Modelling a 'Gold Standard' clinical trial

Teacher resource

Before any new medical treatments can be used, there must be a careful, scientific process of trial and development. Clinical trials are an important step where a new treatment or intervention is tested on human volunteers. Clinical trials answer questions about the safety and efficacy of a treatment. Randomised controlled trials (RCTs) are often thought of as the *gold standard*, or most scientifically rigorous method of undertaking clinical research and trials. RCTs minimise the risk of many different sources of bias. This means that the results of the study are more able to be trusted.

Gut Bugs connection

Science is about asking questions and testing new ideas, but contemporary social issues and environments inform the questions asked. In the current context of rising obesity rates and associated health-related human costs, researchers at the Liggins Institute are examining the link between the human gut microbiome and obesity. They are conducting a clinical trial which investigates the use of GMT (Gut Microbiome Transfer) as a treatment which might support people living with obesity to lose weight.

This resource links to teacher PowerPoint slides: "The Gut Bugs Randomised Control Trial."

About this resource

This resource includes information and instructions to support teachers to model and discuss a randomised controlled trial with students.

Learning objectives

This activity connects with Nature of Science objectives *Understanding about science* and *Investigating in science*. By engaging in this activity students can develop the science capabilities of *gathering and interpreting data* and *using evidence*.

- Understand the scientific purposes and processes of a randomised, double-blinded, placebo-controlled clinical trial via participation and modelling.
- Plan or evaluate a trial that shows whether the scientific evidence generated in a trial is valid.
- Give examples of ways in which scientific research involves problem-solving, risk-taking, failures, uncertainties and surprises.
- Demonstrate understanding of ethical implications of scientific research and clinical trials.
- Discuss the complexities involved in a human clinical trial.

Key words

- clinical trial
- researcher
- participant
- bias
- randomised
- blinding/blinded
- double-blind
- un-blinding
- placebo
- placebo effect
- control
- scientific rigour

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Randomisation

Randomisation means that researchers can't predict whether participants in a study will be assigned to the control group or the treatment group.
There are many methods of randomisation, and the process is often completed using computerised selection.
Randomisation is important to reduce *selection bias*, for example, researchers may unintentionally assign those who look most likely to benefit from the trial to the treatment group.

The most straightforward method for assigning participants into two groups - treatment and control - is *Simple Randomisation.*

Simple randomisation instructions

Provide students with resources. For example:

- Coins
- Deck of cards (e.g. red is control and black is treatment or clubs/hearts is control and spades/diamonds is treatment).
- Die (e.g. even numbers are treatment and odd numbers are control, or 1-3 is treatment, 4-6 is control)
- Random number tables
- Random online generator

Challenge: Support students to use their knowledge of probability to decide on and test a method for simple randomisation. Discuss the effectiveness for each method for small and large sample sizes.

NB: For a small sample size, simple randomisation might result in an uneven number of participants being assigned into each group.
Often clinical trials and especially pilot trials involve a relatively small number of people. It is important to make sure that each group is large enough to produce meaningful evidence.

OR
Give numbered cards to participants. E.g. 20 students are given cards numbered 1 to 20. Use a random online generator to assign numbers to the treatment or control group,

(OR If necessary, use block randomisation to ensure that group sizes are even).

Challenge:
Block or stratified randomisation may be more appropriate for smaller sample sizes (less than 50-100).

Double blinding

Double blinding means that neither the participants nor the researchers know who is getting the treatment. Researchers and participants stay blinded until the treatment is finished and the results are analysed. This reduces bias, for example, scientists might unintentionally look for effects or results they want to see in the treatment group.

Double blinding instructions

The class will be volunteer taste testers in a clinical trial to answer the question:

Can we reduce the amount of sugar in drinks
without a noticeable taste difference?

Discuss with students a hypothetical reason for taking part in this trial, for example, tell students that this could be an important issue in the development of reduced-sugar soft drinks.
Challenge: Ask students to design a method for double-blinding - where participants are assigned to treatment or control groups with no one having any knowledge of treatment or control.
OR follow the method below:

Materials needed

Four large, numbered bottles of coloured sugar water, labelled A, B, C, and D. (2-3 drops colouring per litre - ensure that the colours are identical). One bottle has less sugar than the other three. For example, bottles A, B and C have six teaspoons of sugar per litre of water. Bottle D has three teaspoons per litre.
The group which receives two identical drinks (e.g. A and C) is the control group. The group which receives the different drinks is the treatment group (e.g. B and D).

(If as teacher you want to be 'blinded', ask the Lab Tech to make and label the bottles and to give you a sealed envelope stating which bottle has reduced sugar, to be opened once results have been analysed - this is the 'un-blinding').

