



Clinical trials - from anecdotes to evidence based medicine

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Treatments based on theory and anecdote with extravagant public claims without being properly tested has become past time in medical practice. Only valid unbiased and relevant evidence obtained by methodology of clinical trials should be adopted in medical practice and practice guidelines. In such way clinical decisions are based on evidence rather than on authority. Inevitable part of clinical trials is medical ethics formally defined within the Nuremberg Code, World Medical Association Declaration of Helsinki and guidelines issued by the U.S. Department of Health, Education and Welfare. This paper presents in short history of clinical trials and current status worldwide.

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DEFINITION

Clinical trial is a clinical methodology whose aim is to test the effectiveness of the new drug or medical procedure in the treatment or prevention of the disease. Introduction of clinical trials in clinical practice has revolutionized the medical judgment and heralded the modern era of evidence-based medicine. The history of medical trials as an evolution of scientific thought, traces back to simple observational studies and remedy attempts created from the beginning by the authorities and fashion of the time.

The principal characteristics of the modern clinical trials are: 1. The use of a control and/or placebo group for the purpose of comparison; 2. Masked or blind assessment of the effect of treatment; 3. Random allocation of subjects to treatment and control groups, and 4. Informed consent. All these components of clinical trials have developed gradually and independently over the time as result of the need for an objective, unbiased and evidence-based results upon which medical professionals may rely on in their everyday treatment decision process (1).

HISTORY

It is almost biblical consideration that we need comparison in order to establish the difference, but it was invention and intro-

duction of statistics that has actually made it possible. There are many exemplars of comparative studies from seventeenth century on, with James Lind 1758 scurvy study of six different treatments in twelve scurvy sailors as the paradigm of treatment evaluation (2). Some basic terminology can we also found in the work of these pioneering investigators of the eighteenth and nineteenth century, like patients control group, use of the alternate controls i.e. randomization which made progress in those remote days of medical practice (3). However, the first publish use of the term clinical trial was done in 1931 in *The Lancet* and *The British Medical Journal* which heralded new era in drug development and considered not only scientific but economic and social implications as well as legal responsibilities of the participants, all of which are relevant today (3).

EUROPEAN EXPERIENCE

It is generally agreed that since streptomycin trial in the treatment of pulmonary tuberculosis in 1948 the medical practice has never been the same. It was designed, proposed, conducted and reported by The British Medical Research Council (MRC), tuberculosis unit with Sir Bradford Hill as the most prominent figure, and included several hospitals in London and the away. By September 1947 when trial had started several important events had made favorable conditions for the trial to be done. First of all, in 1943 streptomycin was discovered and proved to be effective against tuberculosis in many laboratory experiments in the USA with few clinical reports of promising results in patients. Medical statistics has approved the method of randomization as valuable one for patients selection in clinical trials, meeting in such way two important components of the trial: control group of patients in order to make comparison (placebo was not discussed at that

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time), and elimination of biases (3-5). Furthermore, it was double-blind trial because neither patients nor the doctors who evaluated the treatment effectiveness (two radiologists and one clinician) knew to which treatment the exact patient was allocated. Tuberculosis was a serious health problem at that time in the UK with 25 000 deaths per year and fifteen years long traditional treatment by bed rest and gold compounds failed to do any better (6). Therefore emerging need for better treatment results was obvious and committee approved the trial. As the amounts of streptomycin in 1947 were limited it was concluded that it should be best and fairly applied through the clinical trial. Neither of the patients, treated and control knew at that time they were enrolled within the clinical trial and whole procedure was strictly confidential for the public. The design and conduct of the trial had been remarkably defined (7-9). This included precise definition of patient entry criteria, random allocation with sealed envelopes, which were opened in the central office indicating in which treatment group the patient was allocated, and this information was proceed to medical officer in the center (10). The time frame for follow-up was decided to be six months while the treatment lasted four months. The case report form was specially done for this trial. Trial coordinator provided regular meetings with participants and discussed the progress and problems of the trial. The treatment dose, route and duration of administration as well as recommendations for acute actions were also prescribed. At the end the public report was done in 1948 stating statistically significant difference in mortality (7% vs. 27% in the control group) what had enormous medical, social and economic implications (4).

USA EXPERIENCE

Nevertheless enthusiasm and good intentions of medical professionals even most reverent ones, have not always rewarded the human kind with health and social benefits. "The Tuskegee study of untreated syphilis in the Negro male" is the study done by the Public Health Service (PHS) in the Macon County, Alabama, USA, lasted almost forty years until it was made public (11). In 1931, when study was commenced, the incidence of the syphilis among southern blacks was very high, the treatment was unattainable for the majority of them and, at that time, it was believed that the syphilis in blacks had more indolent natural course, what made rationale for the study. The study enrolled 399 men with syphilis and 201 uninfected as a control. Although they were said to be in the study, they were unaware of the diagnosis and therefore spread of the disease was not under control. The initial decision for the study to last one year with few months of traditional treatment of the time (mercury, arsenical compounds, bismuth ointments) was revised and the study continued with annual follow-up of participants who remained withhold from the treatment. Although the study participants genuinely believed in the values of

