

Clinical trials: From a tragedy child to the ‘driving force’ of medical advancement

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In modern medicine, the clinical trial is the most dominant form of clinical research which is understood as research conducted in human participants to evaluate the causal-effect between a clinical intervention and health outcome. Clinical trials are well controlled and function under a strict regulatory environment, but have had a convoluted and turbulent history.

How did clinical trials start?

The first documented clinical trials came not out of scientific curiosity but from a lack of resources. It was in around 600 BC and reported in the Book of Daniel, when the health effects of the vegetarian diet vs. red meat and wine was reviewed over a 10-day period by the Babylonian King, Nebuchadnezzar. A few hundred years later, in 1537, a French military surgeon named Ambroise Pare started treating battlefield wounds with mixture of turpentine, egg yolk and oil of roses, due to the insufficient resource of boiling oil, which was the standard care at the time. Pare observed the soldiers he treated with his new concoction were in little pain, their wounds less swollen and in overall better condition than those treated with oil. While this trial was unintentional, Pare's innovation led the way of advancing patient care through experimentation (Gordis, 2014) which is generalisable to all clinical specialism based research. Clinical trials such as this continued throughout the 16th and 17th century with varying degrees of success.

But it was not until 1747, that the first widely accepted, modern day clinical trial was documented. Dr James Lind, a Scottish naval surgeon, planned to study scurvy, which killed thousands of British soldiers yearly. Lind prepared for his experiment by conducting a systematic review of existing knowledge. He narrowed his treatment options and created a comparative trial that included twelve sailors suffering from scurvy. The treatments included cider, vitriol, vinegar, seawater, citrus or nutmeg. Over the course of two weeks, Lind noticed the soldiers on the citrus diet (two oranges and a lemon every day) were able to return to work within a week; much earlier than

any of those in the other groups. While the results were clear, the British Navy did not employ the use of citrus fruits as a treatment for almost 50 years due to the cost. But Lind's research made an impact on the scientific community and this balance with economic reality is still persistent in healthcare research in the present day.

In 1865, the French physiologist Claude Bernard published the book "Introduction to the Study of Experimental Medicine" d urging medical professionals to use scientific methodology in an attempt to promote evidence based standards of care (Bernard, 2018). Bernard was the first to propose the idea of using controls. He wrote;

"To learn we must necessarily reason about what we have observed, compare the facts, and judge them by other facts as controls"

Bernard pioneered clinical trials by introducing elements with rigorous scientific methods thereby improving and quality assuring the validity of clinical trial data. As a result, the idea of controls as a comparative group became a cornerstone for clinical trials leading to the most important breakthrough for clinical research; the use of a placebo. The first '*placebo*' effect in a clinical trial was shown by Austin Flint in 1863, through his trial on patients with rheumatic fever. The active treatment showed no difference to the placebo group within Flint's trial, which indicated the symptoms of rheumatic fever subsided naturally over time. This conclusion marked a shift in medicine and the importance of active drug treatments became central to clinical trials.

Expansion of methodology

A few decades later, the inauguration of medical research institutions became vital in promoting clinical trials. The Medical Research Council (MRC) conducted the first double blind comparative trial from 1943-1944. The MRC examined the effect of Patulin, an extract of *Penicillium Patulinum*, on the common cold. While initial reports suggested that Patulinum could cure the common cold, the Royal Navy decided to conduct a controlled clinical trial of Patulinum to replicate and clarify the somewhat confusing results from the MRC trial. The Royal Navy concluded that Patulinum was ineffective, but the MRC decided they would increase the scale of their trial to include centres across the country. While Patulinum was ultimately unsuccessful, the model of involving researchers, funders, manufactures, patients and the government was unique at that time (Clarke, 2006). The principal investigator at one site concluded:

"It is to be regretted that the work had not produced more helpful results but I do agree that negative results of this kind are very important and I only wish they were more often published since I am sure that a lot of research work is done because other people have not thought it worthwhile to publish their results" (Chalmers & Clarke, 2004).

The use of 'double blinding' (when both the participants and the experimenters do not know which group receives the placebo or the active treatment) marked the next step

and built the foundation of what we know as clinical trials today. The popularisation of 'randomisation' was pioneered by the MRC in their attempt to manage supply of drugs and get rid of bias and eliminate the bias of clinicians putting their healthier patients in the experiment group and sicker patients in the control group. In 1946, Austin Bradford Hill and Philip Hart examined the use of streptomycin on tuberculosis (Dowling, 1975). Their work began the ubiquitous use of randomisation in clinical trials and were thought of as welcoming a new era of medicine.

