

RANDOMIZATION




- An essential tool for testing the efficacy of the treatment
- Each patient has an equal chance of receiving any of the treatments under study
- Study groups are similar in every aspect but the type of treatment being delivered
- BASIC BENEFITS
- Eliminates the selection bias
- Balances the groups with respect to confounding or prognostic variables
- Forms the basis for statistical tests



• DEFINITION

- Randomization is the process of randomly allocating subjects to study groups, ensuring that each subject has an equal chance of being allocated to any of the groups

• HOW IS IT DONE IN PRACTICE?

- A study to test the bioequivalence of a generic antihistaminic drug, consisting of the TEST group (receiving generic drug-TEST) and the REFERENCE group (receiving the original drug-REFERENCE) will require a randomized schedule randomly assigning numbers to the subjects to allocate them to a particular group, giving each participant an equal chance of being in any of the study groups
- 
- 
- 

RANDOMIZATION TECHNIQUES

- The appropriate technique depends on the research objective and design
- The trial protocol contains details of the randomization procedure (according to ICH E6 Section 4.7 should be followed strictly and only broken in accordance with the protocol)

RANDOMIZATION TECHNIQUES

- Simple randomization
- Unequal allocation
- Block randomization
- Stratified randomization
- and other

SIMPLE RANDOMIZATION

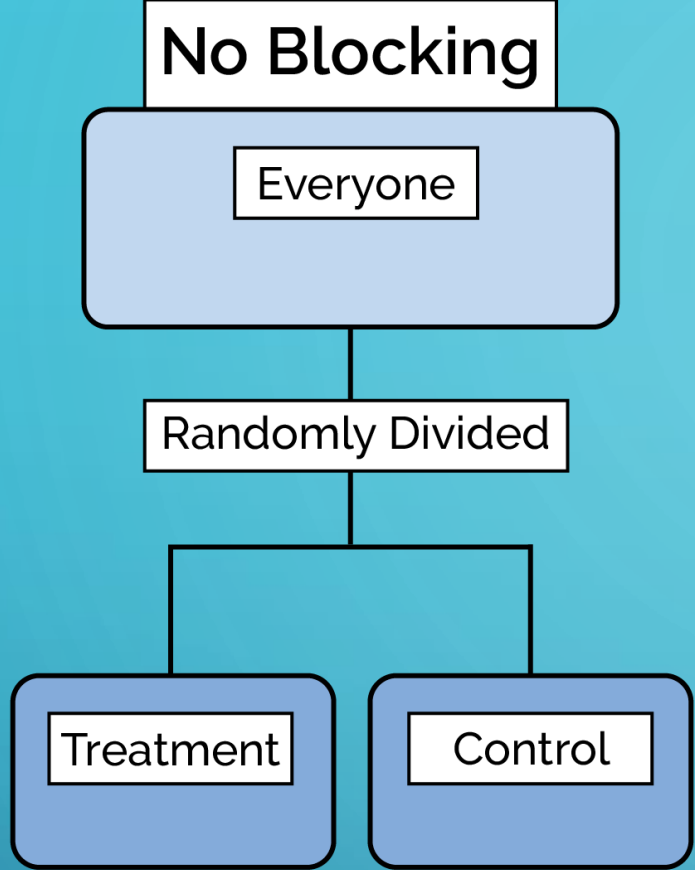
- Basic randomisation technique
- Like flipping a coin – ‘Heads’ for the control group, and ‘tails’ for the treatment group (equal chance for either group)
- **Easy and simple technique**
- **Not suitable** for studies with **small sample sizes** and multicenter studies (can result in an **unequal** number of subjects in the study groups)

