

Milestones in Clinical Research

By Norman M. Goldfarb

Clinical research and its regulatory environment have evolved step-by-step over many years. Since Walter Reed administered written consent forms in a yellow fever transmission study in 1900, the pace of change has accelerated dramatically.

Table 1 includes over 200 milestones that mark sometimes erratic, but generally forward progress. In many cases, the milestones are the first of their kind, but this article generally does not make that claim. The sources in the bibliography tell parts of the story in much more detail, and what a fascinating story it is.

This article will be updated as new information becomes available. For example, the following events have not been identified:

- First clinical trial managed by a contract research organization (CRO)
- First independent (central) IRB
- First Data and Safety Monitoring Board (DSMB)
- First clinical trial with a recombinant DNA product
- First gene therapy clinical trial
- First adaptive clinical trial

There are, no doubt, other milestones that must endure the ignominy of exclusion until their existence is called the author's attention. For example, Table 1 is highly U.S.-centric. Although the author has attempted to verify the information in Table 1, there may be factual errors that cry out for correction.

Unless stated otherwise, the milestones occurred in the United States.

Table 1. Milestones

~600 BCE	Daniel designs and participates in a controlled nutritional study in the court of Nebuchadnezzar II, King of Babylon. Study is reported in the Old Testament sometime later.
~400 BCE	Hippocratic Oath defines responsibilities of physicians to their patients (with no mention of experimentation). Hippocrates, who lived in Greece probably sometime between 460 and 380 BCE, probably did not write the oath.
400- 200 BCE	Charaka Samhita, a textbook in verse of Ayurvedic medicine, is written in India.
~200	Sushruta Samhita, a textbook in verse of Ayurvedic surgery, is written in India.
137 BCE	Attalus III (Philometer), King of Pergamum, tests the effects of extracts from poisonous plants by offering them in beverages to his guests.
162	Galen moves to Rome, where he develops the science of experimental physiology.
~550	Babylonian Talmud (Niddah (30b)) tells story about Cleopatra, who, to settle an argument between two rabbis about how long it takes for male and female fetuses to develop, had slave girls impregnated and operated on at specified

- times to examine the development of the fetuses. The investigators reported that boys developed in 40 days and girls took 80 days.
- ~1030 Avicenna (Abū 'Alī al-Husayn ibn 'Abd Allāh ibn Sīnā), a Persian physician, publishes *The Book of the Canon of Medicine* (Qanun fi al-Tibb), setting forth seven rules for systematically evaluating the effect of drugs on diseases.
 - 1500s Paracelsus (Theophrastus Bombastus von Hohenheim), who traveled widely in Europe, teaches to investigate nature "not by following that which those of old taught, but by our own observation of nature, confirmed by... experiment and by reasoning thereon."
 - 1537 In the middle of a siege battle, physician Ambroise Paré of France runs out of boiling oil, the usual remedy for treating open wounds at the time, and discovers that treatment with a tincture of egg yolk, oil of rose, and turpentine reduces pain, swelling and mortality.
 - 1662 Jan Baptist van Helmont, a Flemish medicinal chemist and disciple of Paracelsus, proposes a randomized test of his treatments vs. that of other physicians with 200 to 500 fever and pleurisy patients, backed by a wager of 300 florins that is not accepted.
 - 1747 James Lind of Scotland conducts a study of the treatment of scurvy, assigning 12 sailors, in pairs, to citrus and five other potential treatments.
 - 1759 Francis Home of Scotland tests measles "vaccine" (blood from a measles patient) in 12 children.
 - 1760 Anton Storck of Vienna tests the effect of hemlock in increasing doses on himself.
 - 1767 English court rules in *Slater v. Baker & Stapleton* that informed consent is required prior to experimental medical treatment. Baker and Stapleton set and then rebroke Slater's fractured but healing leg to test a new device.
 - 1784 Under appointment by Louis XVI of France, a commission led by Benjamin Franklin conducts placebo-controlled and single-blinded (literally, by blindfolding the subjects) studies of the use of magnetism to treat various ailments.
 - 1796 Edward Jenner of England demonstrates that cowpox vaccination protects against smallpox by vaccinating and then exposing 12-year-old James Phipps to someone with smallpox.
 - 1799 John Haygarth conducts placebo-controlled and single-blinded (with sham wooden "medical devices") studies of the use of iron and brass rods to relieve pain.
 - 1803 Thomas Percival of England publishes "Code of Ethics", advising physicians to consult with colleagues before trying new remedies and treatments. Percival separately advises physicians not to inform the patient if the information would adversely affect the patient, the patient's family, or the community.
 - 1809 Scottish physician Alexander Lesassier Hamilton and two other army physicians conduct a clinical trial in which 366 sequentially-admitted sick soldiers are assigned in rotation to three physicians. One physician uses bloodletting; the other two do not. Mortality rate is 29% with bloodletting and 2% without.
 - 1813 Vaccine Act regulates vaccines.
 - 1820 Eleven physicians create the U.S. Pharmacopeia, which includes recommendations of the best drugs for treating diseases.

