Suppose a new medical treatment has been developed that may reduce high blood pressure. The treatment has been extensively tested in the laboratory and on a few volunteers, and the researchers believe that it will work on the general population. Now it is time to find out if they are right.

Historically, doctors found out whether a treatment worked in practice by using it on their patients. They could then compare the patients’ responses to the new treatment and to previous treatments for the same illness, and also compare how responses to the new treatment varied between patients. However, if patients did indeed recover from their condition, there was no way of telling whether it was due to the treatment or to something else. There are many other factors that could have caused the patients to recover: for example, they may have felt better simply because they were being treated by a doctor (a reaction known as the placebo effect); they may have recovered anyway, regardless of the treatment; or perhaps their recovery was due to changes in their personal circumstances or lifestyle. Without taking these and other factors into account, it could be easy to conclude incorrectly that the treatment worked. Doctors would then incorporate it into their everyday practice, mistakenly believing it to be effective.

Evaluating a medical treatment

Sarah Garner and Rachel Thomas consider why well-designed and properly analysed experiments are so important when testing how effective a medical treatment is.

In a medical trial, one group of people is given the new treatment and the other group, a placebo or an existing treatment.
The development of the randomised-controlled trial

In the 19th century, scientists proposed a method of controlling exactly what was happening and recording any changes in the patients’ condition. In these controlled experiments, there were two groups of patients – the study group, which received the new treatment, and the control group, which received a placebo (an inert medication) or an established treatment. The patients were then observed, and the outcomes of the two groups (such as whether each patient lived or died) were recorded and compared.

Some time later, in 1917, the process of ‘blinding’ improved the scientific method even further. If neither the patient nor the researcher knows which treatment the patient is receiving, then the results cannot be interfered with either intentionally or unintentionally. This is known as a double-blind trial (in a single-blind trial, either the patient or researcher knows which treatment is being received).

However, the results could still be deliberately biased to prove that a treatment worked, by including sicker patients in the study group than in the control group. The solution to this, first used by the UK’s Medical Research Council in the 1940s for its study of whooping cough vaccines, is to randomly choose which patients will get the new treatment, and which will get the control treatment.

Controlled trials with random allocation to the two groups became known as randomised-controlled tri...
als or RCTs. By randomising, you not only end up with a random distribution of sicker and healthier patients between the two groups, but also achieve a random distribution of things you do not know about (but which may also affect the patient’s health and therefore the outcome of the treatment). Then – because, in theory, the only difference between the two groups is whether they received the treatment being tested – you can assume that any differences in outcome are most likely due to the treatment and nothing else.

RCTs are now universally used in clinical research to evaluate new treatments.

Designing and analysing RCTs

More people, more power

If you are planning to test your blood-pressure treatment with an RCT, you need to design it carefully. One important question is: How many patients should you include in the trial? This depends on how big an effect the new treatment has: the bigger the effect, the smaller the number of patients you need to distinguish it from the random fluctuations that happen by chance.

Of course, the effect of the treatment is exactly what you want to find out with your RCT. Before you start an RCT, however, you will already have some evidence that the treatment works, perhaps from laboratory or small-scale testing. This allows you to estimate the effect size.

In a healthy patient, blood pressure should be between 90 and 120 mmHg. But patients with high blood pressure will consistently have measurements of more than 140 mmHg, putting them at increased risk of heart attack and stroke. You might estimate that the new treatment will reduce a patient’s maximum blood pressure by 5 mmHg; after treatment, you would expect that the average blood pressure of the study group would be at least 5 mmHg lower than the average blood pressure of the control group.

There are statistical formulae to determine the sample size you need to have a good chance of detecting that estimated effect. For your blood-pressure treatment, these formulae tell you that you would need around 64 patients in each group to detect a treatment difference of 5 mmHg.

How different is different?

The trial has run its course, the participants have been monitored, and you have recorded a difference in blood pressure between the patients in the study and control groups. Thanks to randomising, you know that the two groups were comparable before the trial. So either your new treatment has had an effect, or a very surprising event has occurred: the treatment really has no effect at all and the difference you recorded in your RCT was due to chance alone.

Imagine that the average blood pressure of the study group was 5.2 mmHg lower than the average blood pressure of the control group. How do you decide if that difference is due to chance or to a real effect of the treatment? After all, blood pressure can vary for many reasons, not all of which can be controlled in your RCT.

