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ENDGAMES

STATISTICAL QUESTION

Why randomise in clinical trials?

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Researchers evaluated the efficacy of a 23-valent pneumococcal polysaccharide vaccine in preventing pneumonia in people at high risk. A randomised, placebo controlled, double blind trial was used. A total of 1006 nursing home residents in Japan were recruited. Participants were randomly allocated to 23-valent pneumococcal polysaccharide vaccine (n=502) or placebo (n=504). All participants were followed for at least 26 months.[1]

The primary endpoints were the incidence of all cause pneumonia and pneumococcal pneumonia. The researchers reported that all cause pneumonia and pneumococcal pneumonia were both significantly more frequent in the placebo group than in the vaccine group: the incidence per 1000 person years was 91 versus 55 (P<0.0006) and 32 versus 12 (P<0.001), respectively.

Which of the following, if any, did random allocation of participants facilitate?

a) Minimisation of allocation bias

b) Minimisation of confounding

c) Minimisation of selection bias

d) Double blinding

e) Minimisation of ascertainment bias

Answers

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

The nursing home residents were allocated to vaccine or placebo through simple random allocation, often referred to as random allocation or randomisation. Each participant therefore had an equal probability of 0.5 of being allocated to either treatment. The characteristics of the participants did not influence which treatment group they were allocated to and therefore allocation bias was minimised (*a* is true). Allocation bias is the systematic difference between participants in how they are allocated to treatment. Allocation bias would have occurred if the researchers influenced which treatment group the participants were allocated to. For example, the researchers may have allocated those participants to vaccine who they thought would show the greatest benefit from that intervention. The researchers may have done this, for example, because they favoured the vaccine and wished to demonstrate its effectiveness in comparison to placebo.

The aim of randomising participants to treatment was to achieve two groups similar in baseline characteristics, thereby minimising confounding (*b* is true). Confounding is the difference between treatment groups in baseline characteristics that influence treatment and outcome measures. These factors include demographic characteristics, prognostic factors, and other characteristics that may influence someone to participate in or withdraw from a trial. Therefore, if confounding is minimised then any differences between treatment groups in outcomes at the end of the trial will be due to differences in treatment and not to differences in baseline characteristics. Random allocation will achieve similarity between groups in baseline characteristics only if the sample size is large enough.

The random allocation of participants would not have minimised selection bias (*c* is false). Selection bias is a general term used to describe a systematic difference between the study participants and the population from which they were sampled. When selection bias occurs, it may not be possible to generalise the study results to the population because the sample will not be representative of the population. Selection bias occurs as a result of the sampling process.

Selection bias should not be confused with allocation bias. Selection bias refers to the biased selection of trial participants from the population and not a bias in selecting participants when allocating to treatment. Bias in the selection of participants for allocation to treatment group is referred to as allocation bias.

The random allocation of participants to treatment (vaccine or placebo) was necessary if the double blind nature of the trial was to be maintained (*d* is true). The trial was made double blind by the use of a placebo—an inert substance similar in appearance to the vaccine. Therefore, after randomisation neither the participants nor the assessors knew the treatment allocation. However, if participants were allocated through any other method than random allocation, such as alternate allocation or allocation at the researchers' discretion, then there would have been potential for treatment allocation to have been revealed, and double blinding would not have existed.

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Ascertainment bias, sometimes referred to as detection bias, is the systematic distortion of assessment of outcome measures by the investigators or trial participants because they were aware of treatment allocation. When ascertainment bias occurs on the part of the investigators it is called assessor bias, and when it occurs on the part of the participants it is known as response bias.

Double blinding was essential to ensure that ascertainment bias was minimised. Because random allocation was necessary to ensure that the trial was double blind, it will therefore have facilitated the minimisation of ascertainment bias (*e* is true).

Assessor bias would have occurred if, for example, the researchers favoured the vaccine and wished to show that it was more effective than placebo. The investigators could have been biased in their assessment—subconsciously or otherwise—of pneumonia and pneumococcal pneumonia. The researchers reported that pneumonia was diagnosed clinically and on chest radiography. Pneumococcal pneumonia was diagnosed from blood, pleural fluid, sputum, and urine tests. Response bias is particularly a problem for outcomes measured subjectively. During the study the participants were encouraged to report any symptoms consistent with a respiratory tract infection. Response bias could have occurred if, for example, the participants knew their treatment allocation; they might have been disappointed if allocated the placebo and been more likely to report any such symptoms.

Competing interests: None declared.

1 Maruyama T, Taguchi O, Niederman MS, Morser J, Kobayashi H, Kobayashi T, et al. Efficacy of 23-valent pneumococcal vaccine in preventing pneumonia and improving survival in nursing home residents: double blind, randomised and placebo controlled trial. *BMJ* 2010;340:c1004.

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