

Module II: The Trial Landscape

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The history of clinical trials The first known trial?

605-562 BC:

King Nebuchadnezzar II carried out the first clinical trial

- those who had switched to bread and water appeared more resplendent and well nourished than those who had not.



The history of clinical trials Open wound trial

1537:

Surgeon Ambroise Parè mixes a concoction of oil of rose, turpentine and egg yolk as a replacement for the accepted medicament for treating open wounds.



The history of clinical trials The usage of controls

1747
James Lind proves the effectiveness of lemon juice in preventing scurvy. His experiment is known as one of the first widely known controlled clinical trials. <http://www.jameslindlibrary.org>

BC 1900 1945

The history of clinical trials A land breaking trial in 1948

The first clinical trial with a properly randomized control group was for streptomycin treatment of pulmonary tuberculosis as reported by the Medical Research Council, UK in 1948.

Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. *BMJ* 1948; 2: 769-782.

BC 1900 1945

The history of clinical trials A land breaking trial in 1950

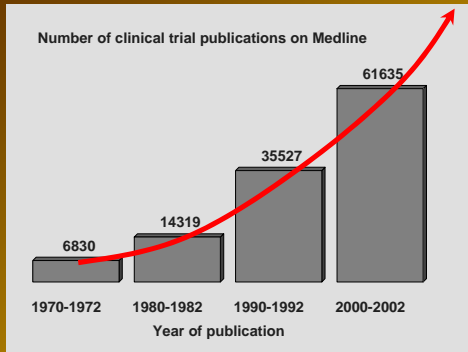
Another randomized controlled trial, for antihistamine treatment of the common cold by the Medical Research Council, UK in 1950, used a placebo control in a double-blind manner.

Medical Research Council (1950). Clinical trials of antihistaminic drugs in the prevention and treatment of the common cold. *BMJ* 2:425-431.

BC 1900 1945

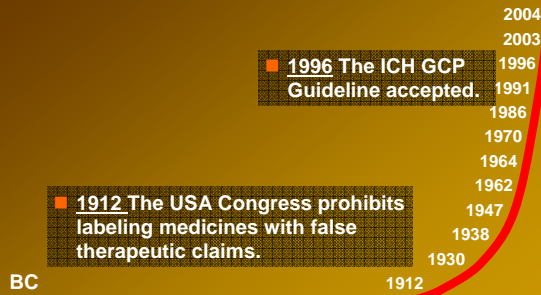
The history of clinical trials

The number of clinical trial publications



The history of clinical trials

Milestones of clinical trial regulations



The history of clinical trials

Milestones of clinical trial regulations

- 1912 The USA Congress prohibits labeling medicines with false therapeutic.
- 1930s Great Britain establish a Therapeutic Trials Committee managing clinical trials to study new drugs.
- 1938 After 107 people die after taking sulfanilamide, the US Food, Drug, and Cosmetic Act enforces the need for manufacturers to demonstrate safety.
- 1947 Post second world war the Nuremberg Codex establishes ten points for the protection of subjects and patients in clinical trials.
- 1962 Passage of the Kefauver-Harris Drug Amendment in the USA; proof of efficacy required for new drug approval, in addition to proof of safety.

The history of clinical trials Milestones of clinical trial regulations

- **1964** The World Medical Association develops the Declaration of Helsinki. This serves as a statement of ethical codes to provide direction for physicians and other participants in medical research involving human subjects.
- **1970** The 1962 US drug effectiveness is amended by ruling that commercial success alone does not constitute substantial evidence of drug safety and efficacy. This must be provided by well-conducted, well-controlled clinical trials.
- **1986** Individual countries such as Great Britain, France, Germany, and the Scandinavian countries issue Good Clinical Practice recommendations. These were soon ordered in 1989 into the GCP recommendations of the European community.

