igniting our potential



Double Blind Trials Workshop

Introduction

LICAL EPRO

These activities demonstrate how double blind trials are run, explaining what a placebo is and how the placebo effect works, how bias is removed as far as possible and how participants and trial medicines are randomised.

Curriculum Links

KS3: Science KS4: Biology SQA Access, Intermediate and Higher: Biology

Keywords

Double-blind trials observer bias placebo effect placebo randomisation clinical trials designing a fair trial

Contents

Activities	Materials
Activity 1 Placebo Effect Activity	
Activity 2 Observer Bias	
Activity 3 Double Blind Trial	Role Cards for the Double Blind Trial Activity Testing Layout

Background Information



Medicines undergo a number of trials before they are declared fit for use (see classroom activity on Clinical Research for details). In the trial in the second activity, pupils compare two potential new sunscreens. This type of trial is done with healthy volunteers to see if the there are any side effects and to provide data to suggest the dosage needed. If there were no current best treatment then this sort of trial would also be done with patients to test for the effectiveness of the new medicine.

How do scientists make sure that medicines are tested fairly? One thing they need to do is to find out if their tests are free of bias. Are the medicines really working, or do they just appear to be working?

One difficulty in designing fair tests for medicines is the placebo effect. When patients are prescribed a treatment, especially by a doctor or expert they trust, the patient's own belief in the treatment can cause the patient to produce a response. For example a patient who is given a pill and told that it will cure his headache may find that his headache is cured - even if the treatment itself is inactive.

Scientists need to make sure that any effects of the medicines they test are actual effects of the compounds being tested, and are not caused by the placebo effect. To do this, they test medicines against placebos (inactive substances that are formulated to resemble the treatment, e.g. sugar pills). This allows the scientists to measure whether effects are due to the medicine or treatment, or due to the patient's expectation of treatment.

Placebo testing is usually only done in trials involving healthy volunteers, because it would be unethical to give ill volunteers an inactive placebo instead of treatment. In trials that test experimental treatments on ill volunteers, the volunteers are given either the experimental treatment or the best available treatment, but both are formulated to resemble each other as much as possible. This way the patient will not know which treatment he or she will be getting. If the patient cannot tell which treatment he or she is receiving, the patient will not be able to expect results specific to that treatment.

Other biases can affect the way that studies are carried out and recorded. Observer bias is the result of expectations scientists have about a new treatment. Scientists may look for effects of the treatment that they are expecting, while missing other effects that they are not expecting. Studies must be designed to minimise observer bias, as it can invalidate results.

In double blind clinical trials, neither the patients nor the researchers know whether any patient is receiving the experimental treatment or not. Double blind clinical trials are also randomised—patients are randomly assigned to one group or another. In clinical trials, randomisation is primarily done through computerised selection.

Randomisation, and assignment of volunteers to groups, is always done by a third party—a Trial Manager. Neither the patients nor the researchers should be able to guess or choose which patient is in which group. The Trial Manager will not reveal which volunteers are in which group until all the data are collected. This is called "unblinding".

Activities

Activity 1: Placebo Effect Activity



Background Information

This activity demonstrates one way that trial volunteers' expectations can affect outcomes. In this activity, pupils will have an opportunity to experience the placebo effect by tasting two types of lemonade. Unbeknown to the class, the drinks will be identical, except one will be coloured red. The class will then be asked to taste-test the drinks, and decide which they found sweeter.

The class will probably choose the red-dyed drink as the sweeter of the two, but even if they do not, the teacher can explain that in similar tests, red-coloured ice lollies and soft drinks are often perceived as sweeter than their clear counterparts, even if the clear versions contain equal amounts of sugar. This is because the people doing the taste-tests expect the red versions to be sweeter.

Patients tend to trust doctors' authority, knowledge of medicine and intention to heal. If a doctor gives a patient pills, injections, or other treatments, the patient will expect those treatments to produce a healing effect, even if they are inactive.

