5. Methods of Treatment Allocation in Randomised Controlled Trials

In most clinical trials patients join when they require treatment, they will then need to be randomised before they can start a trial treatment. Recruitment may therefore take place over many months or years. Because of this random sampling can rarely be used to select patients for a particular treatment as one cannot define a sampling frame. Instead they are randomly allocated a treatment. The four most commonly used methods of random allocation are:

- Simple Randomisation.
- Block Randomisation also called Randomised Permuted Blocks.
- Stratified Randomisation.
- Minimization.

5.1 Simple Randomisation

This is equivalent to tossing a coin as the probability of receiving each treatment is kept constant throughout the trial. It is usually carried out using a pseudo-random number generator, which is then used to create a randomisation list. All the treatment allocations on the list are then used in sequence as patients are recruited.

Imbalance with Simple Randomisation

If simple randomisation is used, the numbers of subjects in each treatment group is a random variable and so resulting groups may not be of equal size. The probability of different degrees of imbalance can be estimated using the binomial distribution. For a trial with two treatment groups and an equal allocation ratio and total size N, the number allocated to each treatment is B[N,0.5].

Table 5.1 Probability of imbalance for difference trial sizes when using simple randomisation

Total Number of Patients	Percentage difference in numbers ≥ 100%	50%	30%	20%
	Ratio of larger to small sample sizes≥ 2:1	3:2	4:3	6:5
20	12%	50%	50%	82%
50	2%	20%	32%	48%
100	0%	6%	19%	37%
200	0%	1%	6%	18%
500	0%	0%	0%	4%
1000	0%	0%	0%	0%

In table 5.1 we see simple randomisation gives equal sized groups that in the long run, but may be quite unequal for small sample sizes.

Effect of Unequal Sample Size on Power

Suppose the total sample size estimated assuming equal size groups is *N* for a power $(1-\beta)$. Suppose that there is imbalance in treatment group sizes due to randomisation with $\frac{n_T}{n_C} = k$. It can be shown that power for a given value of k is

$$1-\Phi\left(z_{\alpha/2}-\left(\frac{2\sqrt{k}}{k+1}\right)\left(z_{\alpha/2}+z_{\beta}\right)\right).$$

for a normally distributed outcome measure. Derivation of this result is set as an exercise. Exercise sheet 4 Q6.

Table 5.2 Loss of power relative to 1:1 for different levels of imbalance

Ratio of group sizes	k or 1/k	Power
6:5	1.2	0.797
4:3	1.33	0.792
3:2	1.5	0.784
2:1	2	0.752

For a given total sample size the power is reduced as the imbalance increases.

Summary: Simple Randomisation

Advantages

- Simple and not predictable.
- Similar treatment group sizes in large trials.

Disadvantages

- Imbalance in treatment groups sizes leads to some loss of power in small trials.
- Does not balance treatment groups for prognostic factors other than by chance. There is the possibility of chance bias due to more people with a particularly poor or good prognosis ending up in one or other treatment group.

The alternative to simple randomisation is an *adaptive randomisation* in which the probability of being allocated to a particular treatment varies from patient to patient. It can depend on the numbers previously allocated to each treatment or the characteristics of patients previously recruited.

5.2 Blocks Randomisation

Block Randomisation, also referred to as *Randomised Permuted Blocks,* aims to keep treatment group sizes in a particular ratio, which is usually 1:1. Blocks of treatment allocations are created with each block containing the treatments in the required ratio. Blocks are then randomly selected to construct a randomisation list. All the treatment allocations on the list are then used in sequence as patients are recruited.

Procedure for Block Randomisation

1. Suppose the number of treatments being compared is *N*. Choose a block length L (>N). With equal allocations this must be an integer multiple of the number of treatments being compared.
2. All sequences of treatment allocations for the chosen block size are then enumerated. For a block size *L* with *N* treatments, the number of unique blocks is $P = \frac{L!}{(M!)^N}$ where M=L/N assuming an equal allocation ratio.
3. Select a sequence of numbers between 1 and *P* at random from random number tables or equivalent.
4. Assemble a randomisation list by selecting the blocks according to the sequence of random numbers.
5. Patients are then allocated in turn according to the list.

Ex5.1 *Assuming equal allocation is required, create a randomisation list of 20 patients for a trial with two treatments using block randomisation with a block size of four and the random number sequence 1, 6, 3, 1, 4.*

L=4 and N =2 gives $P = \frac{4!}{2!\,2!} = 6$ unique blocks .

Using the labels A and B for the two treatment the unique blocks are

1=AABB 2=ABAB 3= BBAA 4=ABBA

5= BABA 6= BAAB

The blocks can then be chosen using the random number sequence and added to the table to create the randomisation list.

Table 5.3 Randomisation list constructed using block randomisation

Patient Num	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Block	1				6				3				1				4			
Treat.	A	A	B	B	B	A	A	B	B	B	A	A	A	A	B	B	A	B	B	A

Summary: Block Randomisation

Advantages compared to Simple Randomisation

- Reduces imbalance in group sizes. For two groups with block length L and allocation ratio of (1:1) the maximum imbalance during the trial is L/2 and group sizes are balanced at the end of each block.
- Prevents bias due to secular (time) trends in prognosis of patient recruited as similar proportions of each treatment are allocated in each time period of the trial.

