

Clinical Trials of New Medicines

Introduction

This activity should reinforce the ideas in the textbook chapter 3 on the design of clinical trials and provide practice in data analysis which is relevant throughout the course.

Part 1

This could be used either as introduction to clinical trials or as an activity once the basic principles have been taught by lecture.

Students can work on the questions in pairs or individually and the answers can then be discussed in the whole class. With some groups the activity could be used as a revision homework.

Answers to questions

Part 1

- (a) A has a larger sample, reducing the effect of chance differences between the two groups.

Patients were assigned at random to the two groups, eliminating bias caused by doctors assigning patients to groups, and reducing the chance that there are significant differences between the groups.

Neither patient nor doctor knew which group each patient was in eliminating bias in reporting the effects.

- (b) (i) 54%
(ii) $65 - 54 = 11\%$

- (c) (i) 30%
(ii) Pain relief is very subjective; people vary in how they perceive pain. The stoicism of one individual could make a large difference to the overall result in this small sample. In a larger sample the percentage change would be much less. Chance events such as an unusually 'stoic' person affect small samples more than large samples.

- (d) The difference between placebo and treatment indicates that there may be a small effect. The same % difference with a larger sample size would give a stronger indication that the drug has an effect.

- (e) If patients are in pain from their arthritis it is wrong to deny them relief by putting them in the control group. A more ethical approach would be to treat the control group with the standard pain control used for arthritis to see whether the new treatment X is better than the standard.

References

Textbook

Chapter 3

Specification

9.3 Medical ethics

12.1 d Causal links

Data

<http://www.jr2.ox.ac.uk/bandolier/booth/painpag/Acutrev/Other/AP019.html>
<http://www.jr2.ox.ac.uk/bandolier/band60/b60-2.html>

Part 2

Suggested teaching approach

The activity reinforces the importance of good trial design and provides good practice in data analysis. It is probably best done in class as the concepts are somewhat abstract and most groups will need class discussion to answer the questions satisfactorily. Students can discuss the questions in pairs and then the answers can be discussed with the whole class.

Answers to questions

1. Randomisation

(a) When randomised most trials show no pain relief from TENS. However when non-randomised most trials show benefit, indicating that there is bias in these results.

(b) The bias was probably introduced by the doctors choice of patients. Perhaps patients with the least pain were assigned to the TENS group. Perhaps patients who already believed that TENS would help them volunteered for the TENS group.

(c) No they do not. If possible bias is reduced by randomisation then TENS shows no benefit.

(d) Yes they show that the outcome is very different without randomisation. In testing the effect of a treatment it is important that all other variables which might affect the outcome are eliminated. Randomisation eliminates the effect of different patient characteristics on the outcome and focuses on the treatment.

2. Double blind

(a) The non-blind trials show a much greater benefit from acupuncture (30% difference between treatment and control) than do the blind trials (8% difference between treatment and control).

(b) Bias may have been introduced if patients really believed in the benefits of acupuncture and therefore expected to feel less pain. They reported according to their expectations.

(c) The blind studies do show a small benefit from acupuncture but it is a very small effect and 50% improve without any treatment. Much larger trials would be needed to eliminate chance with such a small effect.

(d) The difference between the results of blind and non-blind trials is significant and shows that the benefit in the non-blind trials is likely to be due to the patient's attitude not the acupuncture itself. Some might argue that it doesn't really matter in this case what causes the effect if patients really do feel better. This is a valid point of view but it does not justify non-blind trials in general.

You need to look carefully at the design of the trial to be sure that the blind control is suitable, and that the acupuncture treatment is always carried out correctly.

Clinical trials of new medicines

Research into new medicines takes many years and goes through many different stages. The final stages are clinical trials in people.

Stage 1 tests **safety** in healthy volunteers.
Stages 2 and 3 are trials in patients to test **effectiveness**.

Part 1 of this activity allows you to look at the basic features of trial design.

Part 2 of the activity allows you to examine evidence which confirms the importance of some of these features.

PART 1 Basic features of trial design

These features are chosen to eliminate two possible sources of error. One is **bias**; the researcher may introduce their own attitudes or wishes, usually unconsciously. The other is **chance**, if the control and trial groups happen by chance to differ in some characteristic this may influence the results.