By testing a new medicine against a placebo, scientists can find out how effective that medicine is. Patients will expect both treatments to have some effect. Scientists compare the patients' response to a placebo with the patients' response to an experimental treatment. If the experimental treatment is effective, it will produce a significantly stronger response than the placebo.

Materials Needed:

- 2-litre bottle of clear lemonade in an unlabelled, clear bottle
- 2-litre bottle of the same lemonade but dyed red with flavourless food colouring—also in an unlabelled, clear bottle
- 2 paper cups for each pupil

Tell the pupils that they are going to test two drinks and compare their sweetness.

Give each pupil a sample of the clear drink to taste.

Now give each pupil a sample of the red drink to taste.

Ask pupils to raise their hands if they thought:

- The red drink was sweeter
- The clear drink was sweeter

Count how many pupils raise their hands for each drink. Draw a bar graph comparing the two responses.

Now reveal that both drinks were equally sweet. In fact, they were the same drink, but the red one had flavourless food colouring added.

Ask the class:

- Did you expect one drink to be sweeter than the other? Which one? Why?
- Did you have any expectations about what each drink would taste like, based on its colour?
- Did your expectations affect your perceptions of the drink's sweetness? Explain that this is usually the case—and this is an example of the placebo effect
- If a doctor gives you a pill, what would you expect it to do? Make you well, make you feel some side effects



- If researchers are testing a new medicine, and people expect that it will make them well, how do we know if people are responding to the treatment or to their own expectation? *Compare the new medicine with a placebo.*
- What is a placebo?

Explain that a placebo is an inactive treatment that is prepared the same way as the experimental treatment (e.g. both may be in pill form). The placebo is given to some patients in an experiment, and the experimental medicine is given to others. None of the patients know whether they have the placebo or the treatment, so both have similar expectations of the outcome of the treatments. Researchers can compare how both groups of patients respond to the treatment, and determine how much of the effect is due to the expectations raised by the method of treatment, or the placebo effect.

Activity 2: Observer Bias



Background Information

Observer bias comes from the set of expectations that researchers bring to an experiment. It happens when an observer of an experiment expects a particular result. Because scientists have spent a good deal of time researching and developing potential new treatments, they are likely to have expectations about the effects (and side-effects) that their experimental treatments will show. For example, they may expect that a medicine they have spent years researching will work as planned.

Observer bias is subtle and can be difficult to detect. Scientists need to take great care to design their experiments to avoid observer bias, since their expectations may influence their interpretation of results.

To demonstrate how this works, this activity uses the phenomenon of "backward masking" as an example of how observer bias can cause people to draw misleading conclusions.

There is a good deal of urban folklore from the 1960s onward which describes messages that can be heard when certain songs are played in reverse. Most of these are nonsensical, unintentional, garbled sounds, but when listeners expect to hear specific messages, they often do.

Relevant Links

More information can be found on observer bias here: http://www.beep.ac.uk/content/139.0.html

Teacher-led Activity

• The teacher plays a "backward masked" mp3 sample of music, and asks the class to write down what words they heard.

Example:

http://www.backmaskonline.com/music/Beatles%20-%20I%20am%20tired%20REV.mp3

(This sample, from the Beatles' song "I am Tired" is the source of a long-running rumour in the 1960s and 1970s that Paul McCartney was dead. There are many other "back masked" tracks available online, most of which are alleged to contain explicit and offensive messages.)

- Students then fold their papers so their answers are hidden, and trade with each other. They are told not to open their papers until told to do so.
- The teacher then asks the students to hear a specific phrase in the backward-masked mp3 and plays it again. If they hear the phrase, they should raise their hand.

What the track allegedly says, from www.backmaskonline.com:

Beatles - I Am Tired

- Message "Paul is a dead man, miss him, miss him, MISS HIM"
- Truth The Beatles have vehemently denied that this message exists.
- Count the number of students with their hands raised. Now ask the students to open their papers and silently read them. Ask everyone to raise their hand if they read the phrase that the teacher had called out earlier.