A chequered past

Over the past 100 years the scientific aspects of conducting clinical trials and the subsequent medical advances has continued to improve at an exponential rate, however not all advancements have been without their controversies. The deplorable experiments that took places in the 1930s and 1940s where science was put above humanity shone a light on the ethics of clinical trials. The Nuremberg code was introduced in 1947 after the Nuremberg trials, in which Nazi physicians were tried for their nefarious clinical trials during World War II on prisoners in the concentration camps. Also known as the International Code of Medical Ethics, the Nuremberg Code outlined ten principles of experimental requirements that protected human participants. It specified that voluntary consent was mandatory, and the benefit of research outweigh the risks. Despite the Nuremberg code being highly publicized, unethical research still continued in the decades that followed. One came in the form of a 40 year (1932-1972) long study of syphilis. The research involved African-American people in Tuskegee, Alabama, and examined the natural course of the disease. The research participants were not told of their diagnosis, were prevented from being drafted to World War II to ensure they were not treated by the military and even, in 1947, deprived of penicillin, which became the standard treatment for syphilis. This led to numerous deaths and spread of the infection between participants' partners and children (Baker, Brawley, & Marks, 2005). As a result, clinical trials were perceived with fear by the general public and this view has not entirely disappeared.

Modern guidelines

In 1964, the World Medical Association presented a document that promoted voluntary and informed consent of human research subjects; the Declaration of Helsinki (DoH). Unlike the Nuremberg code, this declaration has been updated and revised many times, most recently in 2013. It encompasses international research ethics and outlines rules for research combined with medical care and non-therapeutic research (Nellhaus & Davies, 2017). While the Nuremberg code focuses on research participants' rights, the DoH focuses on clinicians' obligations to research participants. Although not legally binding, the DoH serves as the foundation for all laws that govern medical research across the world. In 1974, the National Research Act was signed and identified the ethical principles of biomedical and behavioural research in humans. This led to the four day meeting in 1976 when basic research ethics guidelines were produced, underlying the Belmont Report of 1979. The report describes the three basic principles of clinical research; respect for participants, beneficence and justice.

In 1982, the World Health Organization (WHO) and the Council for International Organizations of Medical Sciences (CIOMS) issued a document entitled '*International Guidelines for Biomedical Research Involving Human Subjects*'. This document was published to help developing countries apply the principles of the DoH and the Nuremberg Code. Worldwide, many organisations and committees issued various documents and guidelines on the same issue, and a decision was taken to consolidate all these guidelines into one universal guideline to be used globally and the International Conference for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) issued the ICH Guidelines: Topic E6 Guideline for GCP (Administration, 2000). This guideline was approved on 17 July 1996 and implemented for clinical trials from 17 January 1997. The participants were representatives of authorities and pharmaceutical companies from the EU, Japan, the United States, Australia, Canada, the Nordic countries and WHO (Vijayananthan & Nawawi, 2008). But the ethical practice of trials still has problems and unapproved ethics programs are still being introduced every year compromising the quality of practice (Williamson, 2008). The principles and practice of ethics still lacks agreement or guidelines, which can create confusion and so institutions need to consider using standard internationally approved guidelines.

Summary

The development of clinical trials throughout history has built the foundation for ethically and scientifically robust research. The 20th century was clearly marked by radical changes in medical practice, with new experimental designs being implemented. A drift has been seen across healthcare domains over the last decade to develop novel and multidisciplinary diagnostics and treatment methods to better meet public health demands, including novel medical devices, therapies and medical technologies. The advent of evidence-based practice has highlighted the need for standardized techniques and guidelines for protecting the patients involved. Clinical trials are essential to provide the best possible care to current patients and develop available therapies, but clinical trials must continue to evolve. History has shown that standardized clinical trials answer questions other methods of scientific investigation cannot. Modern challenges, including big data, pharmaceutical and medical device research, as well as monetary and time constraints, and expanding public health issues present new challenges and opportunities for clinical research. Finally, the ability to access, store and manipulate data will challenge privacy concerns. As we progress into a new era of clinical research, it is critical that investigators remember the long and storied past that led us to this point.

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