low	L	40	50%	50%
Medium	M	20	25%	25%
High	H	20	25%	25%

Cumulative Details

Sequence	Subject ID	Block	Treatment	Largest % Deviation from Target	Cumulative Sample Size (L, M, H)
1	1001	1	Low	1.25%	(1, 0, 0)
2	1002	1	Medium	2.50%	(1, 1, 0)
3	1003	1	High	1.25%	(1, 1, 1)
4	1004	1	Low	0.00%	(2, 1, 1)
5	1005	2	High	3.75%	(2, 1, 2)
6	1006	2	Low	2.50%	(3, 1, 2)
7	1007	2	Medium	1.25%	(3, 2, 2)
8	1008	2	Low	0.00%	(4, 2, 2)
9	1009	3	Low	1.25%	(5, 2, 2)
10	1010	3	Low	2.50%	(6, 2, 2)
.	.	.	.	.	.
.	.	.	.	.	.
.	.	.	.	.	.

The Randomization List Details report indicates that while it was intended to have an equal number of subjects assigned to each block size, the actual percentages were just a little off due to the discrete nature of the block sizes and total sample size.

Example 3 – Block Randomization within Centers with Two Additional Stratification Factors

Suppose a study is to be conducted at 3 centers with randomization using 2 stratification factors: Gender (Male, Female) and Size (Small, Medium, Large). The treatment allocation will be equal among 3 groups (A, B, C) and randomized by block randomization with custom block-subject allocation such that 40% of subjects are randomized using a block size of 3 and 60% are randomized using a block size of 6. The actual block allocation will be constrained so that the total sample size matches the target if possible. We'll create a randomization list with 1000 subjects and save it to the spreadsheet.

Center 1 is expected to have half as many subjects as the other two. It is also expected that there will be a ratio of males to females of 3:2 and an equal allocation of subjects among the three sizes.

For reproducibility, we'll use a random seed of 90605.6497.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 3** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Randomization Tab	
Randomization Algorithm	**Block Randomization**
Random Seed	**90605.6497**
Block Size Multiplier(s)	**1 2**
Block-Subject Allocation	**Custom**
Custom Block-Subject Allocation	**40 60**
Constrain the actual block allocation…	**Checked**
Search for a randomization list…	**Unchecked**
Maximum Search Iterations	**1000**
Sample Size Entry Type	**Enter the Overall Total Sample Size for the Study**
Overall Total Sample Size	**1000**
Number of Treatment Groups	**3**
Title or Name	**Group**
Assign Equal Sample Sizes to All Treatment Groups	**Checked**
Treatment Group 1 Label	**A**
Treatment Group 2 Label	**B**
Treatment Group 3 Label	**C**

Centers (Strata) Tab	
Number of Centers (Strata)	**3**
Title or Name	**Center**
Assign Equal Sample Sizes to All Centers (Strata)	**Unchecked**
Center (Stratum) 1 Label	**Center 1**
Center (Stratum) 1 Allocation Ratio	**0.5**
Center (Stratum) 2 Label	**Center 2**
Center (Stratum) 2 Allocation Ratio	**1**

Center (Stratum) 3 Label	**Center 3**
Center (Stratum) 3 Allocation Ratio	**1**
Number of Additional Factors	**2**

Stratification Factor 1

Number of Levels	**2**
Title or Name	**Gender**
Use Equal Sample Size Allocation for All Levels	**Unchecked**
Level 1 Label	**Male**
Level 1 Allocation Ratio	**3**
Level 2 Label	**Female**
Level 2 Allocation Ratio	**2**

Stratification Factor 2

Number of Levels	**3**
Title or Name	**Size**
Use Equal Sample Size Allocation for All Levels	**Checked**
Level 1 Label	**Small**
Level 2 Label	**Medium**
Level 3 Label	**Large**

List Options Tab

Include a Column of Sequence Numbers	**Checked**
Include a Column of Subject ID's	**Checked**
Restart Numbering for each Center (Stratum)	**Checked**
Restart Numbering for each Additional…	**Checked**
Subject ID Prefix	**{Set}000**
Include a Column of Block Identifiers	**Checked**
Include a Column of Combined Stratification Codes	**Checked**
Use Abbreviated Codes	**Checked**
Add Code Separators	**Unchecked**
Include a Column of Abbreviated Treatment Codes	**Unchecked**
Include a Column of Unique Randomization Codes	**Unchecked**

Storage Tab

Store Randomization List	**Checked**
Store Randomization List Data Starting In	**1**
Update Column Names	**Checked**

Reports Tab

Show Summary	**Checked**
Show Randomization List	**Checked**
Show Randomization List Details	**Checked**
Show References	**Unchecked**

Output

Click the Calculate button to perform the calculations and generate the following output.