This activity could also be run as a whiteboard activity—the mp3 file can play on the screen, students can "vote" and compare data on screen in graph form.



Questions:

- Were there any differences between the numbers of students who heard the message before and after being told what the message said?
- How would you explain the different results you observed when listening to the backward masked song?
- How can an observer's expectations affect the results of an experiment? The observer may expect that a medicine he or she is testing will work. There is also a danger that a researcher may treat volunteers differently. The researcher may subconsciously communicate their expectations to the volunteers, causing them to respond differently.
- What reasons might scientists have for wanting certain results? Clinical trials cost millions of pounds, researchers might have reputations or jobs at stake, etc.
- How can researchers reduce the effects of experimental bias on their results?

The following activity demonstrates how scientists design **double blind trials** to ensure that scientists' own prejudices influence their results as little as possible.

Activity 3: Double Blind Trial



Background Information:

Double-blind trials help scientists to determine the safety and efficacy of new medicines and therapies, while minimising the impact of observer bias and the placebo effect. In a double-blind trial, neither the scientists running the trial nor the volunteers receiving the treatment know who is receiving which treatment.

A Trial Manager randomly assigns patients to groups. Only at the end of the trial, when all data have been collected, does the Trial Manager reveal which volunteers had which treatment.

In the following activity, students act out the various roles of participants in a double-blind trial to test a new sunscreen:

- One student is a Scientist from the pharmaceutical company which developed the sunscreen
- One student is the Pharmacist who dispenses the cream, labelled so that no one else knows which cream is which
- One student is the Nurse, who applies the cream to volunteers
- One student is the Trial Manager, who randomises the treatments
- Four students are Volunteers

Relevant Links

Find out about the man who first devised double blind trials here: http://www.planet-science.com/about_sy/ news/ps_126-150/ps_issue135.html#6

Here is activity to help discussion on the use of humans in double blind trials: http://www.upd8.org.uk/ activity/170/Double-Blind.html

Materials Needed

Role Cards for the Double Blind Trial Activity (Pages 11 – 12) Testing Layout (Pages 13-18)

Supplies

UV light

This can be purchased at Maplin stores or online at http://www.maplin.co.uk/searchtemplate.asp?criteria=UV%20TORCH These can also be found online at Net PC direct: http://www.netpcdirect.co.uk/led_uv_torches.php

- Four identical bottles labelled A, B, C, and D:
 - 2 bottles will contain SPF 60+ sunscreen (fragrance-free, hypoallergenic)
 - 2 bottles will contain inert hand lotion (as close as possible to the original texture/look of the sunscreen. This will be the "old sunscreen" in the activity.)
- A4 white paper

Note About Sunscreen

Sunscreens contain particulates and compounds which principally absorb, whilst also scattering and reflecting UV light so as to keep it from the skin cells where it causes damage. When a UV light is shone on sunscreen in this activity, the UV light is absorbed and the sunscreen appears dark. (See the Testing Layout for a picture of this.)

According to Cancer Research UK, "Sun creams are covered by legislation that protects consumer rights. The General Product Safety Regulation (1994), the Trade Descriptions Act (1968) and the Sale of Goods Act (1979) all require that products sold to customers are safe and do what they say they do." For further information on sunscreens and the law, follow this link: http://www.cancerhelp.org.uk/help/default.asp?page=5508

Safety Note

Make sure hypoallergenic sunscreen and lotion are used. If a student is allergic, he or she can play the role of the scientist or one of the other roles that does not require the student to touch the cream.



Do not look directly at the UV light and do not shine it directly on skin. Use of the light as described in the activity should cause no harm.

Trial Instructions

Each of the steps below is represented by an image and some summary text. These are at the end of the document and can be projected onto a whiteboard.

