



The evolution of clinical trials

by Susanna J Dodgson

According to the US government website ClinicalTrials.gov a clinical trial is “a research study in human volunteers to answer specific health questions” [1]. Clinical trials so defined 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 (see Box).

“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 three 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, ten 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 ten 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 were clear cut and did not require imported specialist statisticians to prove that the sponsor’s therapy was better than standard care as I observed in a single phase 3 clinical trial for a cancer therapy. This therapy 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.

I wanted to know how clinical trials progressed from being odd things that biblical heroes dabbled in to impress potentates 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 [2]. 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 to have conducted a controlled clinical trial of the modern era (see Box).

“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 ...”.

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 was the most modern of scientists; he 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, like many modern scientists, his interpretation of his clinical trial results was way off the mark; he concluded that citrus fruits cured scurvy because of their action on the

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digestive processes. 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 [5].

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 [6]. 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 1945 during 2004.



James Lind. Published with kind permission from The James Lind Library, www.jameslindlibrary.org.

Clinical trials started to become embodied in legislature 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 greater accountability for marketing food and drugs and the need for testing drugs in clinical trials increased. "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 US 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 the FDA, and drug advertising in medical journals was required to provide complete information to the doctor — the risks as well as the benefits." [7]. The changes in the law are known as the Kefauver-Harris Drug Amendments 1962.

The increase in clinical trial data has led to the increasing number of jobs for medical writers in the pharmaceutical industry. The downside of the increase in clinical trial data has been the lack of control of how these data are reported; I have in a previous article described the practice of guest authorship in which healthcare professionals claim authorship credit for medical journal articles for which they neither wrote nor analyzed the data [8]. This article attracted the attention of a journalist from the Wall Street Journal, and an example I quoted was given in a recent article which she wrote [7]. The dialogue continues as clinical trials generate increasingly greater amounts of data. My hope is that medical writers will take control of clinical trials, have the understanding and the scientific background to design clinical trials, and be increasingly recognized as clinical science professionals.

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The Story Of The Laws Behind The Labels

A series of articles on the FDA's website provide further interesting information about the history of the FDA and laws governing the marketing of food and drugs. www.cfsan.fda.gov/~lrd/history1.html

Language Quiz

The answer to the language quiz on page 12 is **Vietnam**. The official Roman writing was established by missionaries.