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Randomization in Clinical Trials

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3. Minimization method
Stratification

RELATED ISSUES

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Two Independent Groups

Research is often conducted using experimentation involving the manipulation of a least one factor. Commonly used experimental designs include the experimental designs for the two group problem for superiority (i.e. is one treatment superior to another on a primary outcome?), for non-inferiority (is a new treatment no worse than an existing treatment on a particular outcome?), or for equivalence (are two interventions essentially identical to one another on a primary outcome?). Strong conclusions may be drawn from such endeavours providing the design is sufficiently powered and providing there are no threats to the validity of conclusions. The use of randomization in experimental work contributes to establishing the validity of inferences.

The following notes relate to the experimental comparison of two treatments with participants randomized to one of two treatments; such designs can viewed as being RCT designs [RCT === Randomized Control Trial if one treatment is a “control” or more generally RCT === Randomized Clinical Trial].

Simple Random Samples and Random Allocation

Simple random selection and random allocation are not the same. Random selection is the process of drawing a sample from a population whereby the sample participants are not known in advanced. A *Simple Random Sample* of size k is a sample determined by chance whereby each individual in the population has the same equal probability of being selected and each possible subset of size k in the population has the same chance of being selected. It is hoped that a simple random sample will give a sample that is arguably representative of the population, and in doing so help with the external validity or generalizability of the results.

Random Allocation

Random allocation is a procedure in which identified sample participants are randomly assigned to a treatment and each participant has the same probability of being assigned to any particular treatment. If the design is based on N participants and n_1 are to be assigned

to Treatment 1 then all possible samples of size n_1 have the same probability of being assigned to Treatment 1.

Example Purely for simplicity of exposition suppose there are $N = 4$ participants [Angela, Ben, Colin, Dee], two of whom are to be assigned to Treatment 1 and two to Treatment 2. The possible groups that could be assigned to Treatment 1 are; 1. [Angela, Ben], 2. [Angela, Colin], 3. [Angela, Dee], 4. [Ben, Colin], 5. [Ben, Dee], 6. [Colin, Dee]. Rolling a fair six sided die would be one way of performing the random allocation. For instance, if the die lands on the number 3 then Angela and Dee would be assigned to Treatment 1 and Ben and Colin would be assigned to Treatment 2.

The above is the way a methodologist would consider random allocation. However the above does have its practical drawbacks. For instance suppose we consider a case of $N = 60$ participants and 30 are to be assigned to Treatment 1 and the other 30 to Treatment 2. For these parameters there are 155,117,520 possible different samples of size 30 which could be assigned to Treatment 1. Who in their right mind would write out the list of all possible 155,117,520 combinations? Finding a die with 155,117,520 sides might be difficult too! [A computer could be used to randomly generate a number from the integers 1 to 155,117,520 to select a sample.]

As described, random allocation can have practical problems but logically equivalent pragmatic solutions exist (e.g. names in a hat with the first n_1 drawn out allocated to Treatment 1 and the remainder to Treatment 2).

Why Randomly Allocate

Suppose two treatments, Treatment A and Treatment B are to be compared. Further suppose the sample for Treatment A are all men and the sample for Treatment B are all female. If at analysis a difference in the primary outcome between the two groups is found, could we then emphatically attribute this difference as a treatment effect? Clearly under this design the answer to that question would be “No”. Under this design it could be argued that the effect might be due to Sex, or to Treatment, or in fact both might affect the

outcome and their unique effects cannot be determined. In this design, Sex and Treatment are completely confounded and their separate effects cannot be identified. In this design an argument for a *causal* effect due to treatment would not stand close scrutiny because a plausible alternative explanation for any difference is evident.

In any practical situation the participants will have some (identifiable or unidentifiable) characteristics that may be related to the outcome under investigation. A clustering of these characteristics with any one treatment could cause a systematic effect (a systematic bias) between the groups which is quite distinct from any treatment effect (i.e. we would have a confounding effect). *In the long run*, random allocation will equalise individual differences between treatment groups and in doing so will remove extraneous bias and allow the treatment effect to be established uncontaminated by other potentially competing explanations. *In any one experiment* it is *hoped* that random allocation will minimise the effect of possible confounders, reducing extraneous systematic bias, leading to a fair comparison between treatments by reducing the possibility of partial confounding and hence helping to rule out other potential competing causal explanations.

The data generated under an experimental design will, most likely, be assessed using formal statistical methods. The theory underpinning permutation tests and randomisation tests is based on the assumption of random allocation. Accordingly valid and defensible data analysis plans may be devised if random allocation is used.

Simple Randomization

The most commonly encountered situation in practice is a two treatment comparison with a predetermined overall sample size N with a predetermined sample size of n_1 for Treatment 1 and size n_2 for Treatment 2 ($n_1 + n_2 = N$). A total of N opaque envelopes, n_1 containing an identifier for Treatment 1 and n_2 containing an identifier for Treatment 2, may be shuffled. The order of the shuffled envelopes determines the allocation of participants to treatments. This process is relatively simple to organise, preserves the predetermined design parameters, and can be readily extended to situations where multiple treatments are to be compared.