The history of clinical trials Milestones of clinical trial regulations

- **1991** Passage of a European Union directive. Compulsory criteria for the authorization of a medicinal product for sale on the European market are quality, safety, and efficacy. Safety and efficacy must be demonstrated in clinical trials.
- **1996** The ICH GCP Guideline accepted in EU, US and Japan – the ‘bible’ for the conduct of clinical trials.
- **2003** In December 2003 the US launched the Pediatric Research Equity Act (PREA) request the assessment of safety and effectiveness of new drugs or biological products for the claimed indications in children.
- **2004** Directive 2001/20/EC became a legal document in May 2004 in all 25 EC member states. The directive provides new requirements for clinical research teams for investigators conducting non-commercial trials.

The history of clinical trials The Cochrane Collaboration

- The Cochrane Collaboration is an international non-profit and independent organisation
- It produces and disseminates systematic reviews of healthcare interventions and promotes the search for evidence in the form of clinical trials and other studies of interventions.
- The Cochrane Collaboration was founded in 1993 and named for the British epidemiologist, Archie Cochrane.
- <http://www.cochrane.org/>

The history of clinical trials

The Cochrane Collaboration - Principles

- For all but the last century, decisions on how to treat patients were almost always based on personal experience.
- The randomised trial has provided a research design that will provide much more reliable estimates of the relative effects of interventions.
- The results of a single trial will rarely be sufficient in many circumstances. Most trials are too small and their results are not sufficiently robust against the effects of chance.

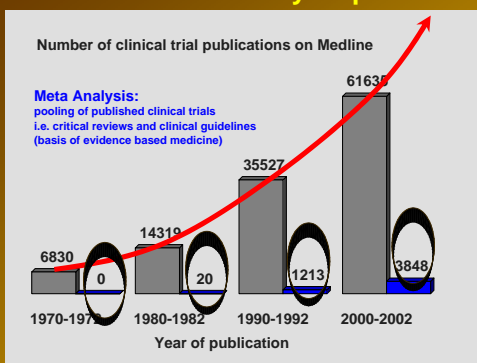
The history of clinical trials

The Cochrane Collaboration – Systematic review

- The amount of information about health care, including that coming from individual randomised trials, is now overwhelming.
- Results from similar randomised trials need to be brought together. Trials need to be assessed and those that are good enough can be combined to produce both a more statistically reliable result
- This combination of trials needs to be done in as reliable a way as possible. It needs to be a so called systematic review.
- If the results of the individual studies are combined to produce an overall statistic, this is usually called a meta-analysis.

The history of clinical trials

The number of meta-analysis publications



The history of clinical trials

The Cochrane Collaboration – Review Groups

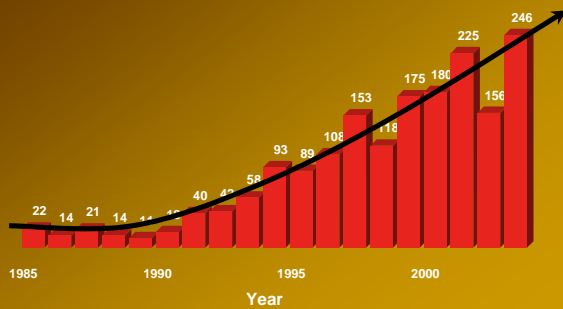
Collaborative Review Groups, examples

- Acute Respiratory Infections Group
- Airways Group
- Anaesthesia Group
- Back Group
- Breast Cancer Group
- Colorectal Cancer Group
- Consumers and Communication Group
- Cystic Fibrosis and Genetic Disorders Group
- Dementia and Cognitive Improvement Group
- Depression, Anxiety and Neurosis Group

The history of clinical trials

The number of “Guideline” publications

Number of "Guidelines" publications on Medline



Conclusion

The history of clinical trials

- **Trial Design:** Started in 1950 by the first randomized placebo control double-blind trials and has recently become a concept in medical practice in terms of evidence based medicine.
- **Ethics and quality:** The Nuremberg Codex in 1947, the Declaration of Helsinki in 1964 and the ICH GCP in 1996.
- **Regulations:** Continuously from 1912 when the USA Congress prohibits labeling medicines with false therapeutic, later on followed for instance by to the passage of a European Union directive in 1991, and the US Pediatric Research Equity Act in 2003.