- 1824 Royal Society for the Prevention of Cruelty to Animals is founded in London.
- 1830 English physician J.W. Willcock writes: "When an experiment is performed with the consent of the party subjected to it after he has been informed that it is an experiment, the practitioner is answerable neither in damages nor on an original proceeding. But if the practitioner performs his experiment without giving such information and obtaining consent he is liable to compensate in damages any injury."
- 1831 English physiologist Marshall Hall proposes principles to govern animal experimentation.
- 1832 Physician William Beaumont signs a contract with Alexis St. Martin, a long-term research subject with a permanent gastric fistula (hole to his stomach), whereby Mr. Martin enlists in the Army for one-year – with no military duties – and receives payment of \$150.
- 1833 Physician William Beaumont publishes research ethical guidelines, including voluntary consent and right to withdraw.
- 1836 Army Surgeon General establishes library, later to become the National Library of Medicine, the world's largest.
- 1836 French physician Pierre-Charles-Alexandre Louis conducts a quantitative epidemiologic study of the treatment of pneumonia with bloodletting. (Bloodletting may relieve pulmonary edema – excess fluid in the lungs.) He finds that the duration of the disease is shorter in patients who are bled sooner rather than later, with the caveat that mortality is 76% higher.
- 1845 Max Simon writes that experimentation is necessary to advance science, but under no circumstances could a physician "sacrifice the interests of the individual to those of society" or to "scientific speculation."
- 1847 American Medical Association adopts a code of ethics, including the "sacred duty" to avoid disclosures that would discourage or depress the patient.
- 1849 In "Physician and Patient," Worthington Hooker discusses the doctor-patient relationship, writing that "the good, which may be done by deception in a few cases, is almost as nothing, compared with the evil which it does in many cases."
- 1852 Physician Marion Sims, the "father of gynecology," reports in the Journal of the American Medical Sciences that on his thirtieth attempt with slave women – probably without their informed consent and perhaps without their consent at all – he successfully repaired a vesicovaginal fistula (without anesthesia).
- 1865 In "An Introduction to the Study of Human Experimentation," French physiologist Claude Bernard states "Never perform an experiment that might be harmful to the patient even though highly advantageous to science or the health of others."
- 1866 American Society for the Prevention of Cruelty to Animals is founded.
- 1871 Court rules in *Carpenter v. Blake* that the physician must fully inform the patient before departing from standard medical practice.
- 1876 Britain passes Cruelty to Animals Act and Animals (Scientific Procedures) Act, protecting animals used in research.
- 1877 American Humane Association is founded to protect animals and, later, children.

