Tidsskriftet Tidsskrift for Den norske legeforening

Crossover trials

MEDICINE AND NUMBERS

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The author has completed the ICMJE form and declares no conflicts of interest.

Most randomised, controlled trials are conducted with parallel groups, but some treatments can be studied more effectively in a crossover trial.

In a randomised trial with parallel groups, the participants are randomised either to treatment A or treatment B. In a crossover trial, each participant receives both treatment A and treatment B.

Different treatment in two phases

Let us start with an example where we studied the effect of a probiotic on irritable bowel syndrome in a double-blind, placebo-controlled trial (1). This was undertaken as a crossover trial, as illustrated in Figure 1. Such trials are conducted in two phases. After inclusion, the participants are randomised to group 1 or group 2. During phase 1, group 1 receives treatment A and group 2 treatment B. In phase 2, this is reversed: group 1 receives treatment B and group 2 treatment A. Between the two phases, there is a treatment-free period in order to wash out the effect of the treatment provided in Phase 1.

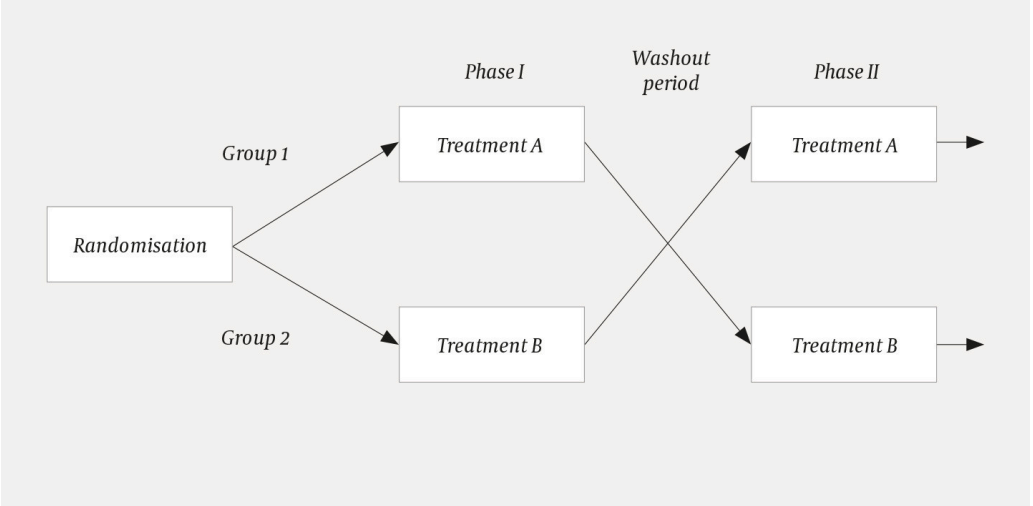

Figure 1 A crossover trial consisting of two treatments and two phases.

This design cannot be used for all types of treatment. For example, it cannot be used to compare the curative effect of two different treatments. However, it can be well suited to comparing the symptom-reducing effect of treatments for chronic ailments. The great advantage of this design is that each participant acts as their own control.

Between-subject variation is often higher than within-subject variation. When each participant acts as their own control, random variation is reduced. Higher statistical power is thereby achieved, and the trial can be conducted with fewer participants than when using parallel groups. On the other hand, since all the participants must complete two phases, the trial may take a longer time and this may also increase the risk of attrition.

Paired data

When analysing the results, it must be taken into account that the data are paired, because the results of treatment A and treatment B will be positively associated within each participant. If the outcome variable is continuous, a simple analysis method could be based on the difference between the outcome variables for treatment A and treatment B. A paired *t*-test with an associated confidence interval may be relevant. In the abovementioned trial, one of the variables was the sum of abdominal ailments measured by a score. The 16 participants who completed the study had a mean score (standard deviation) of 6.44 (1.81) in the active period and 5.35 (1.77) in the placebo period. The difference in scores between the active period and placebo was –1.09 (1.47) in favour of the placebo. The correlation between the scores in the two periods was 0.66. An analysis based on a paired *t*-test returned a 95 % confidence interval of –1.87 to –0.31 and a *p*-value of 0.010.

In some crossover trials it will be appropriate to use a more complex analysis model than a paired *t*-test. For example, it might be relevant to take account of a period effect, such as a systematically higher outcome variable in Phase II than in Phase I. So far we have described crossover trials involving two treatments and two phases. The design can also be generalised to more than two treatments or more than two phases. This can be dealt with by a linear

mixed effects model (2, p. 61–72). If the outcome variable is categorical, other methods will have to be used. We will return to this in a future article in this column.

Higher power than parallel groups

What if the abovementioned trial instead had been conducted with two parallel groups with 16 participants in each? If the results above were from a parallel group trial, a two-sample *t*-test would have returned a 95 % confidence interval of −2.38 to 0.20 and a *p*-value of 0.095, i.e. a wider confidence interval than the crossover trial, even if it had been designed with 16 × 2 = 32 participants, or twice as many as in the crossover trial.

The strength of a crossover trial can also be illustrated by the number of participants needed. Assume that we are planning a trial where the outcome variable has a standard deviation of 1.5, and we want to demonstrate a mean difference of 1.0. When planning a crossover trial and the correlation is assumed to be 0.50, we need a total of 20 participants to achieve a statistical power of 80 % at a significance level of 5 %. If we are planning a trial with parallel groups, on the other hand, we need 37 participants in each group, i.e. a total of 74.

Only some types of treatments and research questions are suitable for a crossover trial. In cases where it is possible, however, this is a very effective design that can be considered.

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Publisert: 2 May 2022. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.22.0013