MJoTA Publisher. Clinical Trials. How drugs are tested on humans: the evolution of clinical trials. MJoTA 2007:1(1):36-37.

CLINICAL TRIALS

How Drugs Are Tested on Humans: The Evolution of Clinical Trials

Republished from MJoTA 2007 1(1):36-37

"A drug tragedy in Europe, the births of thousands of deformed infants whose mothers had taken the new sedative thalidomide, focused public attention on pending U.S. legislation to further strengthen the Federal Food, Drug, and Cosmetic Act. The Drug Amendments of 1962, passed unanimously by the Congress, tightened control over prescription drugs, new drugs, and investigational drugs. It was recognized that no drug is truly safe unless it is also effective, and effectiveness was required to be established prior to marketing ..... Drug firms were required to send adverse reaction reports to FDA, and drug advertising in medical journals was required to provide complete information to the doctor -- the risks as well as the benefits." from www.cfsan.fda.gov

If a manufacturer wants to sell a drug, device or vaccine for use in humans, the manufacturer has to convince the United States Food and Drug Administration that the product works the way the manufacturer claims, and any harm to humans is offset by greater benefits. The way the manufacturer proves this is through clinical trials.

According to the United States government website ClinicalTrials.gov, a clinical trial is "a research study in human volunteers to answer specific health questions". Clinical trials have been the tools for determining whether a therapy works better than nothing for decades, perhaps for millennia.

The first recorded clinical trial was of the biblical Daniel testing the effects of a diet of pulses rather than meat: "In the third year of the reign of Jehoiakim king of Judah came Nebuchadnezzar king of Babylon unto Jerusalem, and besieged it...And the king appointed [4 children] a daily provision of the king's meat, and of the wine which he drank: so nourishing them 3 years, that at the end thereof they might stand before the king...But Daniel purposed in his heart that he would not defile himself with the portion of the king's meat, nor with the wine which he drank [and said to the king]... Prove thy servants, I beseech thee, 10 days; and let them give us pulse to eat, and water to drink. Then let our countenances be looked upon before thee, and the countenance of the children that eat of the portion of the king's meat: and as thou seest, deal with thy servants. So he consented to them in this matter, and proved them 10 days. And at the end of ten days their countenances appeared fairer and fatter in flesh than all the children which did eat the portion of the king's meat. Thus Melzar took away the portion of their meat, and the wine that they should drink; and gave them pulse." (King James Bible, Daniel Ch1).

Daniel's requirement for food that differed from the munificent diet given by King Nebuchadnezzar follows the requirements for open-label clinical trials and was far more successful than most modern clinical trials.

The results from Daniel's unintentional clinical trial were clear cut and did not require imported specialist statisticians to prove that the sponsor's therapy was better than standard care; which is what I observed once when I was working as a medical writer in a small pharmaceutical company in New Jersey. This analysis did not impress the US regulatory body, the Food and Drug Administration (FDA), and the sponsor's new drug application (NDA) for marketing authorization was rejected.

The 3 phases of modern clinical trials are defined according to progression through development. These phases are defined by US statute. Posted on www.FDA.gov are the sections from the Code of Federal Regulations, Title 21, Volume 5.

Simply, the FDA wants to know when, why and how much of each new drug is given to any human. Phase 1 trial protocols are designed as part of the Investigational New Drug (IND) application with volunteers (healthy or with the indicated disease) taking defined doses of drug for a defined time to determine drug doses, pharmacokinetics and side effects of taking this therapy. When the new therapy is determined safe, volunteers with the disease which the new drug is designed to treat are enrolled in phase 2 clinical trials. They are either given placebo or drug. When the minimum dose for maximum effect is calculated, volunteers with the disease are enrolled in larger numbers in phase 3 clinical trials and given placebo or the optimal dose for a defined time. If the drug is still believed to be safe and effective after the 3 trial phases, and if the pharmaceutical company is ready to market the drug, all the documentation associated with development and clinical trials is packaged according to United States FDA requirements and a New Drug Application is filed.