UNEQUAL ALLOCATION

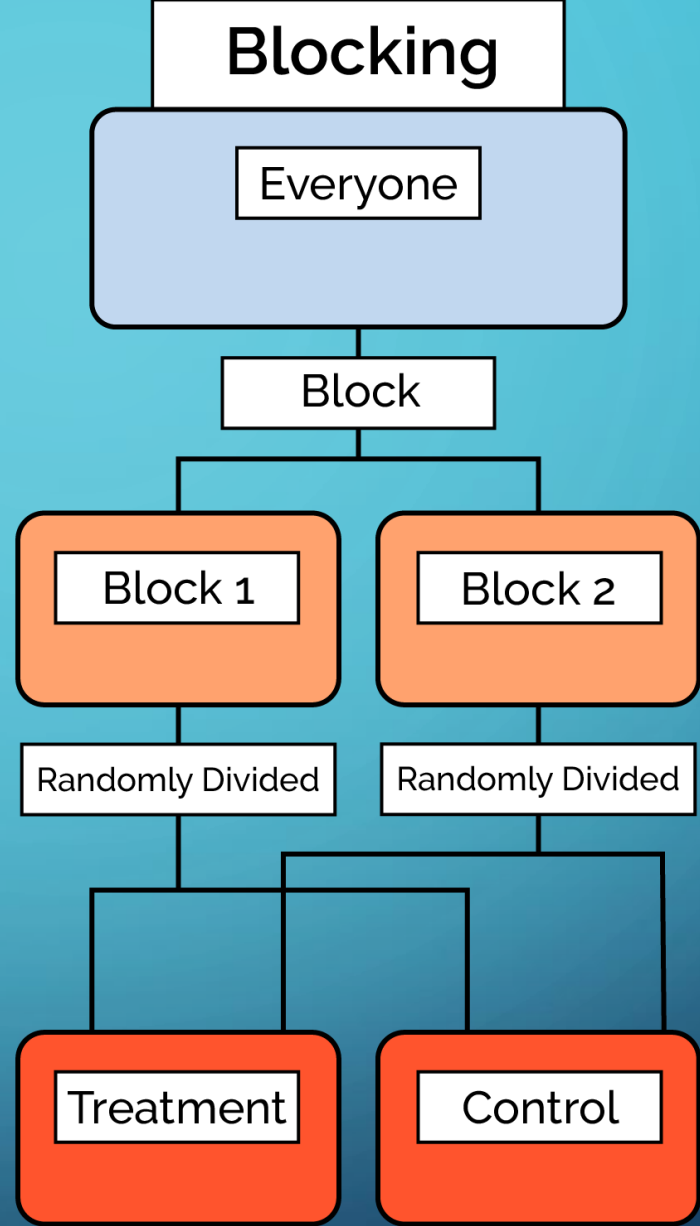
- Ethical reasons or cost (the assignment ratio is often skewed in favor of the treatment group)
- Terminal illness (more subjects in treatment group-ethical), high dropout rate(to reduce survivorship bias) or side effects (studies require more subjects in treatment group)
- Assignment ratio at or below 4:1 is advisable
- Imbalance **affects** the statistical inference due to **inequality** of the study groups

BLOCKING

- Eliminates imbalance in the sample size among study groups
- Splits the sample into 'blocks' of a definite and equal size
- Within each block, equal random allocation is made to each study group
- Requires computer programming using software designed to perform block randomisation (SAS®)



When blocking is used, all of the subjects are divided into two groups based on a blocking criteria and then evenly and randomly divided into the treatment and control groups.



Reference: Data Science Discovery

PARALLEL AND CROSSOVER DESIGNS IN BIOEQUIVALENCE STUDIES

- **PARALLEL DESIGN**

- Subjects are randomly assigned to one of two treatment groups (Treatment(A) or Reference(B)), and both treatment groups are followed in parallel
- Each individual subject in a parallel study receives only one of the two drugs (i.e. Treatment(A) or Reference(B)), for the entire study

- **CROSSOVER DESIGN**

- Each subject receives both drugs (i.e. Treatment(A) and Reference(B)), one in the first part of the study and the other in a second part
- **Standard bioequivalence studies generally use a crossover design**

ASSIGNING BLOCKS FOR A CROSS-OVER DESIGN

- 2 treatments, 2 sequences: ABAB and BABA
- Allocation ratio: 1:1
- Sample size:20
- Block size:4
- Total number of blocks: $20/4=5$

- In one block of size 4, there will be 2 subjects allocated to sequence ABAB and two to BABA
- Possible randomization schedule:

ABAB	BABA	BABA	ABAB	BABA
BABA	BABA	ABAB	ABAB	ABAB
BABA	ABAB	BABA	BABA	BABA
ABAB	ABAB	ABAB	BABA	ABAB

RANDOM NUMBER GENERATORS AND SEED NUMBER

- Allocation is performed using random number generators
- Random number generators provide extremely long series of numbers for which there is an extremely low probability of finding a repeating pattern
- Seed
 - Most random number generators require a seed number. If the generator is given the same seed each time it is called then it will produce the same series of numbers

ASSIGNING BLOCKS (CROSS-OVER DESIGN)

- 1. For a **block of size 4** (from previous example) randomly generate a number for each **sequence** assignment:

- **ABAB = 38255**
- **ABAB = 357**
- **BABA = 462**
- **BABA = 9478**

- 2. Rank the generated numbers from highest to lowest:

- **ABAB = 38255**
- **BABA = 9478**
- **BABA = 462**
- **ABAB = 357**

- 1. For a **block of size 4** (from previous example) randomly generate a number for each sequence assignment:

- **ABAB = 38255**

- **ABAB = 357**

- **BABA = 462**

- **BABA = 9478**

- 2. Rank the generated numbers from highest to lowest:

- **ABAB = 38255**

- **BABA = 9478**

- **BABA = 462**

- **ABAB = 357**

- **3. This is the first block with the following sequence assignments:**

ABAB	BABA	BABA	ABAB	BABA
BABA	BABA	ABAB	ABAB	ABAB
BABA	ABAB	BABA	BABA	BABA
ABAB	ABAB	ABAB	BABA	ABAB

- **4. Repeat for all other blocks**

Number of Sequences=2 (ABAB/BABA)

Sequence allocation ratio=1 1

Number of subjects =60

Subject ID	Period 1	Period 2	Period 3	Period 4	Sequence
01	B	A	B	A	BABA
02	A	B	A	B	ABAB
03	A	B	A	B	ABAB
04	B	A	B	A	BABA
05	B	A	B	A	BABA
06	B	A	B	A	BABA
07	A	B	A	B	ABAB
08	A	B	A	B	ABAB
09	A	B	A	B	ABAB
10	B	A	B	A	BABA
11	A	B	A	B	ABAB
12	B	A	B	A	BABA
13	A	B	A	B	ABAB
14	A	B	A	B	ABAB
15	B	A	B	A	BABA

ASSIGNING BLOCKS (PARALLEL STUDY DESIGN)

- 1. For a **block of size of 4 (with treatments A and B and only one period)**, randomly generate a number for each **treatment assignment**:

A=424

A=53161

B=535

B=75

- 2. Rank the generated numbers from highest to lowest: **ABAB**
- 3. Repeat for all other blocks