Randomization List Summary

Randomization List Summary

Randomization Algorithm	Block Randomization
Random Seed	90605.6497 (User-Entered)
Block Size Multiplier(s)	1 2
Block Size(s)	3 6
Total Number of Blocks	240
Overall Total Sample Size	1017 (Target was 1000)
Number of Treatment Groups	3
Number of Centers (Strata)	3
Number of Stratification Factor 1 Levels	2
Number of Stratification Factor 2 Levels	3

Treatments

Group	Group Code	Sample Size	Allocation % Actual	Allocation % Target
A	A	339	33.33%	33.33%
B	B	339	33.33%	33.33%
C	C	339	33.33%	33.33%

Centers (Strata)

Center	Gender	Size	Stratification Code	First Subject ID	Blocks	Sample Size	Allocation % Actual	Allocation % Target
Center 1	Male	Small	1MS	10000001	10	42	4.13%	4.00%
Center 1	Male	Medium	1MM	20000001	10	42	4.13%	4.00%
Center 1	Male	Large	1ML	30000001	10	42	4.13%	4.00%
Center 1	Female	Small	1FS	40000001	6	27	2.65%	2.67%
Center 1	Female	Medium	1FM	50000001	6	27	2.65%	2.67%
Center 1	Female	Large	1FL	60000001	6	27	2.65%	2.67%
Center 2	Male	Small	2MS	70000001	19	81	7.96%	8.00%
Center 2	Male	Medium	2MM	80000001	19	81	7.96%	8.00%
Center 2	Male	Large	2ML	90000001	19	81	7.96%	8.00%
Center 2	Female	Small	2FS	100000001	13	54	5.31%	5.33%
Center 2	Female	Medium	2FM	110000001	13	54	5.31%	5.33%
Center 2	Female	Large	2FL	120000001	13	54	5.31%	5.33%
Center 3	Male	Small	3MS	130000001	19	81	7.96%	8.00%
Center 3	Male	Medium	3MM	140000001	19	81	7.96%	8.00%
Center 3	Male	Large	3ML	150000001	19	81	7.96%	8.00%
Center 3	Female	Small	3FS	160000001	13	54	5.31%	5.33%
Center 3	Female	Medium	3FM	170000001	13	54	5.31%	5.33%
Center 3	Female	Large	3FL	180000001	13	54	5.31%	5.33%

The summary lists the number of subjects randomized by each strata combination. Notice that just about twice as many subjects are assigned in centers 2 and 3 as in center 1. Also note that the ratio of males to females is about 3:2 within each center. The randomization list had to be expanded to 1017 subjects to avoid incomplete blocks.

Randomization List

Randomization List

Randomization Algorithm	Block Randomization (Block Sizes = 3 6)
Random Seed	90605.6497 (User-Entered)

Sequence	Subject ID	Center	Gender	Size	Stratification Code	Block	Group
1	10000001	Center 1	Male	Small	1MS	1	A
2	10000002	Center 1	Male	Small	1MS	1	B
3	10000003	Center 1	Male	Small	1MS	1	C
4	10000004	Center 1	Male	Small	1MS	1	A
5	10000005	Center 1	Male	Small	1MS	1	C
6	10000006	Center 1	Male	Small	1MS	1	B
7	10000007	Center 1	Male	Small	1MS	2	B
8	10000008	Center 1	Male	Small	1MS	2	A
9	10000009	Center 1	Male	Small	1MS	2	C
10	10000010	Center 1	Male	Small	1MS	3	A
.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.
.	.	.	.	.	.	.	.

The randomization list has a length of 1017 subjects with 339 in each group. Randomization occurred independently within each strata combination. The randomization list will also have been written to the spreadsheet.

