# Clinical trials

## Introduction

This activity illustrates the need for the different features of a clinical trial, using sets of data. Students consider the importance of control groups, randomisation and blinding and compare two trials with different size samples.

## The activity

Students can work through each section, discussing the ideas in pairs. It is probably useful to stop after each section to have a short class discussion to clear up any queries or misunderstandings.

## Suggested answers to questions

1. (a) The critics suggest two variables other than fish oil that might have affected the children's SATs scores. Suggest one more variable that might be relevant.
*Motivation and concentration of the children*
*Overall nutrition or health*
*Teacher's expectations*

(b) Can the research, described above, tell us which of these variables is most likely to have caused the improved scores?
*No. Unless we can show that other variables have not changed between prediction and result there is no way of knowing.*

(c) How could they have used a control group to minimise the possible effects of these other variables? How would they select the control group and the test group to do this?
*A control group where all variables except the fish oil supplements were identical in both groups would reduce the effects of these other variables. (Some might still be a factor due to chance differences in the two groups). Half the class would have to be used as a control, (without anyone knowing who was in which group to eliminate the effects of teacher or pupil expectations). Sample size would then be an issue so several classes would have to be used.*

**How Science Works**

**Af** In many situations, scientists have to observe or measure a sample of the objects or cases they are studying (for example, observations in the field, cases of an illness, etc.). Data are more reliable if systematic sampling and observing/measuring methods are used.

**Bf** Claims about large groups are usually based on measurements on a sample of the population (all the individuals in the group). The sample should be selected randomly, or carefully chosen to represent the population accurately. Failure to do this will introduce bias. The larger the sample, the more confidence we can have in any claim about the population.

**Bk** To test the effectiveness of a specific 'treatment', scientists compare a sample that is given the treatment with a control sample that is not. This is called a (clinical) trial. Because humans' expectations can influence how they report the outcome of a treatment it is important to take precautions to prevent this. In a 'blind' trial, each individual does not know if he/she is in the treatment sample or the control sample. The trial is 'double blind' if the person who measures the outcomes also does not know this.

**Bl** To assess the outcome of a trial, scientists compare the number of successful outcomes in the two groups. To judge that a treatment has 'worked', the difference must be big enough not to be attributable simply to normal variation.

2. Almost all randomised trials show no benefit from TENS, non-randomised trials nearly all show benefit. Which should we believe?

   (a) If the doctors choose which patients go into the treatment group might they choose those in most pain or those in least pain? Suggest one other factor that might influence their choice. How would these choices introduce bias into the results?
   *They may select patients who believe that it would work or actively sought to receive it. This would bias the patients to report benefit.*

   (b) Explain how randomisation would reduce these sources of bias.
   *Randomisation is more likely to include patients with different characteristics in both groups as they will not be selected for any criterion, consciously or unconsciously.*

   (c) Do you think that bias was a significant factor in some of these trials. Explain your answer.
   *The fact that only the non-randomised trials showed benefit strongly suggests that bias is a factor and that the selection was biased so that patients most likely to report benefit are put into the treatment group.*

   (d) The two groups should be selected at random from the population. How would you describe the population to select from in this case?
   *People who have had an operation and are in pain.*

3. (a) Is there a significant difference between the results of the blind and non-blind trials? Explain your answer.
   *In the non-blind there is almost no difference between the proportion with short term improvement in the treatment and control groups, (about 7% difference). In the non-blind studies there is a significant difference ( 30%)*

   (b) Bias might have been introduced in the non-blind trials by patients or doctors
   (i) If you knew you that you were receiving real acupuncture might it influence your reporting of pain?
   *Yes I would be pleased that something is being done and would expect improvement. This could influence my experience of pain.*
   (ii) Might a doctor treat you differently if she knew that you were only getting the sham acupuncture?
   *Yes she would be less likely to communicate optimism and faith in what she was doing. This might affect how I felt.*
   (iii) Explain how the data in Figure 2 indicates that such bias is a real effect.
   *Any of the differences between the blind and non-blind would support this.*

   (c) Explain how double blind trials would eliminate these sources of bias.
   *Because no one knows what you are receiving these psychological influences are removed.*

4. (a) (i) Suggest a reason for the different sizes of the treatment and control groups at the end of trial A
   *Some people may have dropped out*
   (ii) Does this difference matter for the conclusions?
   *No, very few dropped out in either group. If many people drop out then it is important to know why. It may introduce bias.*

   (b) This question is only about trial A.
   (i) What percentage of patients on placebo reported pain relief?
   *51%*

(ii) What is the benefit of receiving treatment X relative to receiving the placebo? (to calculate this divide the number reporting benefit on X by the number reporting benefit on placebo).
*1.2:1*

(iii) How would you describe the population from which the treatment and control groups were selected?
*People with arthritis pain.*

(c) This question is only about trial B.