examinations there is no evidence that they were actually treated of any complications of the disease. The rationale for such decision at that point has remained obscure ever since, and the study continued thereafter for forty years. In 1943, the penicillin was discovered and soon after recommended by the PHS as the effective drug against the syphilis but the participants had remained deprived of the effective treatment. It is interesting that several articles on the study was published in respected medical journals and although some did question the ethical issues of the study it took several years until it was terminated in 1972 (12). I hope, majority will agree, that the knowledge of the natural course of the syphilis accomplished by this study cannot excuse the harms done to the untreated participants. By the end of the study twenty-eight men had died of the syphilis, hundred others were dead of related complications, at least forty wives had been infected and nineteen children had contracted the disease at birth. The ever-lasting question "How could it happen?" should keep alerted scientific, civilized and human world to prevent the history of repetition. The study was proposed and conducted by the PHS whom people, especially uneducated one use to trust for their well-being. However, the PHS failed to justify this trust but abused the racial, social and economic circumstances of the African-American instead; it has created very delicate issue of low participation of the blacks in clinical trials to nowadays. Furthermore, there were many African-Americans among the doctors who approved and conducted the study. It is questionable whether it can be simply assumed that they were deceived with the so-called "racial medicine" concept only, or were driven in their decisions by some other practical reasons rather than tackling the syphilis among blacks in the Macon County. It took too long before the question on rationale and ethical compliance came into consideration. Besides, it is difficult to accept the racial exploitation after the Nuremberg process and Nuremberg Code, which was defined in 1947. Is it ignorance, arrogance, indifference, terror of the authorities that ban the implementation of what has already been comprehended? In my opinion it was a sad failure of humankind and responsibility lays primarily on medical society in its broad sense (13).

ETHICAL ISSUES

Inevitable part of clinical trials is medical ethics. The Hippocratic oath *primum non nocere*, which refers to doctor to make judgment on patient benefit of the treatment, has been extended for the purpose of the medical research to ethical codes and guidelines. The Nuremberg Code of 1947, the Declaration of Helsinki of 1964 and 1971 guidelines issued by the U.S. Department of Health, Education and Welfare are the best known (3,14-17). The hallmark of these codes and guidelines is to ensure protection of human subjects involved within the research, to define the oblig-

ations and the responsibilities of investigators and institutions involved in the research. Since the World-War II and Nuremberg Code, the voluntary consent of the human subject preferably in written form has been established as absolutely essential for clinical trials. In the light of these guidelines I would discuss the already mentioned trials as follow: in the streptomycin trial patients were not told of being enrolled in the study while in Tuskegee trial they were informed of being in the study but completely uninformed on disease and the study objectives. In both studies the written consent was missing. During the streptomycin trial the medical professionals and the institutions did provide the best medical treatment for the participants while the subjects involved in Tuskegee study were hardly given any treatment and their economically and medically disadvantaged situation was actually abused. Furthermore, the results of the streptomycin trial were made public and they had huge social implications, while the Tuskegee study became public after the Senate investigation had been done, but unfortunately African-Americans did benefit from participation in the trial.

CANCER CHEMOTHERAPY TRIALS

Regarding cancer chemotherapy the first clinical trial was done in 1954 by the National Cancer Institute on acute lymphocytic leukemia in which two different schedules of 5-mercaptopurine and methotrexate were investigated in five collaborative centers. By 1970, the number of cooperative cancer groups in the USA had increased substantially and had been established as a proper way to conduct clinical trials. However in these trials the monotherapy was applied in order to achieve the tumor shrinkage rather than to consider the patient survival as the primary objective. In addition, they were not disease orientated and although they did not improve the cancer patients' benefit and would be considered inadequate by today standards they made very important basis for modern cancer clinical trials. The study of Fisher et al. did the breakthrough in 1977 in primary breast cancer. The randomized, double blind trial comparing L-PAM and placebo after mastectomy, for patients with axillary node involvement, showed fewer relapses on L-PAM for premenopausal patients, and subsequent follow-up confirmed the survival advantage. Also in 1977, Bonadonna et al. in Italy prove that the combination of three cytotoxic drugs, today well-known CMF regimen, markedly improves survival in premenopausal patients. Recently, important achievements have been the development of combined modality trials, new drugs, targeting drugs, drug combinations in metastatic disease and as an adjuvant to primary surgical treatment of cancer. The strategy of seeking and destroying cancer has been extended into targeting and controlling cancer. The number of collaborative trial cancer groups in USA and Europe has increased even more today accruing thousands of cancer

patients. Although some rebuke such intensive research for overzealous recommendations of highly toxic and marginally effective regimens, the clear advances in leukemia, lymphoma and breast cancer justify this approach.

CONCLUSION

According to the Cochrane collaboration registry for the last fifty years the third of million clinical trials have been done (18). They undoubtedly have a place in shaping evidence-based medical practice (19). Unfortunately, many of them do not meet either methodological or statistical standards and therefore represent waste of time, the enthusiasm of the participants and otherwise better spent money (20). Also the delay of the distribution of positive results and their implementation in everyday practice has been recognized. On the other hand randomized control trials deliver us from the chaos of well-intentioned but possibly misguided expertise and represent scientific and democratic way of generating knowledge.

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