

ENDGAMES

STATISTICAL QUESTION

Stratified random allocation

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Researchers investigated the effects of manual lymph drainage on the development of lymphoedema related to breast cancer. A randomised single blinded controlled trial was performed. The intervention was a six months' treatment programme consisting of guidelines about prevention of lymphoedema, exercise therapy, and manual lymph drainage. Control treatment consisted of the same programme as the intervention but without manual lymph drainage.¹

Participants were consecutive patients with breast cancer and unilateral axillary lymph node dissection. Randomisation to treatment groups occurred in a 1:1 ratio using stratification by body mass index (≤ 25 or >25) and postoperative axillary irradiation (yes or no). Allocation was achieved using random permuted blocks of size four. In total, 160 patients were recruited, with 79 allocated to the intervention and 81 allocated to control.

The main outcome measures were incidence of arm lymphoedema and time until development of arm lymphoedema. One year after surgery, there was no significant difference between treatment groups in the cumulative incidence rate for arm lymphoedema and the time to development of arm lymphoedema.

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

- All participants in a permuted block had the same stratum values of body mass index and postoperative axillary irradiation
- All four participants in a permuted block were allocated to the same treatment
- Each participant had an equal probability of being allocated to the intervention or control group
- Stratified random allocation minimised confounding due to body mass index and postoperative axillary irradiations at baseline

Answers

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

Participants were randomised to treatment groups in a 1:1 ratio using stratification by body mass index (≤ 25 or >25) and postoperative axillary irradiation (yes or no). Allocation was

achieved using random permuted blocks of size four. This involved identifying groups of four participants from the same stratum—that is, with the same body mass index (≤ 25 or >25) and postoperative axillary irradiation status (yes or no) (*a* is true). Therefore, four possible stratum groups existed—for each stratum of body mass index there were two postoperative axillary irradiation states. The participants in a block were not necessarily consecutive patients. The four patients in each block were randomised to treatment groups in a 1:1 ratio—two to the intervention group and two to the control group (*b* is false). However, the order in which treatments were allocated in each block was random. For a block of four, the interventions could have been allocated in six different ways. If the intervention is denoted by A and control by B, the six possible permutations of allocation are AABB, ABAB, ABBA, BABA, BAAB, and BBAA. One of these permutations would have been selected at random. Because all permutations of treatment allocation in a 1:1 ratio for a group of four participants were possible, with one permutation selected at random, each participant had an equal probability of being allocated to intervention or control (*c* is true).

Body mass index and postoperative axillary irradiation were considered to be important risk factors for development of arm lymphoedema after axillary dissection. The calculated sample size of 160 was small. Simple random allocation (commonly known as randomisation) of participants to treatment groups would not have guaranteed an equal distribution of these risk factors between groups, and unequal distribution would introduce the potential for confounding. Random allocation with stratification by body mass index and postoperative axillary irradiation ensured that these factors were similarly distributed between groups, thereby minimising confounding due to these risk factors (*d* is true).

Although stratified random allocation was used to allocate participants to treatment groups, there was no guarantee that each group would have equal numbers because the sample size was small. Groups are more likely to have equal numbers when sample sizes are large. If treatment groups are not similar in size, baseline characteristics are unlikely to be comparable, and this may lead to confounding. To ensure similar numbers in

each group, randomisation was performed using permuted blocks of size four. Although the total sample size was a multiple of the permuted block size, the numbers in each group were not equal. This was probably because participants with the same body mass index and postoperative axillary irradiation status were not recruited in multiples of four.

Participants were allocated to treatment groups in the example above using stratified random allocation with random permuted blocks of size four. Allocating participants using permuted blocks is described as block randomisation, described in a previous question.² Stratified random allocation and block randomisation are separate methods that do not have to be used in conjunction with each other. Both are examples of restricted randomisation—a term used to describe a method that controls the random allocation procedure to increase the similarity between treatment groups in group size or baseline characteristics.

Block randomisation is typically used to ensure similar numbers in treatment groups. However, when block randomisation is used as the only method of restricted randomisation it may also increase the similarity between treatment groups in baseline characteristics. For example, systematic temporal differences sometimes exist between patients when recruited to a trial. Placing consecutive participants in permuted blocks will ensure that any confounding due to such differences is minimised.

Competing interests: None declared.

- 1 Devoogdt N, Christiaens MR, Geraerts I, Truijien S, Smeets A, Leunen K, et al. Effect of manual lymph drainage in addition to guidelines and exercise therapy on arm lymphoedema related to breast cancer: randomised controlled trial. *BMJ* 2011;343:d5326.
- 2 Sedgwick P. Block randomisation. *BMJ* 2011;343:d7139.

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