- 1. Meet the team. Each pupil who is playing one of the roles in the trial is given a card describing his or her role. Each of these pupils should read his or her card out loud, and explain their character's professional role in the trial and motivations for participating.
- 2. The Scientist from the pharmaceutical company must leave the room at this point.
- 3. The Trial Manager assigns numbers to the volunteers. This is so they are made anonymous, and their identity does not affect which sunscreen they are given.
- 4. The Pharmacist has four bottles of cream. Two are bottles of the new sunscreen which is to be compared with the "old sunscreen".
- 5. The Pharmacist gives random labels (A, B, C & D) to the creams and records which is which. Two of these are the new sunscreen (these contain SPF 60+ sunscreen) and two are the "old sunscreen" (they contain lotion). The old labels from step 4 can no longer be seen. The Pharmacist then gives the creams to the Trial Manager, and the Pharmacist leaves.
- 6. The Trial Manager randomises which volunteer will receive each bottle of cream—volunteers draw a letter A, B, C, or D from a hat. The Trial Manager writes the name of each volunteer next to the letter of the bottle that they drew on a card. The contents of the bottles remain secret. The Trial Manager gives the card matching volunteers to the letter on their bottle of cream, and the bottles, to the Nurse.
- 7. The Nurse applies the creams to the volunteers, according to the Trial Manager's card.
- 8. The Nurse makes each volunteer press their sunscreen-coated hand on a sheet of paper so it leaves a handprint. The nurse marks each paper with the number of the volunteer.
- 9. The Scientist then returns and performs the test: the Scientist turns the lights in the classroom down, then uses the UV light on the papers to see if each volunteer's handprint absorbs it. The Scientist then records the results.
- 10. The Scientist sorts the results into positive (sunscreen appears to work) and negative (sunscreen appears not to work) results.
- 11. The Trial Manager returns and reveals which volunteer had which letter of sunscreen. The Scientist analyses the results, and has to determine:
 - Whether there was a difference between the creams
 - Which was the better sunscreen
- 12. The Pharmacist then reveals which creams are the new sunscreen and which are not.

Questions for Class Discussion



• Scientists who are testing new medicines and therapies usually use double blind trials. Why do you think it is important that the volunteers do not know if they had the new medicine?

If the volunteers know which treatment they receive, this changes their expectations. If the volunteers do not know which treatment they receive, they have similar expectations for the experimental treatment and the placebo or current treatment. This allows scientists to determine which effects are due to the treatment, and which are due to volunteers' expectations. Volunteers cannot affect this particular trial as their expectations do not change the efficacy of a sunscreen. However, if volunteers were asked questions about the way the creams felt, their expectations could affect that.

• Why do you think it is important that the scientist does not know which treatment volunteers received?

When analysing the results, the scientist may look for the results they expect or hope to get. The scientist may be affected by observer bias, and look for different effects in the volunteers with the experimental medicine. In addition, if the scientist knows which volunteers are in which group, the scientist may treat volunteers differently, which may cause the volunteers to realise which group they are in. If this happens, they are unblinded, and the volunteers' expectations may change.

· Why are volunteers selected randomly to be in each group?

The volunteers are put into groups at random so that the groups contain similar mixtures of types of people, which can be more easily compared. This is also done so that they are not inadvertently unblinded by self-selecting for one group or the other. If patients suspect that they have been chosen for one group or the other, this will affect their expectations of treatment.

• Placebos are not used in trials with ill volunteers. Why?

This is unethical if there is already a possible treatment, because giving an ill person a placebo would mean they would receive no treatment at all. When testing medicines on currently ill volunteers, researchers compare the experimental treatment against the current best possible treatment.

• Are there any other places in this trial where the results could be affected by bias? What else can researchers do to make the trials fairer?

Some examples: writing a clear experiment protocol and having it approved by an outside ethics committee, having the results calculated by outside observers.



Scientist

The Scientist has researched a new sunscreen for the past decade, and is convinced it works. The company he works for has invested a good deal of time and money into the development of this product. The Scientist needs to test his new sunscreen to make sure that it works, but he also needs results that are impartial and unbiased. If he tests the sunscreen in a double blind trial, using independent observers, he can test his lotion in a way that minimises bias.

