

Evolution of Clinical Research: A History Before and Beyond James Lind

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ABSTRACT

The evolution of clinical research traverses a long and fascinating journey. From the first recorded trial of legumes in biblical times to the first randomized controlled trial of streptomycin in 1946, the history of clinical trial covers a wide variety of challenges – scientific, ethical and regulatory. The famous 1747 scurvy trial conducted by James Lind contained most elements of a controlled trial. The UK Medical Research Council's (MRC) trial of patulin for common cold in 1943 was the first double blind controlled trial. This paved the way for the first randomized control trial of streptomycin in pulmonary tuberculosis carried out in 1946 by MRC of the UK. This landmark trial was a model of meticulousness in design and implementation, with systematic enrolment criteria and data collection compared with the ad hoc nature of other contemporary research. Over the years, as the discipline of controlled trials grew in sophistication and influence, the streptomycin trial continues to be referred to as ground breaking. The ethical advances in human protection include several milestones – Nuremberg Code, Declaration of Helsinki, Belmont Report, and 1996, International Conference on Harmonization Good Clinical Practice guidance. In parallel to ethical guidelines, clinical trials started to become embodied in regulation as government authorities began recognizing a need for controlling medical therapies in the early 20th century. As the scientific advances continue to occur, there will be new ethical and regulatory challenges requiring dynamic updates in ethical and legal framework of clinical trials.

Key words: History, Clinical Trial, James Lind, Randomization, GCP

“The charm of history and its enigmatic lesson consist in the fact that, from age to age, nothing changes and yet everything is completely different.” - Aldous Huxley

THE evolution of clinical research traverses a long and fascinating journey. The recorded history of clinical trials goes back to the biblical descriptions in 500 BC. The journey moves from dietary therapy – legumes and lemons – to drugs. After basic approach of clinical trial was described in 18th century, the efforts were made to refine the design and statistical aspects. These were followed by changes in regulatory and ethics milieu. This article captures the major milestones in the evolution of clinical trials.

562 BC – 1537: Pre-James Lind Era

The world's first clinical trial is recorded in the “Book of Daniel” in The Bible.¹ This experiment resembling a clinical trial was not conducted by a medical, but by King Nebuchadnezzar a resourceful military leader.¹ During his rule in Babylon, Nebuchadnezzar ordered his people to eat only meat and drink only wine, a diet he believed would keep them in sound physical condition.¹ But several young men of royal blood, who preferred to eat vegetables, objected. The king allowed these rebels to follow a diet of legumes and water — but only for 10 days. When Nebuchadnezzar's experiment

ended, the vegetarians appeared better nourished than the meat-eaters, so the king permitted the legume lovers to continue their diet.¹ This probably was the one of the first times in evolution of human species that an open uncontrolled human experiment guided a decision about public health.

Avicenna (1025 AD) in his encyclopedic ‘Canon of Medicine’ describes some interesting rules for the testing of drugs.² He suggests that in the clinical trial a remedy should be used in its natural state in disease without complications. He recommends that two cases of contrary types be studied and that study be made of the time of action and of the reproducibility of the effects.² These rules suggest a contemporary approach for clinical trials. However, there seems to be no record of the application of these principles in practice.

The first clinical trial of a novel therapy was conducted accidentally by the famous surgeon Ambroise Parè in 1537.¹ ³ In 1537 while serving with the Mareschal de Motegni he was responsible for the treatment of the battlefield wounded soldiers. As the number of wounded was high and the supply of conventional treatment – oil was not adequate to treat all the wounded, he had to resort to unconventional treatment. He describes, ‘at length my oil lacked and I was constrained to apply in its place a digestive made of yolks of eggs, oil of roses and turpentine. That night I could not sleep at any ease, fearing that by lack of cauterization I would find the

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wounded upon which I had not used the said oil dead from the poison. I raised myself early to visit them, when beyond my hope I found those to whom I had applied the digestive medicament feeling but little pain, their wounds neither swollen nor inflamed, and having slept through the night. The others to whom I had applied the boiling oil were feverish with much pain and swelling about their wounds. Then I determined never again to burn thus so cruelly the poor wounded by arquebuses'.² However, it would take another 200 years before a planned controlled trial would be organized. .