Simple Sequential Randomization

A commonly encountered situation is a two group comparison where sample sizes n_1 and n_2 are required to be equal or approximately equal. In a two group trial, the process is analogous to the toss of a coin such that each participant has an equal probability to be allocated to either of the treatments. When the sample size is relatively large, simple randomization is expected to produce approximately equally sized treatment groups however this is not guaranteed and the general recommendation is to only consider this approach where overall sample size is 200 or above.

Possible Problems with Simple Randomization

Simple randomization reduces bias by equalising some factors that have not been accounted for in the experimental design e.g. a group of people with a health condition, different from the disease under study, which is suspected to affect treatment efficacy. Another example is that a factor such as biological sex could be an important prognostic factor. Chance imbalances or *accidental bias*, with respect to this factor may occur if biological sex is not taken into account during the treatment allocation process. An example of a perfect randomization with respect to gender as an important prognostic factor is as shown in Figure 1. Figure 2 depicts an example where there is accidental bias with respect to biological sex.

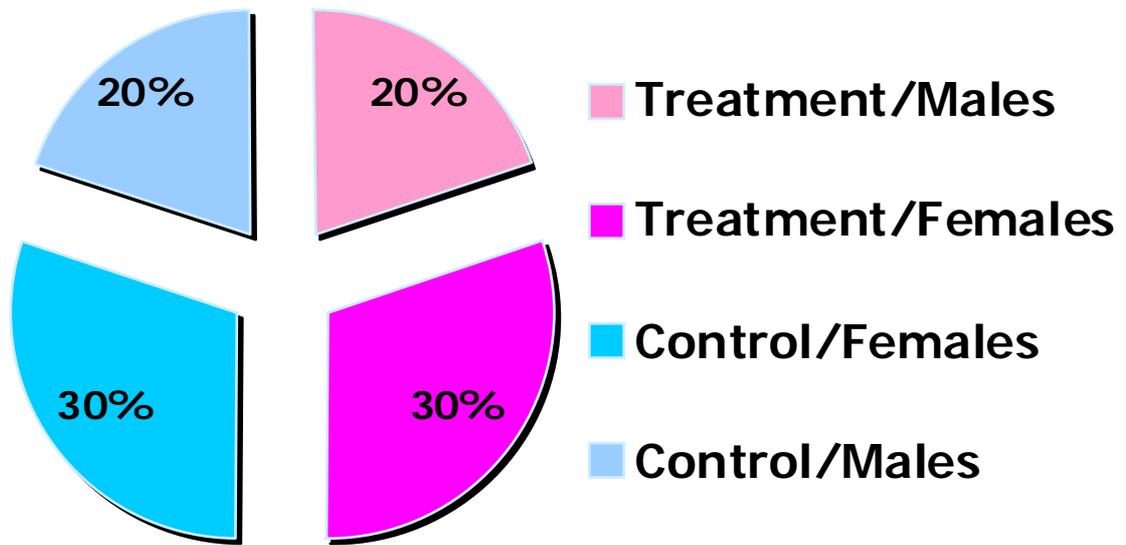


Figure 1: No accidental bias: perfect balance with respect to Sex

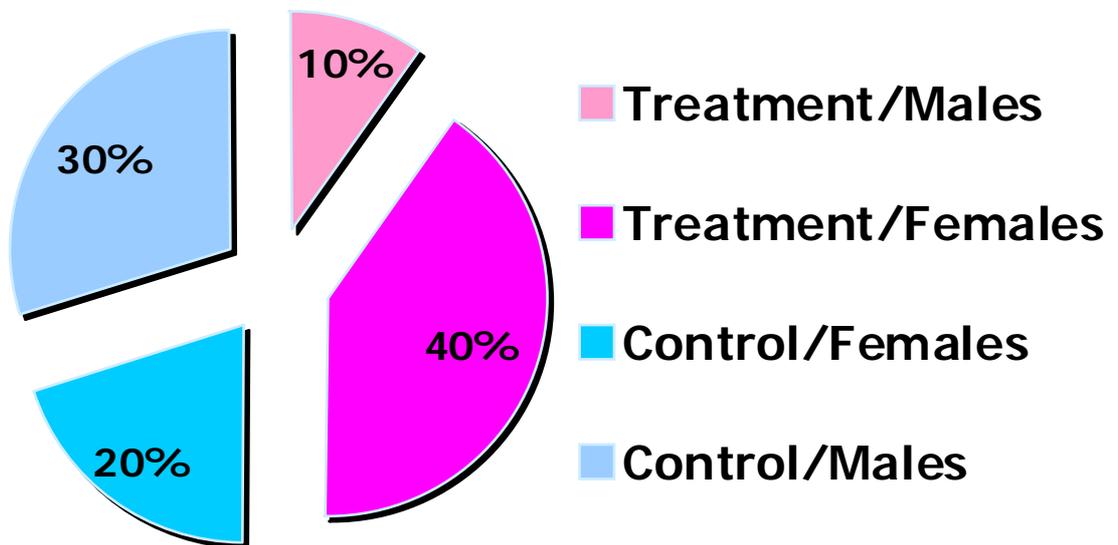


Figure 2: Accidental bias: imbalance with respect to Sex

It may be argued that randomization is too important to be left to chance! In these cases some practitioners may argue for a blocked randomization scheme, or a stratified randomization scheme, or one which deliberately minimises differences between groups on key pre-determined prognostic factors.