A new pain relief drug for arthritis sufferers was tested in two separate trials. Consider the design of two trials in figure 1 and the results of these trials, given in figure 2. Then answer the questions on page 2. You may wish to refer to the information in figure 3 on the features of trial design.

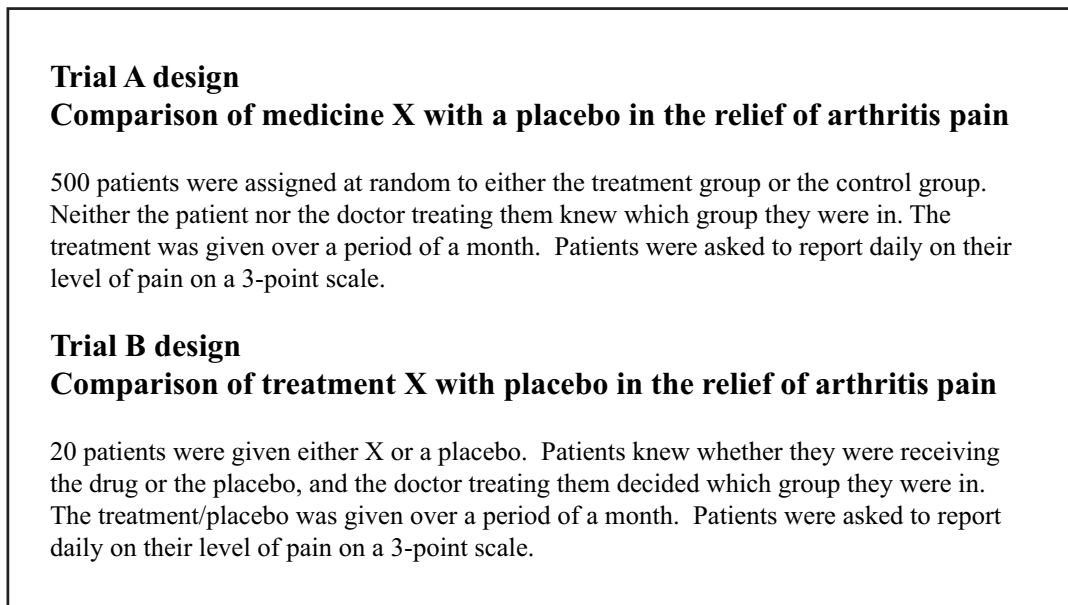


Figure 1

	Number of patients treated with X	Number of patients treated with X reporting pain relief	Number of patients treated with placebo	Number of patients treated with placebo reporting pain relief
Trial A	250	160 (65%)	250	135 (54%)
Trial B	10	7 (70%)	10	3 (30%)

Figure 2 Results of trials on pain relief X

- (a) Point out three differences in the design of the two trials. Explain how these differences mean that the results of trial A are less likely to be affected by **bias** or by **chance**.
- (b) This question is only about trial A.
- What percentage of patients on placebo reported pain relief?
 - Assuming that the placebo effect works on all patients, what percentage of patients receiving treatment X had their condition improved by the treatment rather than by placebo effect?
- (c) This question is only about trial B. The effectiveness of the medicine is judged by the difference between the treatment group and the placebo group.
- What would the percentage differences between X and placebo have been for trial B if just one less person in the treatment group had reported pain relief?
 - Comment on the effect of chance on results in this small sample.
- (d) Do you think trial A shows that X is effective in treating arthritis pain? Explain your answer.
- (e) These trials are useful in testing how effective a medicine really is. However there are ethical problems. Describe the problem in trial A. How might this be overcome by changing the nature of the control?

FEATURES OF A CLINICAL TRIAL

The use of a control group - improvements due to the treatment are compared with improvements in a group which received either a placebo or an already widely used treatment.

Double-blind - so that patients do not know whether they are in the control or treatment group. This eliminates the placebo effect. It also prevents doctors biasing the results by choosing the patients they think are most likely to benefit to get the treatment.

Randomisation - to make sure that any individual differences in the two groups are the same in both groups, even if we don't know which of these differences are important.

Sample size - in small groups any different responses in the two groups might be due to different characteristics of the two groups, such as age, overall health or diet.

