**SUPPLEMENTAL DIGITAL CONTENT**

For

2000 Years of Clinical Trials: The Evolution of Evidenced-Based Practice

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By

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**ABSTRACT:** Although the first documented clinical trial as described in the biblical book of Daniel dates to 606 BC, the prophet Daniel’s nutrition study is contemporary in both approach and topic and could be considered the first *comparative effectiveness research* (CER) trial. This article summarizes the historical evolution of clinical trials and associated regulatory legislation and ethical considerations foundational to nursing and evidence-based practice (EBP) in the 21st century. Distinguishing features of CER, various study designs and checklists, and EBP are detailed. Biblical foundations for research and the Bible’s relevance to modern research methods are discussed.

**KEY WORDS:** Bible; clinical trial; clinical trial history; comparative effectiveness research; ethics; evidence-based practice; nursing; patient-centered outcomes research

Table 1. Timeline of Significant Research Milestones

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| --- | --- |
| **Year** | **Major milestone** |
| 605 BC | Book of Daniel recorded first clinical trial |
| 500 BC | The Hippocratic Oath |
| 1537 | Ambroise Paré—comparative treatment of gunshot wounds |
| 1747 | James Lind—scurvy trial |
| 1800 | Arrival of placebos |
| 1803 | First mention of the need for peer review |
| 1850 | Birth of Florence Nightingale, first nurse researcher and theorist |
| 1870 | Marine Hospital Service established |
| 1887 | National Institutes of Health (NIH) founded |
| 1902 | Marine Hospital Service became the U.S. Public Health and Marine Hospital Service |
| 1906 | Food and Drug Administration’s Pure Food and Drug Act launched. |
| 1912 | Public Health and Marine Hospital Service changed to Public Health Service (PHS) |
| 1928 | Sir Alexander Fleming discovered penicillin |
| 1932-1972 | Tuskegee Syphilis Study |
| 1937 | Elixir sulfanilamide disaster |
| 1938 | Federal Food, Drug and Cosmetic Act |
| 1939-1945 | World War II experiments |
| 1943 | First double-blind controlled trial—patulin for common cold |
| 1944 | Multicenter studies began |
| 1944 | PHS act divided into the Office of the Surgeon General, Bureau of Medical Services, Bureau of State Services, and the National Institutes of Health (NIH) |
| 1944-1974 | Human radiation experiments |
| 1946 | First randomized curative trial—randomized controlled trial of streptomycin |
| 1946 | Communicable Disease Center organized in Atlanta, Georgia |
| 1947 | Nuremberg Code |
| 1948 | Universal Declaration of Human Rights |
| 1950 | CDC's Epidemic Intelligence Service (EIS) founded |
| 1950s | Formal code of nursing ethics developed by the American Nurses Association (ANA) |
| 1951 | Henrietta Lacks unknowingly had cells taken from her tumor for research |
| 1952 | *Nursing Research* journal established |
| 1953 | First International Code of Ethics for Nurses adopted by the International Council of Nurses |
| 1960's | Harvard psilocybin experiments  American Nurses Association establishes Commission on Nursing Research |
| 1962 | Kefauver-Harris Drug Amendment—requirement of rigorous clinical trials |
| 1963 | Milgram experiment |
| 1964 | Declaration of Helsinki |
| 1968 | First Data and Safety Monitoring Board |
| 1970 | Communicable Disease Center (CDC) renamed Center for Disease Control |
| 1970's | *Research in Nursing and Health, Advances in Nursing Science*, and *Western Journal of Nursing Research* journals established |
| 1972 | Office of Technology Assessment authorized |
| 1974 | National Research Act |
| 1974 | FDA formed Bureau of Medical Devices and Diagnostic Products |
| 1976 | Medical Device Amendments Act |
| 1978 | National Center for Healthcare Technology established |
| 1979 | The Belmont Report |
| 1980’s | *Clinical Nursing Research* journal established |
| 1981 | FDA Regulations Title 21 |
| 1982 | FDA approved Humulin, the first genetically engineered drug |
| 1986 | National Center for Nursing Research (NCNR) established within the U. S. Public Health Service (USPHS) |
| 1989 | Agency for Healthcare Policy and Research (AHCPR) established |
| 1990 | International Conference on Harmonization Guidelines |
| 1990 | Safe Medical Devices Act |
| 1991 | Common Rule (Title 45, part 46 in the Code of Federal Regulations) |
| 1992 | Congress changed CDC's name to the Centers for Disease Control and Prevention |
| 1993 | NCNR retitled National Institute of Nursing Research (NINR) and moved to a center within the NIH |
| 1993 | MedWatch (reporting system for adverse events associated with medical devices) |
| 1996 | Agency for Healthcare Policy and Research (AHCPR) renamed Agency for Healthcare Research and Quality (AHRQ) |
| 1996 | Health Insurance Portability and Accountability Act (HIPAA) |
| 1996 | National Bioethics Advisory Commission established |
| 1996 | World Health Organization issued Guidelines for Good Clinical Practice |
| 1997 | Congress requires clinical trial registration |
| 1998 | *Encyclopedia of Nursing Research* published |
| 2000 | NIH released ClinicalTrials.gov website |
| 2009 | American Recovery and Reinvestment Act |
| 2010 | Patient Protection and Affordable Care Act |
| 2010 | Patient-Centered Outcomes Research Institute (PCORI) established |