Block Randomization

Block randomization is commonly used in the two treatment situation where sample sizes for the two treatments are to be equal or approximately equal. The process involves recruiting participants in short blocks and ensuring that half of the participants within each block are allocated to treatment “A” and the other half to “B”. Within each block, however the order of patients is random.

Conceptually there are an infinite number of possible block sizes. Suppose we consider blocks of size four. There are six different ways that four patients can be split evenly between two treatments:

1. AABB, 2. ABAB 3. ABBA, 4. BAAB, 5. BABA, 6. BBAA

The next step is to select randomly amongst these six different blocks for each group of four participants that are recruited. The random selection can be done using a list of random numbers generated using statistical software e.g. SPSS, Excel, Minitab, Stata, SAS. An example of such a random number sequence is as shown;

9795270571964604603256331708242973...

Since there are only six different blocks, all numbers outside the range of 1 to 6 can be dropped to have;

52516464632563312423...

Blocks are selected according to the above sequence. For example the first eighteen subjects would be allocated to treatments as follows:

5	2	5	1	6
BABA	ABAB	BABA	AABB	BB

In the example, one group has two more participants than the other; but this small difference may not necessarily be of great consequence. In block randomization there is almost perfect matching of the size of groups without departing too far from the principle of purely random selection. Note however this procedure is not the same as simple randomization e.g. the first four participants cannot be all allocated to Treatment A and hence all possible combinations of assignment are not possible. Note that simple sequential randomization is the same as block randomization with blocks of size 1.

Stratification

A stratification factor is a categorical (or discretized continuous) covariate which divides the patient population according to its levels e.g.

- sex, 2 levels: Male, Female
- age, 3 levels: <40, 40-59, ≥ 60 years
- recruitment centres
- Menopausal status
- any other known prognostic factor

Using this approach, the treatments are allocated within each stratum using any of the previously discussed methods. The advantages of using this approach are that it gives allowance for prognostic factors and it is very easy to implement.

Minimization

Using this method, the first patient is truly randomly allocated; for each subsequent patient, the treatment allocation is identified, which minimizes the imbalance between groups at that time. For example, consider a situation where there are 3 stratification factors; sex (2 levels), age (3 levels), and disease stage (3 levels). Suppose there are 50 patients enrolled and the 51st patient is male, age 63, and stage III disease.

		Treatment A	Treatment B
Sex	Male	16	14
	Female	10	10
Age	< 40	13	12
	41-60	9	6
	≥ 60	4	6
Disease	Stage I	6	4
	Stage II	13	16
	Stage III	7	4
Total		26	24

Method: Keep a current list of the total patients on each treatment for each stratification factor level. Consider the lines from the table above for that patient's stratification levels only

	Treatment A	Treatment B	Sign of Difference
Male	16	14	+
Age ≥ 60	4	6	-
Stage III	7	4	+
Total	27	24	2+s and 1-

There are two possible criteria:

-Count only the direction (sign) of the difference in each category. Treatment A is “ahead” in two categories out of three, so assign the next patient to Treatment B

-Add the total overall categories (26 As vs 24 Bs). Since Treatment A is “ahead,” assign the next patient to Treatment B

- These two criteria will usually agree, but not always
- Both criteria will lead to reasonable balance
- When there is a tie, use simple randomization
- Balance by margins does not guarantee overall treatment balance, or balance within stratum cells

Problems and Additional Benefits of Randomization

With some methods of allocation an imbalance due to the foreknowledge of the next treatment allocation between the treatment groups with respect to an important prognostic factor may also occur i.e. when an investigator is able to predict the next subject’s group assignment by examining which group has been assigned the fewest patients up to that point. This is known as selection bias and occurs very often when randomization is poorly implemented e.g. Pre-printed list of random numbers can be consulted by an experimenter before next patient comes in, or envelopes can be opened before next patient comes in, or an experimenter can predict the next allocation with “static methods” e.g. the last treatment in each block in block randomisation.

A practical issue in experimentation is *allocation concealment*, which refers to the precautions taken to ensure that the group assignment of patients is not revealed prior to definitively allocating them to their respective groups. In other words, allocation concealment shields those who admit participants to a trial from knowing the upcoming

assignments and can be achieved by coding the treatments and not using their real names. This is called *masking* and is different from *blinding*:

-*Masking* or *allocation concealment* seeks to prevent selection bias, protects assignment sequence before and until allocation, and can always be successfully implemented.

-In contrast, *blinding* seeks to prevent sampling bias, protects sequence after allocation, and cannot always be successfully implemented. For example, it is impossible to implement blinding in a situation where the treatment is a surgical procedure.

In general simple random allocation, as well as having very desirable theoretical properties from a statistical perspective, often permits the implementation of very desirable methodology including masking and can greatly help with preserving the overall conclusions from experimental research.