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ENDGAMES

STATISTICAL QUESTION

Treatment allocation in trials: block randomisation

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Researchers investigated the efficacy of nicotine patches in pregnant smokers. A randomised, double blind, placebo controlled, parallel group, multicentre trial study design was used. The intervention was 16 hour nicotine patches administered until the time of delivery. Participants were pregnant smokers aged over 18 years, whose babies were between 12 and 20 weeks' gestation, and who smoked at least five cigarettes a day. In total, 402 women were recruited from 23 maternity wards throughout France. Participants were allocated to treatment (203 to nicotine patches and 199 to placebo patches) by block randomisation, using a block size of four.[1]

The primary outcome measures included complete abstinence until delivery and birth weight. Complete abstinence was achieved by 5.5% (n=11) of women in the nicotine patch group and 5.1% (n=10) in the placebo group (odds ratio 1.08, 95% confidence interval 0.45 to 2.60). The mean birth weight was 3065 g (standard error 44 g) in the nicotine patch group and 3015 g (44 g) in the placebo group (P=0.41). The researchers concluded that the nicotine patches did not significantly increase smoking cessation rates or birth weights.

Which of the following statements, if any, are true?

a) The objective of block randomisation was to ensure similar numbers of patients in the treatment groups

b) Participants were allocated to treatment four at a time in an alternate order, with the order decided at random

c) Block randomisation ensured a similar distribution of baseline characteristics in each treatment group

d) Maternity wards were allocated to a treatment, with women receiving the treatment that their ward had been allocated

e) Upon recruitment, each participant had an equal probability of being allocated to the intervention group or control group

Answers

Statements *a* and *e* are true, whereas *b*, *c*, and *d* are false.

The aim of the trial was to investigate the efficacy of nicotine patches in pregnant smokers. A randomised placebo controlled trial study design was used. The most straightforward way of allocating participants to treatment in a trial is to use simple random allocation, often referred to as random allocation or randomisation. Each participant is allocated at random and has equal probability of being allocated to any one treatment group. The purpose of random allocation is to achieve similarity of baseline characteristics between treatment groups and therefore to minimise confounding. Confounding is a difference between groups in those factors that affect treatment and outcome measures. These include demographic characteristics, prognostic factors, and other characteristics that may influence someone's decision to participate in or withdraw from a trial. If confounding existed, any differences between treatment groups in outcome may not result from differences in treatment received but from disparities in baseline characteristics. Confounding affects the internal validity of a trial and, in particular, may not permit the inference of causality to be ascribed to differences in treatments received. Internal validity has been described in a previous question.[2]

A balance in the numbers of participants between treatment groups is essential to minimise confounding. However, it is unlikely that simple random allocation will achieve such a balance for trials with small samples. A greater balance in numbers is achieved as sample size increases. In the above trial, permuted block random allocation, also known simply as block randomisation, was used to allocate participants to treatment to ensure similar numbers of participants in the groups (*a* is true).

Block randomisation with blocks of four was used to allocate women to treatment. This involved selecting groups of four consecutive women as they were recruited. Women were allocated to treatment in a 1:1 ratio. Therefore, within each group of four two were allocated to the intervention and two were allocated to the placebo. The order in which women were allocated in each block was random (*b* is false). For blocks of size four, there are six different ways in which treatments could have been allocated. If the intervention is denoted by A and placebo by B, the six possible permutations of allocation were AABB, ABAB, ABBA, BABA, BAAB, and BBAA. One of

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these permutations would have been selected at random for each group of four women. Allocating the women at random within a block in a 1:1 ratio ensured that the two groups had similar numbers of participants.

If women were allocated alternately to treatment within groups of size four (as in statement *b*), it might have been possible to predict the allocation sequence, which may have compromised the double blinding. There would then have been the potential for selection and allocation biases; the researchers in charge of recruitment could have dictated the order in which, if at all, women were recruited and then allocated to treatment. Selection and allocation biases have been described in a previous question.[3]

A total of 402 women were recruited to the trial, with 203 allocated to nicotine patches and 199 to placebo. The trial was a multicentre one, with women recruited from 23 maternity wards. For each ward, women were recruited in groups of four and the four women on that ward were then allocated to treatment using block randomisation as described. It was therefore possible that the total number of women recruited on a ward was not a multiple of four. Consequently, equal numbers of women may not have been allocated to each treatment on each ward. This explains the difference in the total numbers of participants allocated to the treatment groups. However, the women were more evenly distributed between the treatment groups than they might have been if simple random allocation had been used.

The block size in the trial above could have been any size providing it was a multiple of two—the number of treatment groups. The block size may be fixed or may change during treatment allocation in a trial. The advantage of varying block sizes is that it ensures that treatment allocation is not predictable. This would be an advantage if the trial had not been double blind. However, large block sizes tend to give a greater imbalance between treatment groups in the number of participants. If participants are allocated in a 1:1 ratio, as in the above trial, the number of participants allocated to the groups would never differ by more than half the block size. For the study above, women were allocated using a block size of four, so for any one maternity ward, the numbers in the two groups would not differ by more than two.

Although block randomisation ensures similar numbers of participants in the treatment groups, it does not ensure that the distribution of baseline characteristics is similar between groups (*c* is false). Some imbalance between treatment groups in baseline characteristics is expected, particularly for trials with small samples. Stratified random allocation could have been used to achieve a similar distribution between treatment groups in certain important characteristics and therefore minimise confounding. For example, if age was an important prognostic factor, stratified randomisation would have involved categorising participants according to their age (say <25, 26-35, and >36 years). Within each subgroup (stratum) of age, women would be randomised to treatment. Block randomisation should still have been used, with groups of four women allocated according to their age stratum. Otherwise there would be no control in the balance of numbers and the objective of stratified random allocation might have been lost. Because women were recruited in groups of four as they presented in sequence to a maternity ward, the randomisation of women in the above trial was in effect stratified by maternity ward. The advantage of this is that it minimised confounding between treatment groups in those characteristics that might vary between maternity wards across France. Stratified random allocation will be described in a future question.

As described above, women were recruited in groups of four as they presented in sequence to a maternity ward. Within each group of four women on a ward, two were allocated to the intervention and two were allocated to placebo at random (*d* is false). If the maternity ward had been allocated one treatment (intervention or placebo), and all women on the ward had received the same treatment (as in statement *d*), the method of randomisation would have been cluster random allocation. In the example above the maternity wards were clusters—natural groupings of women. Cluster random allocation has been described in a previous question,[4] and it will be explored further in a future question. Cluster random allocation is used to overcome practical and contamination problems that may arise when trial participants are randomised. Such problems are more likely when blinding cannot be used in a trial. For example, in a trial that investigated the effectiveness of a physical activity programme on physical and psychological health in schoolchildren compared with no intervention, it would be difficult to implement the intervention in a school for some children but not for others. Such practical problems would be reduced if schools, rather than the children, were randomised to treatment. In the above trial, because blinding was achieved with the use of placebo patches, no problems would have occurred in implementing the intervention, so it was not necessary to randomise wards to treatment.

Block randomisation is an example of restricted random allocation. This term describes a method that controls the process of random allocation to achieve greater equivalence between treatment groups in size and baseline characteristics. Despite it being a restricted process of allocation, the allocation sequence for each block of four women was chosen at random from all possible permutations. Therefore, each woman had an equal probability of being allocated to the intervention or control on recruitment (*e* is true). However, once the allocation sequence for a group of four women had been selected, the treatment a woman received was predetermined.

Competing interests: None declared.

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4 Sedgwick P. Cluster randomised controlled trials. *BMJ* 2012;345:e465.

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