

Oranges and lemons: understanding clinical trials

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We devote a fair amount of space in *Positive Living* to reporting the results of clinical trials, but do you understand why medical research is done this way? This *Backgrounder* looks at the science behind [clinical](#) [1] Pertaining to or founded on observation and treatment of participants, as distinguished from theoretical or basic science. trials.

It's May 1847, on board the British naval ship *Salisbury*, and after weeks at sea there is an all-too familiar sickness. Scurvy, a revolting and foul-smelling affliction of sailors, is taking its toll on the crew. As more and more members of the ship's company become ill with the disease, the naval surgeon on board, James Lind, decides to perform an experiment.

Scurvy – which we now know is caused by a deficiency of vitamin C – has been known since ancient times, and throughout history many different treatments were used. But while some of these had at least a partial effect in treating the disease, there was no clear evidence of what approach worked best. Lind set out to answer this question, and his experiment is now regarded as the world's first ever clinical trial.

On the 20th of May, Lind selected 12 of the scurvy-afflicted sailors for his experiment. "Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of the knees," he later wrote. The 12 were moved into a cabin on the ship, and Lind ordered that they all be given the same rations. He divided the group into twos, and gave each pair of men a different scurvy treatment from the many which were popular at the time: a quart of cider a day for the first pair; 25 drops of 'elixir of vitriol' (weak hydrochloric acid) for the next; the next three pairs were given two spoonfuls of vinegar; a pint of sea-water; or a spicy nutmeg paste and a drink of barley water.

The remaining pair were given two oranges and a lemon each day, which, Lind recorded, "they eat with greediness at different times upon an empty stomach." The fruit supply ran out after just six days, but by that time the outcome of the experiment was clear: the condition of the men who received the fruit had improved so much that one of them was returned to duty while the other was appointed nurse to the remaining ten.

Lind's experiment showed that of the six different treatments, citrus fruits were the most effective anti-scurvy medicine. (It still took many years before the British navy figured out that giving citrus juice prevented scurvy, and it wasn't until 1932 that the link between vitamin C and scurvy was established).

This story illustrates one of the main characteristics of clinical trials to this day: participants are divided into different groups (arms) and, as far as possible, are treated identically except for the drug or treatment being studied. Doing this helps to eliminate the possibility of other factors influencing the results of the trial.

The number of arms is different for different trials, but by having at least two arms, researchers can compare the results between arms to determine which treatment works best.

In a [placebo-controlled](#) [2] **A method of investigation of drugs in which an inactive substance (the placebo) is given to one group of participants, while the drug being tested is given to another group. The results obtained in the two groups are then compared to see if the investigational treatment is more effective in treating the condition.** trial, one of the study arms is designated the 'control group', and is given no treatment at all, or more commonly a [placebo](#) [3] **A dummy medical treatment, designed to have no pharmacological effect, administered to the control group of a clinical trial.** – a pill with no medicine in it, just inactive compounds. Having one group of people who did not take any treatment gives the researchers a reference point against which to measure the [effectiveness](#) [4] (Of a drug or treatment). The maximum ability of a drug or treatment to produce a result regardless of dosage. A drug passes efficacy trials if it is effective at the dose tested and against the illness for which it is prescribed. In the standard procedure, Phase II clinical trials gauge efficacy, and Phase III trials confirm it. of the drug in the other arm(s). Essentially the control group is there to answer the question 'What would have happened if we gave no treatment at all?'

A placebo (Latin for 'I will please') is given to compensate for the so-called [placebo effect](#) [5] **A physical or emotional change, occurring after a substance is taken or administered, that is not the result of any special**

property of the substance. The change may be beneficial, reflecting the expectations of the participant and, often, the expectations of the person giving the substance., which occurs when a person's symptoms are altered in some way by the act of taking a treatment, even when the 'treatment' is inactive. Cases have been reported where symptoms subsided, clinical signs of disease disappeared or blood test results improved despite the fact that the patient was taking a placebo. Likewise, people in placebo arms of clinical trials sometimes report the same **side effects** as those taking the real treatment (this is sometimes referred to as the 'nocebo effect', from the Latin 'I will harm').