- 1879 S. Potter and Eugene F. Storke conduct double-blind experiment at the Milwaukee Academy of Medicine, comparing a homeopathic remedy to a sugar pill.
- 1880 German physician Gerhard Armauer Hansen, co-discoverer of the leprosy bacillus, loses his license to practice medicine after deliberately infecting the eye of a patient with leprosy bacilli.
- 1883 Caroline Earl White founds the American Anti-Vivisection Society to protect animals from experimentation.
- 1884 Possibly after successful experiments with dogs, Louis Pasteur first tests an antidote to rabies on an infected child, but only after pleadings from the child's mother and consultations with two medical colleagues, who advise him that the child's death is inevitable without treatment.
- 1886 Dr. Charles Francis Withington, in "The Relation of Hospitals to Medical Education," advocates a "Bill of Rights" to "secure patients against any injustice from the votaries of science" because researchers "had no right to make any man the unwilling victim of such an experiment."
- 1887 Marine Hospital Service establishes Hygienic Laboratory to monitor arriving ship passengers for cholera, yellow fever, and other infectious diseases. Dr. Joseph Kinyoun is the sole employee for at least 14 years.
- ~1890 Russian physician D. V. Dmitriev creates an informed consent form for a volunteer donating part of his thyroid gland for transplantation. The document includes sections on explanation, risks, benefits, voluntariness, cost and procedures.
- 1895 Chemist Edwin E. Slosson writes in the New York Independent, "A human life is nothing compared with a new fact in science....the aim of science is the advancement of human knowledge at any sacrifice of human life....We do not know of any higher use we can put a man to."
- 1896 William Henry Welch begins publication of the Journal of Experimental Medicine.
- 1898 American Journal of Physiology begins publication.
- 1900 German bacteriologist Albert Neisser, discoverer of the gonococcus bacillus and co-discoverer of the leprosy bacillus, is fined 300 marks for testing a potential syphilis vaccine on five women and three girls.
- 1900 "Instructions of the Prussian Minister of Culture to the Directors of Clinics, Polyclinics, and Other Health Care Institutions" Prussia prohibits medical interventions for other than therapeutic purposes without informing the subject of potential adverse consequences and obtaining consent.
- 1900 While Walter Reed is traveling, Yellow Fever Board physician James Carroll survives yellow fever after deliberately exposing himself to mosquitoes carrying the virus; physician Jesse Lazear dies after deliberate or accidental exposure.
- 1900 Walter Reed uses written consent form (in English and Spanish) in a study of yellow fever transmission at Camp Lazear in Cuba; stipend is \$100 plus an additional \$100 if the subject is infected by the experiment.
- 1901 USDA Division of Chemistry is promoted to Bureau of Chemistry, with a new emphasis on drugs.
- 1902 Hygienic Laboratory launches three formal research programs under the direction of Ph.D.s.