© Centre of the Cell



ctivity 3: Role Cards for the Double Blind Trial Activity

Pharmacist

The Pharmacist makes sure that the new and old sunscreens are manufactured to resemble each other as closely as possible. The Pharmacist also tests the contents of the sunscreens to make sure that they are made as directed and contain the correct ingredients and nothing else. The pharmacist keeps a record of which sunscreens are in which bottles. She is also independently employed, and does not work for the same company as the Scientist.

© Centre of the Cell



Nurse

The Nurse checks the health of all of the volunteers in the trial, and watches for any reactions they might have to the lotions. The Nurse works for a testing centre that is independent of the company that pays for the Scientist's research. The Nurse makes sure that the trial volunteers are all treated the same way, so that the results of the test will be accurate.



Activity 3: Role Cards for the Double Blind Trial Activity

Trial Manager

The Trial Manager recruits the volunteers and puts them into groups. She makes sure that the trial follows a specific structure, or protocol, to ensure that all sources of bias or inaccuracy are minimised. She is interested in producing accurate information from this trial rather than a specific outcome.

ctivity 3: Role Cards for the Double Blind Trial Activity

© Centre of the Cell

© Centre of the Cell



Volunteer 1

This volunteer wants to test this sunscreen because her sister had skin cancer, and she wants to help researchers who are working on new ways to prevent sun damage.

Activity 3: Role Cards for the Double Blind Trial Activity



Volunteer 2

Volunteer 2

This volunteer was curious about participating in clinical trials. He heard about this trial on an advert on the radio, and decided to volunteer.

© Centre of the Cell



Volunteer 3

© Centre of the Cel

Some studies offer a small sum of money to healthy volunteers as compensation for their time and expenses. This volunteer signed up to the trial for the money.

Activity 3: Role Cards for the Double Blind Trial Activity



Volunteer 4

This volunteer had a friend who had been in a clinical trial before, and enjoyed the experience. This volunteer also thought it might be a fun thing to do that could help scientists.

Activity 3: Role Cards for the Double Blind Trial Activity

© Centre of the Cell

© Centre of the Cell

Materials

Activity 3 Role Cards for the Double Blind Trial Activity

Step 1: Meet the team



These people are all involved with the trial.

Step 2: The scientist must leave the room



This is so that the scientist is not biased when comparing the results of the test.



The Trial Manager assigns numbers to the volunteers so they are made anonymous, as their identity does not affect which sunscreen they are given.

Step 4: Labelling



The Pharmacist has two bottles of the new sunscreen to be compared with the old sunscreen.



The pharmacist gives the bottles of sunscreen random labels. Only the pharmacist knows which sunscreen is inside each bottle. The old labels from step 4 can no longer be seen. The pharmacist then gives the creams to the Trial Manager, and leaves.

Step 6: Assign letters to volunteers



The Trial Manager randomises which volunteer will receive each bottle of cream - volunteers draw a letter A, B, C, or D from a hat. The trial administrator records on a card the name of each volunteer next to the letter of the bottle that they drew. the contents of the bottles remain secret. the trial administrator gives the card matching volunteers to the letter on their bottle of cream, and the bottles, to the nurse.

Step 7: Put sunscreen on volunteers



The Nurse applies the creams to the volunteers, according to the Trial Manager's record card.

Step 8: Assign numbers to volunteers



The Nurse makes each volunteer press their sunscreen-coated hand on a sheet of paper so it leaves a handprint. The nurse marks each paper with the number of the volunteer.



The Scientist then performs the test: the Scientist turns the lights in the classroom down, then uses the UV light on the papers to see if each volunteer's handprint absorbs it. The Scientist then records the results.

Step 10: Sort results



The Scientist sorts the results into positive (sunscreen appears to work) and negative (sunscreen appears not to work) results.



The Trial Manager returns and reveals which volunteer had which letter of sunscreen. The Scientist analyses the results, and has to determine:

- Whether there was a difference between the creams
- Which was the better sunscreen

Step 12: reveal which is sunscreen



the Pharmacist then reveals which creams are the new sunscreen and which are not.