(i) What is the benefit of receiving treatment relative to receiving the placebo?
*1.33:1*

(ii) If only one less person receiving X had reported pain relief what would this ratio be?
*1:1*

(iii)Comment on the effect of chance on results in this small sample.
*The results are clearly unreliable because just one person can alter the conclusions.*

(d) What conclusions would you draw about the effectiveness of X?
Possible small benefit.

*In discussion the students could be told that the researchers who did trial A calculated that, even with this sample size, there was the possibility of chance effects. They only had confidence that the ratio of treatment to placebo was somewhere between 0.98 and 1.6 and concluded that the difference may not be significant.*

(e) From what you know about double-blind trials how would you expect patients' reports of pain relief to be different if they had known whether they were receiving treatment of placebo in trial A?
*More pain relief would be reported from those receiving the treatment and less from those not receiving it.*

(f) From what you know about the importance of randomisation how might the results of trial A have been different if doctors had been allowed to decide which patients got the treatment and which the placebo?
*For example; It might have appeared to have less benefit as doctors would not have wanted to give a placebo to those in great pain.*

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## Introduction

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.** Good trials will be designed to have the following features:

1. **The use of a control group**
2. **Randomisation**
3. **Double blind**
4. **Large enough sample size**

## The activity

Look at evidence that shows the need for each of these features and discuss answers to the questions in pairs.

### 1. Control group

In 2007 twenty six children in a year 6 class in a primary school were given fish oil food supplements. The school reported that, in SATS tests in English, 98% achieved the national average, although before the trial only 68% had been predicted to reach this level. The maths results were similarly better than the expectation for the class.
A newspaper headline reported the research as follows;

## Pupils' daily dose of fish oil boosts exam performance[1]

Critics said, “How do we know the predictions were accurate?” or “perhaps they had a better teacher” .

1. (a) The critics suggest two variables, other than fish oil, that might have affected the children’s SATs scores. Suggest one more variable that might be relevant.

   (b) Can the research, described above, tell us which of these variables is most likely to have caused the improved scores? Explain your answer.

   (c) How could they have used a control group to minimise the possible effects of these other variables? How would they select the control group and the test group to do this?

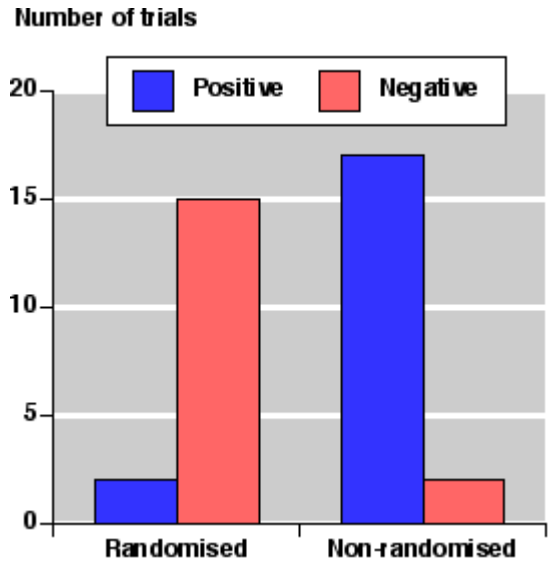
[1] **http://www.thisislondon.co.uk/news/article-23411954-details/Primary+school+sees+dramatic+rise+in+results+after+pupils+take+fish+oils/article.do**

## 2. Randomisation

Does randomisation matter? Is it really necessary to randomly select who is in the treatment group and who in the control group when they are testing a new treatment? 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 studies patients were assigned to the two groups by the use of random numbers, randomised studies. There were 17 randomised and 19 non-randomised trials

In Figure 1 a positive result means that the patient reported pain relief.

**Figure 1: Effect of randomisation on outcome of trials of TENS in acute pain**




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

2. Almost all randomised trials show no benefit from TENS, non-randomised trials nearly all show benefit. Which should we believe?

   (a) If the doctors choose which patients go into the treatment group might they choose those in most pain or those in least pain? Suggest one other factor that might influence their choice. How would these choices introduce bias into the results?

   (b) Explain how randomisation would reduce these sources of bias.

   (c) Do you think that bias was a significant factor in some of these trials? Explain your answer.