- 1902 USDA Bureau of Chemistry creates Drug Laboratory.
- 1902 After 13 children die from diphtheria antitoxin contaminated with tetanus spores, Biologics Control Act authorizes Hygienic Laboratory to regulate the production of vaccines and antitoxins.
- 1902 Albert Moll's book, "Medical Ethics", recommends that advisory boards of physicians, lawyers and other learned men consider the ethical aspects of planned human experiments.
- 1903 Italian civil authorities reprimand a physician for successfully infecting a man with malaria through inoculation.
- 1905 American Medical Association establishes Council on Pharmacy and Chemistry to set standards for drug manufacturing and advertising, and fight against quack patent medicines.
- 1906 "The Jungle," by Upton Sinclair, publicizes lack of purity in meat products, leading to passage of the Pure Food and Drug Act.
- 1906 Pure Food and Drug Act prohibits adulteration or misbranding of drugs, with the burden of proof on the FDA.
- 1906 Richard Pearson Strong, head of the Philippine Biological Laboratory, inoculates 24 inmates of Manila's Bilibid Prison with an experimental cholera vaccine contaminated with plague bacilli, resulting in 13 deaths.
- 1906 In "Book on the Physician Himself," Daniel Webster Cathell advises doctors to "be careful never to speak of anything you do for a patient as an experiment... for every body is more or less opposed to physicians 'trying experiments' upon themselves or theirs."
- 1907 William Osler, in "The Evolution of the Idea of Experiment," writes "For man absolute safety and full consent are the conditions which make such tests allowable. We have no right to use patients entrusted to our care for the purpose of experimentation unless direct benefit to the individual is likely to follow."
- 1907 Dr. Albert Leffingwell, in "Illustration of Human Vivisection," writes "At the beginning of a new century we are confronted by great problems. One of these is human vivisection in the name of scientific research. We appeal, then, to the medical press of America to break that unfortunate silence which seems to justify or, at least, to condone it. Now and henceforth, will it not join us in condemning every such vivisector of little children, every such experimenter upon human beings?"
- 1907 Joseph Goldberger reviews 26 published studies reporting data on the frequency of urinary infection in cases of typhoid fever.
- 1909 American Humane Society reports that the U.S. has 104 associations devoted to preventing cruelty to animals, 45 to children, and 185 to both, with combined participation of approximately 42 million people.
- 1910 Rockefeller Institute Hospital opens, devoted entirely to clinical research.
- 1912 U.S. Supreme Court rules in "Dr. Johnson's Mild Combination Treatment for Cancer" case that Pure Food and Drug Act does not prevent drug companies from making false claims for their products.
- 1912 Shirley Amendment makes false drug claims illegal.
- 1913 George Bernard Shaw uses the term "guinea pig" to compare the role of

- children in child-rearing to the role of human subjects in medical experiments.
- 1914 Mary Schloendorff, a patient at New York Hospital, consents to an examination under ether of a fibroid tumor, but prohibits the doctor from performing an operation. Once the patient is unconscious from the ether, the doctor removes the tumor, and the patient later develops gangrene, requiring the amputation of several fingers. In the case of *Schloendorff v. Society of New York Hospital*, future Supreme Court Justice Benjamin Cardozo writes "Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault, for which he is liable in damages."
- 1915 Public Health Service researcher Joseph Goldberger conducts study on 11 inmates of Rankin Prison in Mississippi that demonstrates the role of diet in pellagra, a disease caused by a deficiency of the vitamin niacin. The inmates recover and receive pardons for their participation.
- 1919 Amendments to Biologics Control Act require submission of product samples for government inspection and approval prior to distribution.
- 1923 R.A. Fisher and W.A. MacKenzie perform statistical randomization in an agricultural experiment.
- 1923 The "Friends of Medical Progress," later renamed the "American Association for Medical Progress," is founded in Boston to support medical research.
- 1927 Food and Drug Administration is created from USDA Bureau of Chemistry.
- 1928 Cooperative Clinical Group is formed to perform multi-site research on syphilis.
- 1930 Ransdell Act renames Hygienic laboratory the National Institute of Health (NIH) and expands its functions.
- 1930 NIH assigns newly-established Division of Biologics Control responsibility for regulating biologics.
- 1930 Paul Martini of Germany employs single-blind design in drug studies.
- 1931 J.B. Amberson, B.T. McMahon, and M. Pinner publish negative results of matched-pair randomized, placebo-controlled clinical trial, comparing sanocrysin (sodium gold thiosulphate) to distilled water for the treatment of pulmonary tuberculosis.
- 1931 After a local pediatrician prepares and administers a faulty tuberculosis vaccine that kills 75 children in Lubeck, German government enacts "Regulation on New Therapy and Experimentation", requiring human experiments to be preceded by animal experiments.
- 1931 "Circular of the Minister of the Interior of the German Reich Concerning Guidelines for Innovative Therapy and Human Experimentation" differentiates between therapeutic research, primarily intended to benefit the patient, and non-therapeutic research, primarily intended to advance knowledge.
- 1931 UK Medical Research Council creates Special Committee on Clinical Trials.
- 1933 German Law on Animal Protection requires government approval for experiments that may cause appreciable pain or damage to animals.
- 1936 In Russia, Scientific Medical Council of the People's Commissariat of Health Care adopts regulations governing the development of new drugs and procedures with human research subjects, addressing issues of risk, harm, consent and assent, and prior animal studies.

