

ENDGAMES

STATISTICAL QUESTION

Clinical trials: units of randomisation

Philip Sedgwick *reader in medical statistics and medical education*

Centre for Medical and Healthcare Education, St George's, University of London, London, UK

Researchers evaluated the efficacy of a short course of oral prednisolone for acute asthma in children of school age. A randomised double blind placebo controlled crossover trial study design was used. The intervention was parent initiated treatment with the corticosteroid prednisolone (1 mg/kg/day) or placebo when an episode of acute asthma occurred. For each episode, treatment with prednisolone or placebo was chosen at random. Participants were 230 children aged 5-12 years with a history of recurrent episodes of acute asthma. Each child could contribute a maximum of eight episodes of acute asthma to the data collection over a three year study period.¹

The primary outcome measure was the mean daytime symptom score over seven days according to a paediatric asthma diary. The daytime symptom score measured the children's perspectives about their asthma symptoms and how they were limited by their symptoms. The participants contributed a total of 308 episodes of asthma that needed parent initiated treatment: 155 episodes were treated with prednisolone and 153 with placebo. The mean daytime symptom score was 15% lower in episodes treated with prednisolone than in those treated with placebo (P=0.023).

The researchers concluded that a short course of oral prednisolone initiated by parents when their child experienced an episode of acute asthma significantly reduced asthma symptoms. However, the benefits of treatment were modest, and it was suggested that these should be balanced against potential side effects of repeated short courses of an oral corticosteroid.

Which one of the following was the unit of randomisation?

- The child
- The episode of acute asthma
- The parent initiated treatment (prednisolone or placebo)

Answers

The episode of acute asthma (answer *b*) was the unit of randomisation.

The aim of the trial was to evaluate the effectiveness of oral prednisolone for episodes of acute asthma in children of school age. A randomised double blind placebo controlled crossover

trial study design was used. The crossover trial study design has been described in a previous question.² The intervention was parent initiated treatment with prednisolone (1 mg/kg/day) or placebo. Each child could contribute a maximum of eight episodes of acute asthma to data collection over the three year study period. Each time an episode of acute asthma occurred it was treated with prednisolone or placebo, with the episode allocated to treatment at random. The randomisation of each episode of acute asthma to treatment, in conjunction with the use of a placebo, meant that both the participants and the researchers could be blinded to treatment allocation, thereby minimising ascertainment bias.³

For each child the allocation of episodes of acute asthma to treatment was in balanced blocks of four, with two episodes allocated to each treatment in a random sequence. There are six different ways in which a child's episodes of acute asthma could have been allocated to treatment within a block of size four. If the intervention is denoted by A and placebo by B, then the six possible permutations of allocation were AABB, ABAB, ABBA, BABA, BAAB, and BBAA. One of these sequences was chosen at random for each child. Therefore, each child could receive a maximum of four courses each of prednisolone and placebo during the study.

The unit of randomisation is defined statistically as the "who" or "what" that is randomly allocated to treatment. Therefore, in the trial above the unit of randomisation was the episode of acute asthma (answer *b*). Each time an episode of acute asthma occurred it was randomised to treatment with prednisolone or placebo. Therefore, by definition, the unit of randomisation was not the course of treatment (prednisolone or placebo; answer *c*) that the episode of acute asthma was allocated to.

The crossover trial study design is typically used when the condition being investigated is chronic and treatment is for the short term relief of symptoms rather than a cure. For the above trial the condition being investigated presented as episodes of acute asthma, so it was possible to randomise separate episodes to treatment. This is in contrast to the traditional crossover trial study design where participants are allocated to a treatment for a predefined period of time—for example, three weeks—termed the treatment period. The unit of randomisation would then be

the condition under investigation for a duration equal in length to the treatment period. A previous question describes such a study design.²

The crossover trial in the study above is described as a “within subjects” study design. Participants received both treatments in a random order, and the effectiveness of oral prednisolone was established by comparison with placebo within subjects. The effectiveness of oral prednisolone could have been investigated using the traditional “between subject” clinical trial study design.⁴ Children would have been randomly allocated to a treatment and received the same treatment for all their episodes of acute asthma during the study period. At the end of the study, the effectiveness of treatment would be established by comparing the outcomes between the independent groups of children. Because the children would have been randomly allocated to treatment in a between subjects study design, the child (answer *a*) would be the unit of randomisation. Sometimes in a clinical trial with a between subject study design, clusters

of participants—for example, general practices or schools—are randomly allocated to a treatment, and all members within the cluster receive the treatment that their cluster is allocated to.⁵

The unit of randomisation would then be the cluster. In the study above, a crossover trial study design was used in preference to a between subject study design because it enabled a more precise comparison of oral prednisolone with placebo.

Competing interests: None declared.

- 1 Vuillermin PJ, Robertson CF, Carlin JB, Brennan SL, Biscan MI, South M. Parent initiated prednisolone for acute asthma in children of school age: randomised controlled crossover trial. *BMJ* 2010;340:c843.
- 2 Sedgwick P. What is a crossover trial? *BMJ* 2014;348:g3191.
- 3 Sedgwick P. Non-response bias versus response bias. *BMJ* 2014;348:g2573.
- 4 Sedgwick P. What is a superiority trial? *BMJ* 2013;347:f5420.
- 5 Sedgwick P. Treatment allocation in trials: cluster randomisation. *BMJ* 2014;348:g2820.

Cite this as: *BMJ* 2014;348:g3297

© BMJ Publishing Group Ltd 2014