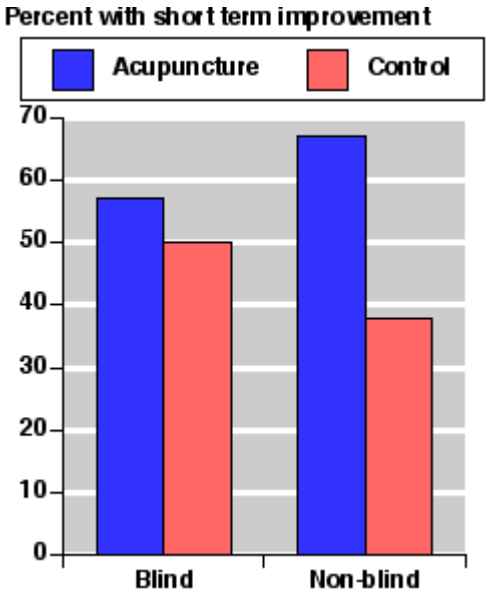
   (d) The two groups should be selected at random from the population. How would you describe the population to select from in this case?

### 3. Double blind

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

Figure 2 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 with a sham acupuncture being used on the controls.

**Figure 2: Effect of blinding on outcome of trials of acupuncture for chronic back pain**




http://www.jr2.ox.ac.uk/bandolier/band60/b60-2.html

3. (a) Is there a significant difference between the results of the blind and non-blind trials? Explain your answer

(b) Bias might have been introduced in the non-blind trials by patients or doctors

(i) If you knew you that you were receiving real acupuncture might it influence your reporting of pain?

(ii) Might a doctor treat you differently if she knew that you were only getting the sham acupuncture?

(iii) Explain how the data in Figure 2 indicates that such bias is a real effect.

(c) Explain how double blind trials would eliminate these sources of bias.

**4. Sample size**

It is much more expensive to run a clinical trial with a large number of patients. Is it worth the expense? Figure 3 compares the results of two trials of the same remedy, ointment X, for the relief of arthritis pain.

**Trial A**
**Comparison of medicine X with a placebo in the relief of arthritis pain.**

In this trial 286 patients were assigned at random to either the treatment group or the control group. The control group received a placebo.
Neither the patient nor the doctor treating them knew which group they were in.
The trial continued over a period of a month. Patients were asked to report daily on their level of pain on a 3-point scale.

**Trial B**
**Comparison of treatment X with placebo in the relief of arthritis pain.**

In this trial 12 patients were assigned at random to either the treatment group or the control group. The control group received a placebo.
Neither the patient nor the doctor treating them knew which group they were in.
The trial continued over a period of a month. Patients were asked to report daily on their level of pain on a 3-point scale.

**Figure 3 Results of trials on pain relief X**

| | 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** | 138 | 70 (51%) | 141 | 58 (41%) |
| **Trial B** | 6 | 4 (67%) | 6 | 3 (50%) |

4. (a) (i) Suggest a reason for the different sizes of the treatment and control groups at the end of trial A

(ii) Does this difference matter for the conclusions?

(b) This question is only about trial A.
(i) What percentage of patients on placebo reported pain relief?
(ii) What is the benefit of receiving treatment X relative to receiving the placebo? (to calculate this divide the number reporting benefit on X by the number reporting benefit on placebo).
(iii) How would you describe the population from which the treatment and control groups were selected?

(c) This question is only about trial B.
(i) What is the benefit of receiving treatment relative to receiving the placebo?
(ii) If only one less person receiving X had reported pain relief what would this ratio be?
(iii)Comment on the effect of chance on results in this small sample.

(d) What conclusions would you draw about the effectiveness of X?

(e) From what you know about double-blind trials how would you expect patients' reports of pain relief to be different if they had known whether they were receiving treatment of placebo in trial A?

(f) From what you know about the importance of randomisation how might the results of trial A have been different if doctors had been allowed to decide which patients got the treatment and which the placebo?

**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. This comparison makes it less likely that any benefits are due to factors other than the treatment being tested.

**Double-blind** - so that patients do not know whether they are in the control or treatment group. This allows us to estimate the placebo effect. It also prevents doctors biasing the results by communicating their expectations to the patients.

**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. It means that doctors cannot introduce bias by assigning patients with different characteristics to the two groups.

**Adequate sample size** - in small groups any different responses in the two groups might be due to chance arising from different characteristics of the two groups, such as age, overall health, social class 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.

**Bias -** may lead to results that are consistently better or worse than other trial designs. This is often because the researcher introduces their own attitudes or wishes, either in allocation of patients or in interpretation of outcomes. It usually happens unconsciously.