Placebo - a medicine which contains no active ingredient. Patients receiving a placebo often show improvement if they believe that it has an effect.

Ethics - The World Medical Association holds the view that 'in general it is ethically unacceptable to conduct placebo-controlled trials if a proven therapy is available for the condition under investigation'.

Figure 3

Part 2 Evidence to support use of randomisation and blinding in trials

Randomisation - Why do researchers need to randomise the treatment and control groups when they are testing a new treatment? Can't they just give the treatment and see if people get better?

A Canadian study looked at the use of a post-operative pain relief called transcutaneous nerve stimulation, TENS. In some studies patients were assigned to the TENS group or the control group by their doctors. These are non-randomised studies. In other randomised studies, patients were assigned to the groups by the use of random numbers. There were 17 randomised and 19 non-randomised trials

Figure 4 shows how the overall conclusion of a trial can depend on whether the treatment was randomised or not. A positive result means that the patient reported pain relief.

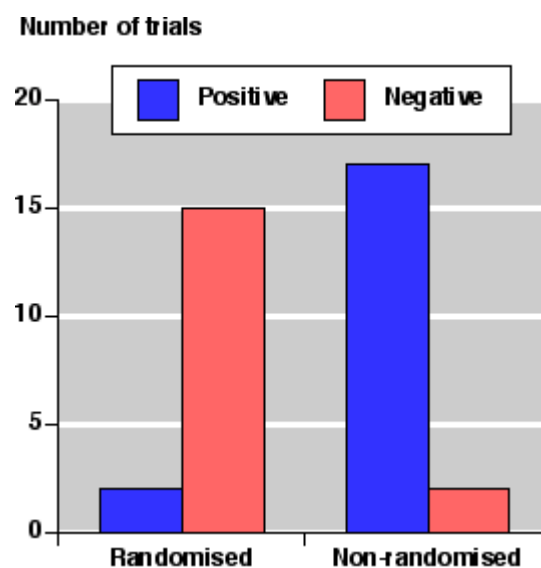


Figure 4: Effect of randomisation on outcome of trials of TENS in acute pain

1. (a) Describe the significant difference between the results of the randomised and non-randomised trials.
- (b) Suggest how bias might have been introduced in the non-randomised trials
- (c) Do these results convince you that TENS works or not? Explain.
- (d) Do these results convince you that randomisation is important? Explain.

Read more about this study at

<http://www.jr2.ox.ac.uk/bandolier/booth/painpag/Acutrev/Other/AP019.html>

Double blind trials - Why is it important that neither the doctor nor the patient knows which treatment they are getting?

Figure 5 compares the results of blind and non-blind trials. There were about 140 patients in each of the four groups. The treatment under study was the use of acupuncture to treat chronic back pain. The control group was treated with 'sham' acupuncture.

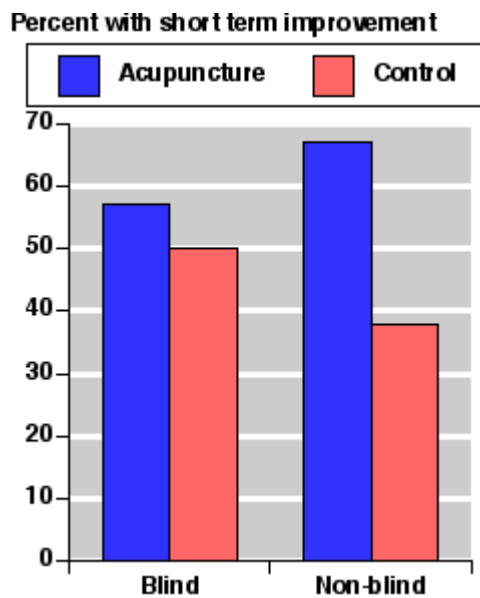


Figure 5: Effect of blinding on outcome of trials of acupuncture for chronic back pain

2. (a) Describe the significant difference between the results of the blind and non-blind trials.
- (b) Suggest how bias might have been introduced in the non-blind trials
- (c) Do these results convince you that acupuncture works for back pain or not? Explain.
- (d) Do these results convince you that blinding is important? Explain

Read more about this study at
<http://www.jr2.ox.ac.uk/bandolier/band60/b60-2.html>

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