*Note:* The following references provided substantial information for this table:

LifeProNow. (2019, December 3). *The history of clinical research.* <https://www.lifepronow.com/2019/12/03/the-history-of-clinical-research/>

IMARC. *The history of clinical research: A timeline provided by IMARC.* (n.d.) <https://cdn2.hubspot.net/hub/149400/file-410979295-pdf/docs/CRT_Timeline_download.pdf>

Table 2. Phases of Clinical Trials

|  |  |
| --- | --- |
| **Trial phase** | **Description** |
| Pre-clinical studies (also called laboratory studies) | * Before a medication can be used in humans, extensive preclinical studies (in vitro [test tube or cell culture] or in vivo [animal model]) are performed. * The level of harm typically is measured in terms of toxicity. * How a treatment works in an animal may be very different than how the same treatment will work in humans. Increasingly, toxicologic testing in animals and preclinical animal studies in drug development are being questioned because of poor correlation with human results and increasing concerns regarding animal rights and other ethical concerns. |
| Phase 0 | * A newer exploratory trial design targets the pharmacokinetics and pharmacodynamics of an investigational new drug (IND). * Limited number of subjects are given a micro-dose (less than 1% of the therapeutic dose). * The goal is to quickly establish whether an agent will work as desired in humans and to quickly eliminate ineffective drugs. * Studies are very short (normally less than a week). * Not all drugs or interventions undergo phase 0 evaluation. |
| Phase I | * Usually conducted in humans to find the highest dose (through dose escalation) that can be given safely without severe side effects. * Depending on the disease, these trials may target patients with the disease of interest (such as cancer) or may target safety in healthy individuals. * The overall number of subjects is usually small, and time of study enrollment is relatively short (months to a year). * For pharmacological studies, outcomes target how the body absorbs, distributes, and eliminates the drug or substance. * Inactive treatments typically are not used, depending on the study design. * This phase trial carries the most potential risk and is typically the most labor-intensive due to the need to closely monitor subjects. * Safety is the main concern. |
| Phase II | * Typically, everyone gets the same dose; in some studies, participants are randomly assigned to different treatment groups. * These groups may get different doses or get the treatment in different ways or combinations to see which provides the best balance of safety and response. * Placebos (inactive treatments) typically are not used in phase II trials, but many exceptions exist. * Larger numbers of patients receive treatment in phase II trials compared to phase I, so less common side effects may be seen. * If enough patients benefit from the treatment and side effects are acceptable, phase III clinical trials begin. |
| Phase III | * These studies usually compare the safety and effectiveness of a new treatment against the current standard treatment. * Most phase III clinical trials include many subjects. * Trials are often conducted at multiple sites. * Normally, these studies take longer than phase I and II studies. * Placebos may be used in some phase III studies, but never used alone if an effective treatment is available. |
| Phase IV | * These studies target drugs already approved by the U.S. Food and Drug Administration (often comparing two acceptable treatments for equipoise or superiority) and are commonly referred to as post-marketing surveillance studies. * Studies are often large and may involve thousands of subjects--required to demonstrate a difference between a known or thought-to-be effective treatment or treatments. * Typically, this is safest type of clinical trial because the treatment has already been studied and found effective and likely has been given to many people. * Phase IV studies look at safety, frequently over a longer time than earlier studies, and within a larger or more inclusive group of subjects. This includes looking for rare complications and interactions. * These studies may look at other aspects of treatment, such as quality of life, utilization, or cost-effectiveness. |