Randomisation
in Clinical Trials

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What is randomisation?

Randomisation is a procedure to randomly allocate patients in a clinical trial to different treatment groups. The simplest form is flipping a coin to decide whether a recruited patient will receive treatment A or treatment B, but other, more complex random algorithms are commonly applied. Usually the random choice of treatment will be between a new treatment and a comparator.

What is a comparator?

A comparator in a clinical trial is a reference treatment to which the experimental treatment is compared. When the aim of a trial is to evaluate the efficacy or safety of a treatment, a comparator is needed to reason that observations are due to treatment (and not e.g. characteristics of the patients in the study).

In the Pioglitazone trial...
Placebo was used a comparator. Remission rate of the Pioglitazone group was compared to the rate of the Placebo group.

How do we know a treatment is better?

If we want to know whether a new treatment A can be given instead of treatment B (or no treatment), we compare patients treated with A and patients treated with B (or untreated). If the outcome under treatment A is better, then we would like to conclude, that treatment A is more efficacious.
However, what would happen, when the clinical scientist allocated the patients at will? Sicker patients might be allocated to treatment A, because they are believed to be in stronger need of a treatment and, consequently, healthier patients might be allocated to treatment B (or no treatment). In the end, treatment A might look worse, solely due to sicker patients in this group. Observing the outcome, the scientist, however, might incorrectly conclude, that treatment B (or even not treating patients) is better than treating with A. This misconception can be avoided, by not allowing the scientist to choose which patient is allocated to which treatment group and using a randomised treatment allocation.

Example Pioglitazione trial

The phase IIb randomised, placebo controlled trial of Pioglitazone for oral premalignant lesions [1] studied the effect of 15mg Pioglitazone 3x daily for 24 weeks as compared to placebo. For each patient the histological and clinical change in the oral lesions was evaluated and the proportions of patients with complete or partial response were calculated for the Pioglitazone and Placebo group.

What is different in rare diseases? Nothing!

Yes, sample sizes are typically smaller in rare diseases than in common diseases, but nonetheless randomisation is necessary for valid inferences and to reduce the risk of false conclusions.

How is the treatment effect estimated?

The treatment effect is estimated as the difference between the treatment group and the comparator group regarding a specified outcome variable.

In the Pioglitazone trial...
14/26= 46% of the patients in the treatment group and 8/25=32 % in the Placebo group had a complete or partial remission of oral premalignant lesions. Here, the treatment effect of Pioglitazone compared to placebo is estimated as 46% - 32% = 14% [1].

Why randomise?

Because non-randomised trials are misleading!
Only if the treatment is the only systematic difference between the treatment and comparator group, the observed difference can be attributed to the treatment (and not to other differences between the groups like e.g. age or severity of the disease).

In the Pioglitazone case...
A non-randomised trial raised false hope! The remission rate of Pioglitazone was overestimated as 15/21 = 68%, possibly because patients were healthier [2, 3].

What if important prognostic factors are known?

A factor can be forced to be balanced by stratified randomisation, meaning that patients are randomised separately within each level of the factor.

For example, if it is known that gender affects the outcome, randomisation is stratified for gender so that both treatment groups contain roughly the same proportion of both men and women.

Possible benefits for patients

- A proper randomisation is key for valid conclusions on the treatment effect
- Statistical power (the ability to find an existing treatment effect) may be increased by stratified randomisation (balancing known prognostic factors)
- Randomised controlled trials generate the highest level of evidence and minimise the risk of false conclusions.
- Unbiased treatment estimates from randomised controlled trials can be used for planning future trials. Thus, the efficiency of future trials is improved.

Possible downsides

- Prognostic factors must be known in order to account for them. This may be difficult in small populations.
- The number of accountable prognostic factors is limited, especially in small populations and rare diseases.
- Randomisation works best with many patients. When there are only very few patients in each group, imbalances can occur despite randomisation

More information

[1] National Cancer Institute (NCI). Pioglitazone for Oral Premalignant Lesions. https://clinicaltrials.gov/ct2/show/NCT00951379. Accessed 3 Aug 2017.
[2] Miller K, Wuertz B, Ondrey FG. Pioglitazone and metformin as potential chemopreventative treatments in Fanconi anemia related oral squamous carcinoma [abstract]. Proc. 106th Annu. Meet. Am. Assoc. Cancer Res. Philadelphia; 2015. p. Abstract nr 914.
[3] Lasch, F. et al., 2017. A plea to provide best evidence in trials under sample-size restrictions: the example of pioglitazone to resolve leukoplakia and erythroplakia in Fanconi anemia patients. Orphanet Journal of Rare Diseases, 12(1), p.102. Available at: http://ojrd.biomedcentral.com/articles/10.1186/s13023-017-0655-8.

Contact details

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