Randomization List Details

Randomization List Details for Strata Combination 1 of 18

Strata Combination	Center = "Center 1" Gender = "Male" Size = "Small"
Randomization Algorithm	Block Randomization (Block Sizes = 3 6)
Number of Blocks	10
Sample Size	42
Number of Treatment Groups	3

Block-Subject Allocation

Block Size	Number of Blocks	Subjects Assigned	Allocation %	
			Actual	Target
3	6	18	42.86%	40%
6	4	24	57.14%	60%

Treatment Groups

Group	Group Code	Sample Size	Allocation %	
			Actual	Target
A	A	14	33.33%	33.33%
B	B	14	33.33%	33.33%
C	C	14	33.33%	33.33%

Cumulative Details

Sequence	Subject ID	Block	Group	Largest % Deviation from Target	Cumulative Sample Size (A, B, C)
1	10000001	1	A	4.76%	(1, 0, 0)
2	10000002	1	B	4.76%	(1, 1, 0)
3	10000003	1	C	0.00%	(1, 1, 1)
4	10000004	1	A	4.76%	(2, 1, 1)
5	10000005	1	C	4.76%	(2, 1, 2)
6	10000006	1	B	0.00%	(2, 2, 2)
7	10000007	2	B	4.76%	(2, 3, 2)
8	10000008	2	A	4.76%	(3, 3, 2)
9	10000009	2	C	0.00%	(3, 3, 3)
10	10000010	3	A	4.76%	(4, 3, 3)
.	.	.	.	.	.
.	.	.	.	.	.
.	.	.	.	.	.

(Output continues with a separate Randomization List Details report for each strata combination.)

The Randomization List Details reports indicate the allocation within each strata combination. The number of male subjects with Size = Small in Center 1 is 42. Note that the number of subjects randomized using each block size matches closely our specified percentages of 40% and 60%.

Example 4 – Complete Randomization and Imbalance

In this example we'll demonstrate the imbalance that can occur when using complete randomization by generating a simple randomization list with 20 subjects and 2 treatment groups, A and B.

For reproducibility, we'll use a random seed of 60608.

Setup

If the procedure window is not already open, use the PASS Home window to open it. The parameters for this example are listed below and are stored in the **Example 4a** settings file. To load these settings to the procedure window, click **Open Example Settings File** in the Help Center or File menu.

Randomization Tab	
Randomization Algorithm	**Complete Randomization**
Random Seed	**60608**
Search for a randomization list…	**Unchecked**
Maximum Search Iterations	**1000**
Sample Size Entry Type	**Enter the Overall Total Sample Size for the Study**
Overall Total Sample Size	**20**
Number of Treatment Groups	**2**
Title or Name	**Treatment**
Assign Equal Sample Sizes to All Treatment Groups	**Checked**
Treatment Group 1 Label	**A**
Treatment Group 2 Label	**B**

Output

Click the Calculate button to perform the calculations and generate the following output.

Randomization List Summary

Randomization Algorithm	Complete Randomization
Random Seed	60608 (User-Entered)
Overall Total Sample Size	20
Number of Treatment Groups	2

Treatment	Treatment Code	Sample Size	Allocation % Actual	Allocation % Target
A	A	7	35%	50%
B	B	13	65%	50%

Randomization List

Randomization Algorithm	Complete Randomization
Random Seed	60608 (User-Entered)

Sequence	Subject ID	Treatment
1	101	B
2	102	A
3	103	B
4	104	A
5	105	B
6	106	B
7	107	B
8	108	A
9	109	B
10	110	A
11	111	B
12	112	B
13	113	A
14	114	B
15	115	B
16	116	B
17	117	B
18	118	B
19	119	A
20	120	A

The randomization list generated using complete randomization has nearly twice as many subjects assigned to group B as A. The actual randomization is imbalanced between groups even though the target was to assign equal sample sizes to both treatment groups.

To search for a balanced randomization list, check **Search for a randomization list...** or open **Example 4b**.

Randomization Tab

Search for a randomization list… ..... **Checked**

Output

Click the Calculate button to perform the calculations and generate the following output with balanced groups

Randomization List Summary

Randomization Algorithm	Complete Randomization
Random Seed	60608 (User-Entered)
Overall Total Sample Size	20
Number of Treatment Groups	2

Treatment	Treatment Code	Sample Size	Allocation % Actual	Allocation % Target
A	A	10	50%	50%
B	B	10	50%	50%

Randomization List

Randomization Algorithm	Complete Randomization
Random Seed	60608 (User-Entered)

Sequence	Subject ID	Treatment
1	101	B
2	102	A
3	103	B
4	104	A
5	105	A
6	106	B
7	107	A
8	108	A
9	109	B
10	110	B
11	111	A
12	112	B
13	113	A
14	114	A
15	115	B
16	116	B
17	117	A
18	118	B
19	119	B
20	120	A

Note: This list was generated by searching for a randomization list in which the final group sizes exactly match the target group sizes. One or more generated lists did not meet the required criteria and were discarded. The number of search iterations to obtain this list was 3.