- 1937 Austin Bradford Hill recommends randomization by alternately assigning subjects in clinical trials in "Principles of Medical Statistics."
- 1938 Sales of Elixir Sulfanilamide are stopped after a poisonous ingredient kills 107 people, mostly children. Scandal leads to passage of the Food, Drug, and Cosmetic Act.
- 1938 Food, Drug, and Cosmetic Act requires pharmaceutical companies to prove drug safety.
- 1938 H.S. Diehl, in "Cold Vaccines: An Evaluation Based on a Controlled Study" describes the use of a saline solution as placebo.
- 1940 FDA is transferred from USDA to the Federal Security Agency, which becomes the Department of Health, Education, and Welfare in 1953.
- 1941 Office of Scientific Research and Development establishes Committee on Medical Research to fund and coordinate research on military medical problems.
- 1944 Biologic Control Act is amended to require biological product – not just establishment – licensing.
- 1944 Public Health Service Act authorizes NIH to conduct clinical research.
- 1946 Nuremberg Code, the first internationally-recognized code of ethics for human research, requires voluntary and informed consent, minimizing risks to subjects, and results that are valuable to society.
- 1946 American Medical Association adopts code of ethics for research on human subjects.
- 1946 Bradford A. Hill recommends the use of fully randomizing subjects in clinical trials.
- 1946 British Medical Research Council begins placebo-controlled, randomized clinical trial of whooping-cough vaccination, published in 1951.
- 1947 Carroll Wilson, General Manager of Atomic Energy Commission (AEC), uses the term "informed consent" in a letter to Robert Stone about AEC-sponsored human experiments using radioactive isotopes.
- 1947 NIH issues over \$4 million in research grants.
- 1948 World Medical Association updates and clarifies Hippocratic Oath in Declaration of Geneva.
- 1948 United Nations General Assembly adopts Universal Declaration of Human Rights, including the right to "security of person."
- 1948 Philip D'Arcy Hart and Marc Daniels publish paper on a placebo-controlled, randomized clinical trial for tuberculosis treatment with streptomycin, in the British Medical Journal.
- 1948 Andrew Ivy publishes "The History and Ethics of the Use of Human Subjects in Medical Experiments."
- 1949 World Medical Association adopts "International Code of Medical Ethics," stating that "a doctor owes to his patient complete loyalty."
- 1951 Durham-Humphrey Amendment requires that drugs unsafe for self-medication be labeled for sale by prescription only.
- 1951 Armed Forces Medical Policy Council replaces Office of Medical Services to develop and review Department of Defense medical and health policies, plans