RULES REGARDING BLOCKING

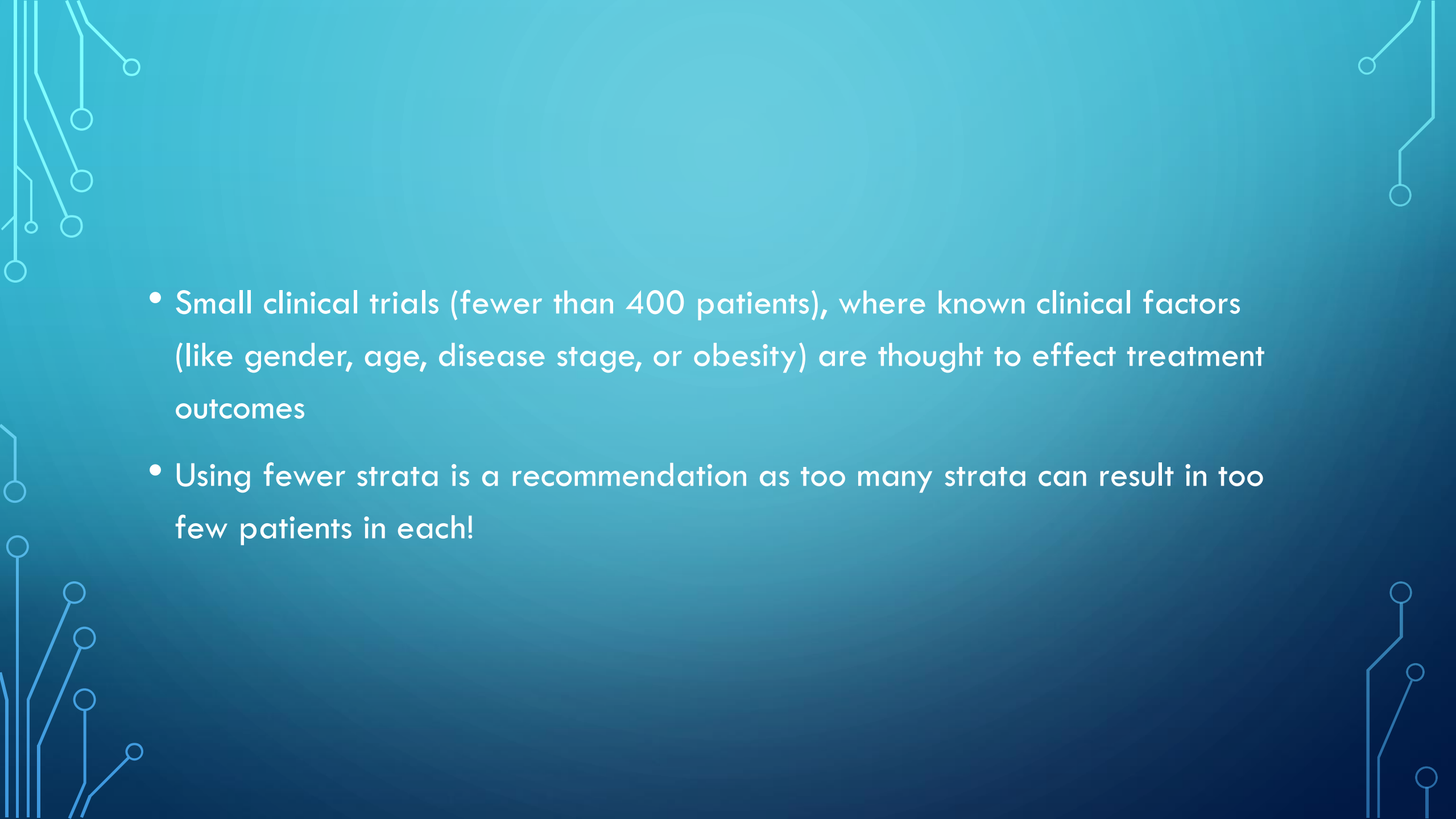
- 1. The block size must be a multiple of the number of study groups
- Example: 2 groups- possible block size = 4,6,8,.....
- ensures that the random allocation of subjects (within a block) to each study group generates an **equal** distribution between the two-study groups
- For 3 groups (if a block size is 12), 4 slots each are allocated to each study group
The combination of allocations should be **balanced amongst the groups.**
- 2. The number of subjects should be a multiple of the block size
- (20 subjects/block size 4=5 blocks)
-)

ADVANTAGES OF BLOCKING

- Balanced sample size between groups
- Suitable for studies with ongoing recruitment
- This is because blocks can be left vacant and filled before randomisation occurs, reducing chronological bias

STRATIFIED RANDOMIZATION

- Uses blocks within strata
- Subjects are subdivided into strata and blocking is then used for each stratum
- Ensures a balance of clinical/prognostic factors as the study may not have valid results if factors are not well balanced

- 
- Small clinical trials (fewer than 400 patients), where known clinical factors (like gender, age, disease stage, or obesity) are thought to effect treatment outcomes
 - Using fewer strata is a recommendation as too many strata can result in too few patients in each!

WILLIAMS DESIGN IN CROSS-OVER STUDIES

- The Williams design is a special case of the cross-over and Latin square designs
- Each subject receives each treatment
- Design is balanced over periods
- Every treatment follows every other treatment the same number of times
- With the limited sample size, the Williams design is the most efficient design and minimizes the potential impact of the carryover effect

A Williams Design for the Cross-over Trial
 The number of treatments in this trial = 4
 The random seed number = 1547934360
 The seed is generated automatically.