Pharmaceutical therapies may be further tested after they are FDA-approved, these post-marketing clinical trials are known as phase 4 clinical trials. Phase 4 trials are also run by pharmaceutical company wanting to explore the effectiveness of their drug in treating diseases other than the 1 for which the FDA approved it (http://prsinfo.clinicaltrials.gov/definitions.html). Phase 4 trials can be risky: the results of a phase 4 trial of the pain reliever rofecoxib, resulted in its withdrawal from the market in September 2004, and, 6 months later, the withdrawal of another of its class, valdecoxib, from another

CLINICAL TRIALS

pharmaceutical company.

I wanted to know how clinical trials progressed from being odd things that biblical heroes impressed potentates with to being complex and legal mechanisms by which all therapies and devices are tested. The James Lind Library, launched in 2003 by The Royal College of Physicians of Edinburgh, is an online resource for tracking clinical trials, www.jameslindlibrary.org. The first recorded clinical trial they report is the biblical Daniel's, the second was from 11th century China and the third from 16th century France. But the Edinburgh surgeon James Lind (1716-94) who investigated the best treatment for scurvy and from whom the library takes its name was probably the first person clinical investigator running a controlled clinical trial of the modern era

"On the 20th of May 1747, I selected 12 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 1 place, being a proper apartment for the sick in the fore-hold; and had 1 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 25 drops of elixir vitriol 3 times a day ... Two others took 2 spoonfuls of vinegar 3 times a day ... Two of the worst patients were put on a course of sea-water ... Two others had each 2 oranges and 1 lemon given them every day ... The 2 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; 1 of those who had taken them, being at the end of 6 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 ...". Taken from Dr James Lind's "Treatise on Scurvy" published in Edinburgh in 1753, and quoted by Dr Peter Dunn (1997;76;64-65 Arch. Dis. Child. Fetal Neonatal Ed)

Dr Lind reacted to a problem which had not been in existence before improvement in sail engineering enabled ships to leave land and sail oceans and seas without landing for months. However, his interpretation of his clinical trial results was right in general and wrong in specifics; he concluded that citrus fruits prevented or cured, which is correct, but he suggested this effect was through their action on the digestive processes, which is not correct. How Dr Lind interpreted his results is irrelevant; after a lag of 50 years, directly because of James Lind, British sailors' rations included citrus fruits.(Cook DG. Postgrad Med J. 2004;80:224-229)

After the report of this scurvy trial in 1753, the number of reports of clinical trials increased. The number of clinical trials reported in journals indexed by the US National Library of Medicine has steadily increased since 1950, when "A controlled investigation of streptomycin treatment in tuberculosis" was reported by Long and Ferebee (Public Health Reports vol 65 pp1421-51). During 1974, 175 papers had "clinical trial" in the title and "controlled" in the keywords, this had increased to 215 during 1984, 715 during 1994, and 1,945 during 2004.

Clinical trials became required by law as governing authorities began recognizing a need for regulating pills, potions and ointments 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 more accountability for marketing food and drugs, and clinical trials of drugs increased. The changes in the law are known as the Kefauver-Harris Drug Amendments 1962.

The increase in clinical trial data led to the increasing number of jobs for medical writers in the pharmaceutical industry in Europe and the United States. The downside of the increase in clinical trial data has been the lack of control of how these data are reported; in a 2005 article published by the European Medical Writers Association (emwa.org), I described the practice of guest authorship in which healthcare professionals claim authorship credit for medical journal articles which they did not write from data they neither collected nor analyzed. This article attracted the attention of a journalist from the Wall Street Journal, and an example I quoted was given in an article she wrote (Dec 13, 2005. p p A1). The dialogue continues as clinical trials generate increasingly more data.

Medical writers understand medical science, clinical data and the rules and regulations of their reporting. My hope is these pharmaceutical industry professionals will have more control in the design of clinical trials and in the analysis of the data.

by SJ Dodgson PhD