1747: James Lind and Scurvy Trial

James Lind is considered the first physician to have conducted a controlled clinical trial of the modern era¹⁻⁴. Dr Lind (1716-94), whilst working as a surgeon on a ship, was appalled by the high mortality of scurvy amongst the sailors. He planned a comparative trial of the most promising cure for scurvy.¹⁻⁴ His vivid description of the trial covers the essential elements of a controlled trial.

Lind describes ""On the 20th of May 1747, I selected twelve patients in the scurvy, on board the Salisbury at sea. 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. They lay together in one place, being a proper apartment for the sick in the fore-hold; and had one diet common to all, viz. water gruel sweetened with sugar in the morning; fresh mutton-broth often times for dinner; at other times light puddings, boiled biscuit with sugar, etc., and for supper, barley and raisins, rice and currants, sago and wine or the like. Two were ordered each a quart of cyder a day. Two others took twenty-five drops of elixir vitriol three times a day ... Two others took two spoonfuls of vinegar three times a day ... Two of the worst patients were put on a course of sea-water ... Two others had each two oranges and one lemon given them every day ... The two remaining patients, took ... an electary recommended by a hospital surgeon ... The consequence was, that the most sudden and visible good effects were perceived from the use of oranges and lemons; one of those who had taken them, being at the end of six days fit for duty ... The other was the best recovered of any in his condition; and ... was appointed to attend the rest of the sick. Next to the oranges, I thought the cyder had the best effects ..." (Dr James Lind's "Treatise on Scurvy" published in Edinburgh in 1753)

Although the results were clear, Lind hesitated to recommend the use of oranges and lemons because they were too expensive.³ It was nearly 50 years before the British Navy eventually made lemon juice a compulsory part of the seafarer's diet, and this was soon replaced by lime juice because it was cheaper.

Lind's Treatise of 1753, was written while he was resident in Edinburgh and a Fellow of the Royal College of Physicians, contains not only his well known description of a controlled

trial showing that oranges and lemons were dramatically better than the other treatments for the disease, but also a systematic review of previous literature on scurvy.⁵

In 2003, Royal College of Physicians established The James Lind Library to commemorate 250th anniversary of publication of Dr Lind's pioneering contribution "Treatise on Scurvy". The James Lind Library (www.jameslindlibrary.org) was created to improve public and professional general knowledge about fair tests of treatments in healthcare and their history.⁵ This library is a website (www.jameslindlibrary.org) that introduces visitors to the principles of fair tests of treatments, with a series of short, illustrated essays. In 2003, Scientific American awarded the Library a Sci/Tech web award. The publicity and popularity of the James Lind Library has made 20 May to be designated International Clinical Trials Day, because James Lind's celebrated controlled trial began on that day in 1747.⁵

1800: Arrival of Placebo

It took another century before the emergence of another important mile stone in the history of modern clinical trial: the placebo. The word placebo first appeared in medical literature in the early 1800s.¹ Hooper's Medical Dictionary of 1811 defined it as "an epithet given to any medicine more to please than benefit the patient." However, it was only in 1863 that United States physician Austin Flint planned the first clinical study comparing a dummy remedy to an active treatment. He treated 13 patients suffering from rheumatism with an herbal extract which was advised instead of an established remedy. In 1886, Flint described the study in his book *A Treatise on the Principles and Practice of Medicine*. "This was given regularly, and became well known in my wards as the 'placeboic remedy' for rheumatism. The favorable progress of the cases was such as to secure for the remedy generally the entire confidence of the patients."

1943: The First Double blind Controlled Trial - Patulin for Common Cold

The Medical Research Council (MRC) UK carried out a trial in 1943-4 to investigate patulin treatment for (an extract of *Penicillium patulinum*) the common cold.⁶ This was the first double blind comparative trial with concurrent controls in the general population in recent times.⁶ It was one of the last trial with non-randomized or quasi-randomized allocation of subjects.⁶ The MRC Patulin Clinical Trials Committee (1943) was chaired by Sir Harold Himsworth, and its statisticians were M Greenwood and W J Martin. This nationwide study enrolled over a thousand British office and factory workers suffering from colds. This was quite a challenging endeavor in wartime,

The study was rigorously controlled by keeping the physician and the patient blinded to the treatment. The treatment allocation was done using an alternation procedure.