Disadvantages

- More complicate than simple randomisation.
- With a small block length it may be possible to predict the next allocation. For this reason a block size of 2 is never used. One way to reduce predictability is to use a random mixture of block of different sizes. e.g. for two treatments use blocks of sizes 4, 6 and 8.

5.3 Allocation and Prognostic Factors

Block randomisation only balances the design with respect to size. As with simple randomisation, it does not balance treatment groups for prognostic factors. By chance, the composition of the two groups may differ. For example, suppose a small proportion of eligible patients have a particularly poor or good prognosis. From table 5.1 above it can be seen that these could be unequally distributed between treatment arms, causing chance bias, particularly were numbers with a particular good or poor prognosis are small

Since it is desirable to have treatment groups that have a similar composition in terms of important prognostic factors, it makes sense to vary the allocation probability to achieve this. Two methods that allow this are *Stratified Randomisation* and *Minimization*. Nevertheless block randomisation is still relevant, as it is required for stratified randomisation.

Stratified Randomisation

A small number of prognostic factors can be balanced using this form of randomisation by using different block randomisations for groups or strata of patients. Before the trial begins strata need to be defined either by a categorical variable such as gender or by dividing a continuous variable such as age into bands.

Procedure for Stratified Randomisation

1. Select a categorical variable that defines the strata e.g. age banding (-64, 65-74,75+)
2. Construct separate randomisation list for each strata using block randomisation.

Stratification may be extended to two or more factors, but the number of block randomisation lists required rapidly becomes large. For example 3 factors each with just 2 levels would requires $2^3 = 8$ separate lists. As well as the added complexity, with many lists there may be many incomplete blocks left at the end of the trial that could cause imbalance unless the trial is large.

Note that if simple randomisation is used to prepare the list for each strata in place of block randomisation, the benefit of stratified randomisation is lost, as the resulting randomisation list will be no different to simple randomisation.

Summary Stratified Randomisation

Advantages

- Balances groups on prognostic factors used to stratify.

Disadvantages

- More complex to organize and administer, which could lead to mistakes.
- Only feasible with a small number of strata / prognostic factors.

Minimisation

To carry out minimization one begins by selecting the factors we wish to control. These need to be categorical variable or converted into such by banding.

There are two type of minimization, *deterministic* and *stochastic*, the difference between which is explained below.

Procedure for Minimisation

1. For each levels of each factor being controlled, a running total is kept for the numbers of parents assigned to each treatment.
2. When a new patient is recruited, the totals for that patient's characteristic are added together for each treatment group. The patient is then assigned to
   (i) the treatment group with smaller total. **(deterministic minimization)**

   or

   (ii) probabilistically using a larger probability (say 0.6 or 0.7) for the treatment group with the smaller total. **(stochastic minimization)**
3. After each patient is entered into the trial, the relevant totals for each factor are updated based on the treatment allocation that took place, ready for the next patient.

4. If totals are equal, simple randomisation is used. Hence, the first patient is allocated using simple randomisation as all totals are zero at the start of the trial.

Ex 5.2 *The table below summarizes the minimization totals after 50 patients have been recruited into a trial with two minimization factors Sex and Hospital. Fill in the characteristics of the 51st and 52nd patients. Using these characteristics apply deterministic minimization to allocation the 51st and 52nd patients showing the up-dated minimization totals and the treatment allocation for each patient*

Factor	Sex				Hospital								Treatment
Level	Male		Fem.		I		II		III		Total		Allocated
Treat	A	B	A	B	A	B	A	B	A	B	A	B	
Patient No													
50	16	14	10	10	13	12	9	6	4	6	26	24	A
51	16	**15**	10	10	13	12	9	**7**	4	6	26	25	B
52	16	15	10	**11**	13	**13**	9	7	4	6	26	26	B

Total that changed in bold

Characteristics of Patient 51: Sex = M Hospital = II

Treatment	Sex	Hospital	Total
A	16	9	25
B	14	6	20

Characteristics of Patient 52: Sex = F Hospital = I

Treatment	Sex	Hospital	Total
A	10	13	23
B	10	12	22

We have used deterministic minimisation in this example for illustrative purposes, but deterministic minimization can be predictable based on knowledge of previous allocations. Stochastic minimisation is recommended but this is complicate without specialist software.

Summary: Minimization

Advantages

- Balance can be achieved on a larger set of prognostic factors than for stratified randomisation.

Disadvantages

- Complicated as randomisation list cannot be prepared in advance but depend on the characteristics of patients as they are recruited to the trial. It is tedious to do without specialist software.

Comparison of Stratified Randomisation and Minimization

Stratified randomisation maintains balance on all combinations of factors. If a study is stratified on say gender and severity (mild, severe), balance between treatments would be maintained on each four combinations (male & mild), (male & severe), (female & mild) and (female & severe).

Minimisation maintains balance between treatments for each level of a factor but not on combinations of factors.