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INDEPENDENT, OBJECTIVE AND EVIDENCE-BASED

Why is it important for people to be "randomized" in trials?

In the late 1940s, groups of researchers in Europe and the USA led one of the most important developments of modern medical science: refining the methods for testing treatments in random control trials. Volunteers are divided into groups randomly - by chance, like being in a lottery. One of the groups will use the treatment being tested. The experiences of the other group of people will provide control or comparison data to see what difference the treatment makes. There will not be differences because, for example, one group has healthier people in it. This simple step provided a way to find out if a treatment was effective, useless or even harmful.

Proof of how important these scientific techniques are came quickly. The first modern trial of a medicine began in England in 1948. There, a drug was put under trial for tuberculosis, a life-threatening chronic lung disease. Over in the USA, researchers in neonatal medicine were watching with great interest and excitement. Neonatal medicine or neonatology is the specialty concerned with looking after newborn babies. These doctors were worried about a major outbreak of a new kind of visual loss affecting thousands of the prematurely born babies they were looking after. They called this disease retrolental fibroplasia. Today it is called ROP (retinopathy of prematurity). The retina is the light-sensitive layer at the back of the eye. With ROP, the retina can be so badly damaged by disease that the person loses all their sight.

A few years earlier, some other doctors in the USA had seen that babies born preterm or premature appeared to do better if they got a lot more oxygen than normal. With the arrival of the incubator during the 1940s, it was now possible to keep tiny premature babies in a completely controlled environment and regulate the amount of oxygen around them. This was one of many developments happening at the same time - and there were dramatic improvements in the chances of survival for these tiny babies.

But there was also this outbreak of blindness of epidemic proportions in the babies. Nurses in England and Australia suggested it could be the oxygen and published some analyses of the outcomes in their hospitals - but there were many other theories too. As always when there is a new disease or a new treatment, competing theories develop quickly. The role of science is to test these so-called hypotheses to find out which are more likely to be right. But most forms of research are not formal tests. Medical journals fill with individual reports and all sorts of studies that are not designed to be able to reliably test an

hypothesis. It does not take long for a confusing picture of conflicting research results to build.

That process of contradictory research piling up happened quickly as large numbers of babies started developing ROP. Hospitals around the world started publishing reports that appeared to show that babies exposed to high concentrations of oxygen did not get ROP. Other researchers tried to compare what was happening in different groups of babies. That research put a major question mark on the use of high levels of oxygen, but it could not provide a definitive answer either.

At the big new Babies Hospital in New York, a group of neonatal specialists had been watching closely what the English researchers had done with tuberculosis. They had done their first trial of a treatment for babies having these eye problems. One of them was William ("Bill") Silverman (1917-2004). He explained what happened next:

"By early 1953, controversy about the causal role of supplemental oxygen rose to a fever pitch. Finally, the US Public Health Service convened a conference in Bethesda, Maryland in the hope of devising a plan that might put an end to the international disaster (by this time the strange disease had blinded around 10,000 infants throughout the world). It was immediately clear that there were 2 highly vocal opposing camps at the meeting. One side argued that a formal, randomized trial of oxygen restriction must be conducted without further delay, because there were 3 competing outcomes of interest: blindness, death, and brain damage. The opposition maintained that there was sufficient evidence extant to prove that oxygen was the cause of ROP blindness; a controlled trial was not only unnecessary, they argued, it was immoral! Finally, after an all-night debate, a compromise was hammered out. Eighteen hospitals agreed to participate in a randomized clinical trial for 3 months."

There was still a lot of opposition - one expert had told a national funding agency considering an application for a trial, "...these guys are going to kill a lot of babies by anoxia to test a wild idea." (Anoxia is too little oxygen.)

The "wild idea" turned out to be right. The trial results were made public in 1954, and the publicity that

followed ensured that the level of oxygen in incubators was reduced, ending that ROP epidemic. Only one-third as many babies in the control group of the trial had developed ROP as the babies getting the high oxygen. Because the trial had not been done before the incubators were introduced into wide use, it had taken 12 years for the problem to be understood and for this particular part of the oxygen controversy to be solved. Until trials are done, it is almost never possible to be certain that a treatment works as it meant to do.

Researchers continued to struggle with the question of exactly how much oxygen is ideal: when the oxygen levels are lower, more sight will be saved but more babies might die. Because of this trial, however, many more people had come to realise the importance of randomising people in trials. A few months later, another national trial was published showing that the polio vaccine was effective, and the random control trial became more widely recognised as important in medical science.

Bill Silverman criticised what he called "the impatient let's-try-it-and-see approach" that can fill the field with misleading information and lead to people being convinced in hypotheses that have not been properly tested: "The twelve-year struggle to halt the outbreak provided a sobering demonstration of the need for planned evaluation of all medical innovations before they are accepted for general use."

*Author: German Institute for Quality and Efficiency in Health Care (IQWiG)*

**Glossary**

## evidence

Evidence is what we call scientific proof from well-conducted, good-quality scientific trials that have been carefully designed to answer specific questions. Depending on the types of questions, different scientific research methods (types of study) are most appropriate to find reliable answers to these questions. Randomized controlled trials (RCTs), for example, are the best way to get reliable evidence on the effectiveness of medical treatments (interventions). This type of study, however, is not the best form of evidence for all possible questions, and does not provide the best answers to all kinds of questions, either. Epidemiological studies, for example, are very suitable for establishing well-founded proof for the spreading of a disease in the population.

## retina

The retina lines the back of the eye, and the lens projects images onto it. The retina is sensitive to light. It helps us see fine details, contrasts and colours. The retina captures the images focused by the lens and communicates them through nerves to the brain.

## Sources

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Our information is based primarily on systematic reviews of the effects of health care. Systematic reviews are necessary to gain an objective picture of health care. In order to do this, a clear question is formulated. Researchers then find all the relevant studies that could answer this question. They then evaluate those studies.

You can find a list of the evidence and other scientific literature on which this information is based at [www.informedhealthonline.org](http://www.informedhealthonline.org)

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