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A nurse allocated the treatment in strict rotation in a separate room. The nurse filed the record counterfoil separately, and detached the code label for the appropriate bottle before asking the patient to visit the doctor. ⁶ The statisticians considered this an effective random concurrent allocation. However, the outcome of the trial was disappointing as the analysis of trial data did not show any protective effect of patulin.⁶

1946 First Randomized Curative Trial - The Randomized Controlled Trial of Streptomycin

The idea of randomization was introduced in 1923. However, the first randomized control trial of streptomycin in pulmonary tuberculosis was carried out in 1946 by MRC of the UK.^{6,7} The MRC Streptomycin in Tuberculosis Trials Committee (1946) was chaired by Sir Geoffrey Marshall, and the statistician was Sir Austin Bradford Hill and Philip Hart, who later directed the MRC's tuberculosis research unit, served as secretary. Marc Daniels, as the "registrar" coordinated the clinicians at the participating hospitals. The trial began in 1947. As the amount of streptomycin available from US was limited, it was ethically acceptable for the control subjects to be untreated by the drug—a statistician's dream. ⁶ This trial was a model of meticulousness in design and implementation, with systematic enrolment criteria and data collection compared with the ad hoc nature of other contemporary research.⁸ A key advantage of Dr Hill's randomization scheme over alternation procedure was "allocation concealment" at the time patients were enrolled in the trial. Another significant feature of the trial was the use of objective measures such as interpretation of x-rays by experts who were blinded to the patient's treatment assignment.⁸

Sir Bradford Hill had formed his allocation ideas over several years (with randomisation replacing alternation in order to better conceal the allocation schedule), but had only tried them out in disease prevention. Dr Hill instituted randomization – a new statistical process which has been described in detail in the landmark BMJ paper of 1948.⁷

"Determination of whether a patient would be treated by streptomycin and bed-rest (S case) or by bed-rest alone (C case) was made by reference to a statistical series based on random sampling numbers drawn up for each sex at each centre by Professor Bradford Hill; the details of the series were unknown to any of the investigators or to the co-coordinator and were contained in a set of sealed envelopes, each bearing on the outside only the name of the hospital and a number. After acceptance of a patient by the panel, and before admission to the streptomycin centre, the appropriate numbered envelope was opened at the central office; the card inside told if the patient was to be an S or a C case, and this information was then given to the medical officer of the centre. Patients were not told before admission that they were to get special treatment. C patients did not know

throughout their stay in hospital that they were control patients in a special study; they were in fact treated as they would have been in the past, the sole difference being that they had been admitted to the centre more rapidly than was normal. Usually they were not in the same wards as S patients, but the same regime was maintained

Sir Bradford Hill had been anxious that physicians would be unwilling to give up the doctrine of anecdotal experience. However, the trial quickly became a model of design and implementation and gave a boost to Dr Hill's views and subsequent teaching, and resulted, after some years, in the present virtually universal use of randomised allocation in clinical trials. ⁶ The greatest influence of this trial lay in its methods which have affected virtually every area of clinical medicine. ⁸ Over the years, as the discipline of controlled trials grew in sophistication and influence, the streptomycin trial continues to be referred to as ground breaking. ⁸

Evolution of Ethical and Regulatory Framework

The ethical framework for human subject protection has its origins in the ancient Hippocratic Oath, which specified a prime duty of a physician - to avoid harming the patient. However, this oath was not much respected in human experimentation and most advances in protection for human subjects have been a response to human abuses e.g. World War II experiments.

The first International Guidance on the ethics of medical research involving subjects - the Nuremberg Code was formulated in 1947. Although informed consent for participation in research was described in 1900, the Nuremberg Code highlighted the essentiality of voluntariness of this consent. ⁹ In 1948, Universal Declaration of Human Rights (adopted by the General Assembly of the United Nations) expressed concern about rights of human beings being subjected to involuntary maltreatment. ⁹ The brush with thalidomide tragedy helped the U.S. pass the 1962 Kefauver-Harris amendments, which strengthened federal oversight of drug testing and included a requirement for informed consent. ¹⁰

In 1964 at Helsinki, the World Medical Association articulated general principles and specific guidelines on use of human subjects in medical research, known as the Helsinki Declaration. The Helsinki Declaration has been undergoing changes every few years the last one being in 2008. However, the use of placebo and post-trial access continue to be debatable issues.

In 1966, the International Covenant on Civil and Political Rights specifically stated, 'No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his consent to medical or scientific treatment.'⁹ Dr. Henry Beecher's 1966 study of abuses and the discovery of human exploitation of Tuskegee study in the 1970s reinforced the call for tighter regulation of government funded human research.¹⁰ The US National Research Act of 1974 and Belmont Report of 1979

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were major efforts in shaping ethics of human experimentation. In 1996, International Conference on Harmonization published Good Clinical Practice, which has become the universal standard for ethical conduct of clinical trials.