SeqNo	Period1	Period2	Period3	Period4
1	Drug2B	Drug1A	ActCtrl	Placebo
2	ActCtrl	Drug2B	Placebo	Drug1A
3	Placebo	ActCtrl	Drug1A	Drug2B
4	Drug1A	Placebo	Drug2B	ActCtrl

4x4 Latin square,
 randomly generated sequences,
 taking into consideration the rules of
 Latin square design

For an even number of treatments,
 the design is a Latin square

‘The Construction of a Williams Design and
 Randomization in Cross-Over Clinical Trials
 Using SAS’ Wang, Wang, Gong

The Randomization Schedule for the Trial
 The number of treatments in this trial = 4
 The random seed number = 1547934360
 The seed is generated automatically.

Sub_ID	Sequence
001	Drug2B–Drug1A–ActCtrl–Placebo
002	ActCtrl–Drug2B–Placebo–Drug1A
003	Placebo–ActCtrl–Drug1A–Drug2B
004	Drug1A–Placebo–Drug2B–ActCtrl
005	Placebo–ActCtrl–Drug1A–Drug2B
006	ActCtrl–Drug2B–Placebo–Drug1A
007	Drug1A–Placebo–Drug2B–ActCtrl
008	Drug2B–Drug1A–ActCtrl–Placebo
009	Drug2B–Drug1A–ActCtrl–Placebo
010	Placebo–ActCtrl–Drug1A–Drug2B
011	ActCtrl–Drug2B–Placebo–Drug1A
012	Drug1A–Placebo–Drug2B–ActCtrl
013	ActCtrl–Drug2B–Placebo–Drug1A
014	Drug1A–Placebo–Drug2B–ActCtrl
015	Drug2B–Drug1A–ActCtrl–Placebo
016	Placebo–ActCtrl–Drug1A–Drug2B
017	Drug2B–Drug1A–ActCtrl–Placebo
018	Drug1A–Placebo–Drug2B–ActCtrl
019	Placebo–ActCtrl–Drug1A–Drug2B
020	ActCtrl–Drug2B–Placebo–Drug1A
021	Drug1A–Placebo–Drug2B–ActCtrl
022	ActCtrl–Drug2B–Placebo–Drug1A
023	Drug2B–Drug1A–ActCtrl–Placebo
024	Placebo–ActCtrl–Drug1A–Drug2B

4 seq. are
 randomly
 allocated to
 every 4
 subjects

A Williams Design for the Cross-over Trial
 The number of treatments in this trial = 3
 The random seed number = 1538941171
 The seed is generated automatically.

SeqNo	Period1	Period2	Period3
1	ActCtrl	Placebo	TestDrg
2	TestDrg	ActCtrl	Placebo
3	Placebo	TestDrg	ActCtrl
4	TestDrg	Placebo	ActCtrl
5	Placebo	ActCtrl	TestDrg
6	ActCtrl	TestDrg	Placebo

The Randomization Schedule for the Trial
 The number of treatments in this trial = 3
 The random seed number = 1538941171
 The seed is generated automatically.

Sub_ID	Sequence
001	Placebo-ActCtrl-TestDrg
002	TestDrg-ActCtrl-Placebo
003	ActCtrl-TestDrg-Placebo
004	TestDrg-Placebo-ActCtrl
005	ActCtrl-Placebo-TestDrg
006	Placebo-TestDrg-ActCtrl
007	TestDrg-Placebo-ActCtrl
008	ActCtrl-Placebo-TestDrg
009	Placebo-TestDrg-ActCtrl
010	ActCtrl-TestDrg-Placebo
011	Placebo-ActCtrl-TestDrg
012	TestDrg-ActCtrl-Placebo
013	ActCtrl-Placebo-TestDrg
014	Placebo-TestDrg-ActCtrl
015	TestDrg-ActCtrl-Placebo
016	TestDrg-Placebo-ActCtrl
017	ActCtrl-TestDrg-Placebo
018	Placebo-ActCtrl-TestDrg

For an odd number of treatments, the design is a combination of two Latin squares.