Procedure

1. The teacher as *Trial Manager* is responsible for assigning the randomised groups and for setting out the drinks. The Trial Manager then takes no part in the trial or the analysis.
2. No one except the Trial Manager (or the Lab Tech) will know which group received the treatment or control until the results have been analysed.
3. Assign two pairs of students to the role of *Researchers*. They will ask participants to taste two different drinks and record results in a simple table but will not know what is in the drinks. You will need to ensure participants do not find out how other participants are responding – discuss with the class how this could best be achieved.
4. The remainder of the class are *participants*.

5. Randomly assign the two groups to the Researchers. This means that no one knows who is receiving the 'treatment" (the reduced sugar drink) and who is receiving the control).
6. Participants are given two mini paper cups each. Researchers pour a measured amount of each drink for each student. Participants try the drinks and tell the researchers which drink has more sugar, or if they think the drinks are the same.
7. Researchers record the results in a table. Once all results are recorded, display the results for students to analyse or conduct a class discussion.
8. What do the results show? Discuss possible sources of bias.
9. Unblind the class once results have been analysed and discussed.

Results for Sugar Testing in Drinks

Participant number	Bottle _____	Bottle _____	Both bottles are the same

A placebo-controlled trial

A placebo-controlled trial compares a treatment group with a control group. Without a control group it is not possible to state with any certainty whether a treatment has an effect.
The control group receives a 'dummy' or placebo treatment. For example, if the treatment group receives capsules filled with a new medicine, the control group will receive capsules that look identical but are filled with an inactive substance which will have no effect.

The placebo effect

The *placebo effect* is a form of patient bias. This is when the treatment leads to improvement or reported improvement through patients believing that the treatment works, yet they have only been given the dummy or placebo.

Demonstrating the placebo effect

Do this activity **before** *you teach students about the placebo effect.*

Materials

Three bottles of identical sugar water - one bottle colourless, one red, one blue.

Procedure

1. Students are told that one drink will taste sweeter than the others.
2. Discuss with students their expectations for sweetness - which one will taste most sweet? Once they decide which is going to be sweeter than the others, let them think they are correct.
3. Do a taste test - record results - and discuss.

A note about ethics in clincal trials: *Tell students:*

There are strict ethical procedures and controls which must be adhered to when conducting clinical trials. All research proposals and trials need to go through a process of ethical review and approval before research can even begin. The ethics process is like a pre-flight check to ensure that risks of harm have been eliminated or minimised. Universities and research institutes have Ethics Committees which conduct these checks. Researchers must provide detailed information about their trial and show how any risks of harm to participants have been minimised. Ethics also requires that potential participants are informed about any risks and that they knowingly consent to taking part in the trial.
A key concern is the ethical principle of "*do no harm*".
Another key ethical principle is that research must not involve deception.

Discuss with the class: Did the trial above (demonstrating the placebo effect) involve deception? Would this trial have passed an ethics review process? Why/why not?
Are there any circumstances in which it might be acceptable for a trial to involve deception?

Extra for experts

A *nocebo* effect is the opposite of the placebo effect. This occurs when a participant is expecting a negative effect, and this causes the treatment to have a negative outcome or perceived negative outcome. For example, if a participant is expecting side effects to occur, they may feel symptoms or be more sensitive to symptoms that might be associated with the expected side effects.

If we don't give the control group a placebo, we can't cancel out the placebo/nocebo effect.

Questions for Class Discussion

1. Why is it important that participants are randomly assigned to either the treatment or placebo groups?

To reduce selection bias, where researchers may assign those who look most likely to benefit from the trial to the treatment group. The results of the study are more able to be trusted.

2. Why is it important that the researchers do not know who received the placebo or the treatment?

Researchers might treat participants in the treatment and placebo groups differently, which might lead to participants guessing which group they are in. Scientists might look for effects or results they want to see and ignore others. This is called observer bias.

3. Why is it important that the participants do not know whether they received the placebo or the treatment?

It is important that participants do not have any expectations one way or the other for the treatment, and that they are unable to associate any changes they might notice with the treatment. In other words, in drug trials there is often a strong expectation or hope for improvement. Participants can be quick to notice changes, and to attribute them to the treatment. What we get from blinding is an ability to cancel out the effects due to intention.

4. The control group is the group that does not get the treatment. Why is it important that the control group receive a placebo? Why not give them nothing - no treatment at all?

It is to do with the placebo effect. People who get the treatment, knowing the other group got nothing, might start to act or feel different or better, just because they expect the treatment to work. Meanwhile, the people who get no treatment at all may start to act or feel different or worse, because they know they are not receiving treatment.

Further questions for research and discussion

- Is it ethical to give a placebo to a person who needs treatment?
- Discuss the ethics of placebo use in the Gut Bugs trial.
- Discuss the ethics of giving cancer patients a placebo in a clinical trial for a new cancer drug.

For more information:

Understanding randomised controlled trials
Designing a research project: Randomised control trials and their principles
Gut Bugs Case study: Gut Bugs trial design