The possibility of being given a placebo can sometimes be a disincentive for people to participate in clinical trials, and can cause considerable angst in diseases like HIV where people often participate in trials specifically because they want or need access to a promising new therapy. Because of this, clinical trials are bound by strict **ethics** [6] **(In clinical trials) The process of determining that a proposed clinical trial conforms to a wide range of moral, scientific and ethical standards, to ensure that participants in the trial are not abused, mistreated or unfairly taken advantage of. Before a clinical trial can go ahead, it must be given approval via an independent ethics process.** to ensure that, as far as possible, trial participants are not disadvantaged regardless of which arm of the trial they are assigned to. These rules vary from trial to trial, but typically, as soon as it becomes clear that a study drug is effective in those who take it, it is offered to the participants in the placebo arm.

Because of the potential impact of the placebo effect, trials are often **double-blinded** [7] **A clinical trial design in which neither the participating individuals nor the study staff knows which participants are receiving the experimental drug and which are receiving a placebo (or another therapy). Double-blind trials are thought to produce objective results, since the expectations of the doctor and the participant about the experimental drug do not affect the outcome; also called double-masked study.** to ensure that trial participants have no way of knowing whether they are getting the real drug or the placebo. Even the trial doctors normally don't know who is getting which – thus the 'double' in double-blind. This is to prevent doctors from giving subliminal hints which might influence a person's belief about whether they are taking the real drug or placebo.

The intention of all of this subterfuge is to ensure that, as far as possible, the clinical trial represents an unambiguous and verifiable scientific experiment with trustworthy results. There's a good scientific reason for this.

The 'subjects' of clinical trials are real live human beings who live real lives and respond to treatments in subtly different ways, and these can affect the results of clinical trials. To compensate, trials are designed ahead of time with specific objectives in mind and are **powered** to make specific findings. The 'power' of a given trial is a statistical measure of the trial's ability to draw conclusions from its data, and is related to the size of the study: clinical trials with lots of participants tend to be more reliable than smaller studies, but even with small studies statistically verifiable conclusions can be drawn if the study is designed properly.

Because of this, sometimes when studies report unexpected results it can be hard to draw conclusions. In a study which is powered to determine whether a new drug reduces **viral load** [8] A measurement of the quantity of HIV RNA in the blood. Viral load blood test results are expressed as the number of copies (of HIV) per milliliter of blood plasma. by more than a set amount, it isn't always valid to draw conclusions about, say, the change in CD4 count in participants, unless the study has been designed to make these observations.

When trial results are reported (in Positive Living and elsewhere) you'll often see references to some findings which were 'not *statistically significant*'. This is a measure of the likelihood that the same result might have occurred purely by chance.

A real-life example of this is the '2NN' trial comparing the non-nucleosides efavirenz and nevirapine: looking at the results of this trial, you might notice that about 44 percent of participants taking nevirapine experienced treatment failure within 48 weeks, compared with 38 percent of those taking efavirenz. While at first this suggests that efavirenz is clearly superior to nevirapine, a statistical analysis showed that, due to the relatively small number of people in each study arm, the result was not statistically significant and this finding can therefore not be relied upon.

Sometimes it seems like the speed at which medical research, especially in HIV, can be glacially slow. Years can go by as potential new drugs are tested through multiple clinical trials, each stage carefully working towards the next. It's frustrating if you're waiting for new therapies, but we all benefit in the long run, as the process ensures the scientific validity of the research findings.

- [clinical trials](#)
- [Clinical trials database background information](#)

Links:

- [1] <http://www.napwa.org.au/glossary/term/475>
- [2] <http://www.napwa.org.au/glossary/term/507>
- [3] <http://www.napwa.org.au/glossary/term/106>
- [4] <http://www.napwa.org.au/glossary/term/486>
- [5] <http://www.napwa.org.au/glossary/term/508>
- [6] <http://www.napwa.org.au/glossary/term/498>
- [7] <http://www.napwa.org.au/glossary/term/484>
- [8] <http://www.napwa.org.au/glossary/term/416>