What statisticians do is to allow for some variation; rather than rely on one average for each group, they calculate a range of values for each group that they are pretty confident will include the true value. This range of values is called a confidence interval. If the confidence intervals in your blood-pressure study are 141.2–148.9 mmHg in the control group and 135.7–139.3 mmHg in the study group, you can see that the two...
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fact that 5% of the time (or 1 in 20 times) they will be wrong due to chance alone. To be even surer that you have the right value, you have to measure more patients and even then, the only way to be 100% sure is to measure the whole population!

If the result turns out not to be statistically significant, one of the key questions to ask is whether you included enough patients in the trial. Perhaps the effect of the treatment is smaller than you estimated – with a larger sample size, you might have detected a difference between the two groups of patients.

Applying RCTs to the real world

A well-designed and properly analysed RCT is a very powerful tool for medical researchers – providing doctors with the information they need to make the right decisions when treating their patients. Nonetheless, RCTs do have limitations.

Firstly, it is not enough to know that the new treatment makes a statistically significant difference. Is the difference also clinically significant – for example, does a decrease in maximum blood pressure of 5 mmHg make a real difference to a patient’s health and well-being? After all, in our example, the treatment still did not reduce the blood pressure to the confidence intervals do not overlap. Statisticians, therefore, say that the observed difference between the two groups is statistically significant – and you can assume that it really was caused by the treatment.

But how confident is confident? Statisticians usually say that 95% confident is good enough; this means that they are prepared to live with the fact that 5% of the time (or 1 in 20 times) they will be wrong due to chance alone. To be even surer that you have the right value, you have to measure more patients and even then, the only way to be 100% sure is to measure the whole population!

Before 1994, doctors recommended that patients with lower back pain rest in bed. However, after reviewing all the available evidence, the Clinical Standards Advisory Group realised that bed rest was not beneficial and was perhaps even harmful. This led to a radical change in treatment, with patients being advised to remain active.

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Evidence can change views

A systematic review of the evidence for minocycline, an antibiotic that was heavily promoted as the best cure for acne, was recently conducted to investigate its efficacy and its safety.

One side effect of minocycline is potentially fatal autoimmune liver problems. These problems are rare and can have a number of causes. Most doctors do not come across them, and even if they do, the connection might not necessarily be made with the drug.

It was only when all the information was reviewed together that the link was made. A systematic review showed that there was no evidence that minocycline was any better at curing acne than any other known treatment. Given the risks, the authors of the review concluded it should not be used in preference to other treatments (Garner et al., 2003).

Acknowledgement

If you enjoyed this article but would like to learn more about the mathematics involved, read the original, longer version of this article, which appeared in Plus magazine, a free online magazine which opens a door to the world of mathematics with all its beauty and applications.

Reference


Web references

w1 – For more information about recommendations for bed rest, see the ‘management’ section of the article ‘low back pain and sciatica’ on the Patient UK website (www.patient.co.uk) or use the direct link: http://tinyurl.com/y9gghww
w2 – You can read a good explanation of how treatment effects and sample size can affect statistical power in Jerry Dallal’s Little Handbook of Statistical Practice: www.jerrydallal.com/LHSP/sizenotes.htm
w3 – For the original version of this article, including more details of the
February 2010: Evaluating a medical treatment, visit: http://plus.maths.org/podcast

The charity Sense About Science has produced a useful guide about interpreting medical claims in the press (I’ve got nothing to lose by trying it). It can be downloaded free from the Sense About Science website (www.senseaboutscience.org.uk) or via the direct link: http://tinyurl.com/63vz4l


Plus Magazine offers a range of articles, podcasts and classroom activities addressing the mathematics behind health and medicine: ‘Do you know what’s good for you?’ See: http://plus.maths.org/wellcome

If you enjoyed this article, you might like to browse the other medicine-related articles in Science in School. See: www.scienceinschool.org/medicine

Dr Sarah Garner is the associate director for research and development at the National Institute for Health and Clinical Excellence (NICE), which bases its recommendations to the medical community on systematic reviews.

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W4 – To learn more about the thalidomide disaster and also about recent research into thalidomide and limb formation, see: Zimmer C (2010) Answers begin to emerge on how thalidomide caused defects. New York Times 16 Mar: D3. www.nytimes.com

W5 – The Cochrane Collaboration is an international network of people helping healthcare providers, policy makers, patients, their advocates and carers make well-informed decisions about human healthcare. See: www.cochrane.org

W6 – The National Institute for Health and Clinical Excellence (NICE) is an independent organisation responsible for providing UK national guidance on promoting good health and preventing and treating ill health. See: www.nice.org.uk

W7 – To learn more about Plus, the free online mathematics magazine, visit: http://plus.maths.org

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