In parallel to ethical guidelines, clinical trials started to become embodied in regulation as government authorities began recognizing a need for controlling medical therapies in the early 20th century. The FDA was founded in 1862 as a scientific institution and became a law enforcement organization after the US Congress passed the Food and Drugs Act in 1906. After that, legislation progressively demanded greater accountability for marketing food and drugs and the need for testing drugs in clinical trials increased. The regulatory and ethical milieu will continue to evolve as new scientific disciplines and technologies become part of drug development.

Evolution of Clinical Trials in India

India has recently been recognized as an attractive country for clinical trials. But the country's journey in clinical research field has a long history. India has a rich heritage of traditional medicine – Ayurveda. The classic ayurvedic texts contain detailed observations on diseases and in-depth guidance on remedies. It is likely that these descriptions are based on direct observations made by the ancient ayurveda experts. However, there is no recorded documentation in the ancient texts of any clinical experiments. Hence, one has to fall back on current history of medical research in India.

The major historic milestones of the Indian Council of Medical Research reflect, in many ways, the growth and development of medical research in the country over the last nine decades. First meeting of the Governing Body of the Indian Research Fund Association (IRFA) was held on November 15, 1911 at the Plague Laboratory, Bombay, under the Chairmanship of Sir Harcourt Butler.¹¹ At the 2nd meeting of the Governing Body in 1912, a historic decision was taken to start a journal for Indian Medical research. Between 1918-20, several projects on beriberi, malaria, kala azar and indigenous drugs were initiated. In 1945, a Clinical Research Unit - the first research unit of IRFA attached to a medical institution- was established at the Indian Cancer Research Centre, Bombay. In 1949, IRFA was redesignated as the Indian Council of Medical Research. Over next 60 years, ICMR established many national research centers in the fields of nutrition, tuberculosis, leprosy, viral disease, cholera, enteric disease, reproductive disorders, toxicology, cancer, traditional medicine, gas disaster, genetics, AIDS etc.

The Central Ethical Committee of ICMR on Human Research constituted under the Chairmanship of Hon'ble Justice (Retired) M.N. Venkatachaliah held its first meeting on September 10, 1996. Several subcommittees were constituted to consider ethical issues in specific areas e.g., Epidemiological Research; Clinical Evaluation of Products to be used on Humans; Organ Transplantation; Human Genetics,

etc. The committee released Ethical Guidelines for Biomedical Research on Human Participants in 2000 which were revised in 2006.⁹

Schedule Y of Drugs and Cosmetics Act came into force in 1988 and established the regulatory guidelines for clinical trial (CT) permission. The schedule did force the industry to conduct Phase III clinical trials for registration of a new drug and supported growth of a predominantly generic Indian pharmaceutical industry. However, this schedule only permitted clinical trials at a phase lower than its global status. This phase lag obstructed integration of India in global clinical development.

The next major step has been revision of Schedule Y in Jan 2005.¹² As compared to Schedule Y 1988, which had narrow and restrictive definitions of clinical trial phases, the amended Schedule Y 2005 provided pragmatic definitions for Phase I to IV.¹² The definitions and guidelines for clinical trial phases are broad and rational. The earlier restrictions on number patients and centers in early phases stipulated in Schedule Y 1988 were removed allowing the sponsor company freedom to decide these in relation to protocol requirements. The phase lag requirements gave way to acceptance of concurrent Phase II-III as part of global clinical trials.

Schedule Y 2005 legalized Indian GCP guidelines of 2001. This schedule stipulated GCP responsibilities of ethics committee (EC), investigator and sponsor and suggested formats for critical documents e.g. consent, report, EC approval, reporting of serious adverse event. These amendments in Schedule Y have been a major step forward in direction of GCP compliant trials and have provided the much-needed regulatory support to GCP guidelines.

Since the Scurvy trial, clinical trials have evolved into a standardized procedure, focusing on scientific assessment of efficacy and guarding the patient safety. As the discipline of drug development is enriched by novel therapies and technologies, there will always be a continuing need to balance medical progress and patient safety. As the scientific advances continue to occur, there will be new ethical and regulatory challenges requiring dynamic updates in ethical and legal framework of clinical trials.

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