- and programs, including human research, and is replaced in turn by the Assistant Secretary of Defense (Health & Medicine) in 1953.
- 1951-1962 Department of Defense exposes over 200,000 enlisted men to radiation during atmospheric tests of atomic bombs in Nevada.
 - 1952 Air Force adopts AFAR 80-22 regulations governing clinical research at its medical facilities and requiring that the School of Aviation Medicine Research Council approve human experiments.
 - 1953 NIH opens Warren Grant Magnuson Clinical Center hospital for intramural research, with Medical Board Committee to review the use of any nonstandard, hazardous procedures, as well as healthy "normal volunteers."
 - 1953 Secretary of Defense Charles E. Wilson signs a top-secret memorandum adapting the Nuremburg Code, with addition of written and witnessed consent, for its experimental research in the fields of atomic, biological and chemical warfare. Top-secret classification limits use of the new rules.
 - 1954 World Medical Association adopts "Resolution on Human Experimentation," broader in scope than the Nuremburg Code, emphasizing the investigator's responsibility over the subject's willingness (informed consent).
 - 1950s Double-blind experimental design becomes popular for drug studies.
 - 1955 National Cancer Institute conducts randomized cancer trial on acute leukemia and solid tumors.
 - 1955 C. Gordon Zubrod leads the creation of cancer cooperative groups, supported by the Cancer Chemotherapy National Service Center (CCNSC) at NIH.
 - 1957 In *Salgo v. Leland Stanford Jr. University Board of Trustees*, American College of Surgeons uses the term "informed consent" while expressing its disapproval of the concept in an amicus brief.
 - 1957 NIH issues over \$100 million in research grants.
 - 1961 Chemie Grunenthal withdraws thalidomide from the European and Canadian markets after it causes about 10,000 thalidomide birth defects, including about 17 in the U.S. The tragedy leads to passage of Kefauver-Harris Drug Amendments.
 - 1962 Kefauver-Harris Drug Amendments to the Food, Drug and Cosmetic Act require pharmaceutical companies to prove drug efficacy, require firms to submit adverse reaction reports to the FDA, require drug advertising to include complete information about risks and benefits, and require informed consent from clinical study subjects.
 - 1962 U.S. Army publicly issues AR 70-25, expanding regulation of human research beyond atomic, biological and chemical warfare, but not to "ethical medical and clinical investigations" that might benefit the subjects.
 - 1962 Army Surgeon General Leonard D. Hatton clarifies in a meeting with Harvard Medical School representatives that the Army's medical research principles, based on the Nuremburg Code, are guidelines, not rigid rules.
 - 1962 FDA initiates Drug Efficacy Study Implementation (DESI) program to review effectiveness of drugs marketed prior to 1962.
 - 1963 Stanley Milgram publishes controversial "Obedience to Authority" studies in which research subjects ("teachers") punished slow-learning fake students with fake electric shocks. Deception of subjects violated principles of informed consent.

- 1964 World Medical Association's "Declaration of Helsinki" requires informed consent. In contrast to the legal form of the Nuremberg Code, it takes the form of ethical guidelines.
- 1964 Drug Information Association (DIA) founded.
- 1965 Henry Beecher, a professor at Harvard Medical School, delivers a lecture at Brook Lodge Conference Center describing published articles in scientific journals based on at least 50 ethically-questionable research protocols.
- 1966 Henry Beecher, a professor at Harvard Medical School, publishes "Ethics and Clinical Research" in the New England Journal of Medicine (NEJM). The article, detailing ethically-objectionable clinical trials, such as the transplantation of malignant melanoma tissue from a daughter to her mother, had been rejected by the Journal of the American Medical Association the previous year. Joseph Garland, Editor of the NEJM, negotiated Beecher down from at least 50 to just 22 examples.
- 1966 New York State Board of Regents censures and places on one year probation Drs. Chester M. Southam and Emmanuel E. Mandel for an experiment involving the injection of live cancer cells into patients without informing them and, in some cases, against objections by their physicians.
- 1966 Public Health Service (PHS), parent of NIH, issues "Policy Statement" requiring informed consent and the use of "committees of institutional associates" composed of professional and public members to review and approve PHS-funded research.
- 1966 Laboratory Animal Welfare Act requires registration of animal research facilities and establishes rules for animal care.
- 1966 NIH issues over \$1 billion in research grants.
- 1967 John Fletcher writes "Human Experimentation: Ethics in the Consent Situation," discussing issues of informed consent (or lack thereof).
- 1968 Radiation Control for Health and Safety Act gives FDA authority over devices that emit electronic radiation.
- 1968 Maurice Henry Pappworth writes "Human Guinea Pigs: Experimentation on Man," arguing that medical researchers often take unnecessary risks with the health of subjects without the subjects' knowledge.
- 1968 NIH opens John E. Fogarty International Center to coordinate international research.
- 1969 The Hastings Center, a private bioethics research institute, is formed with lead funding of \$25,000 per year from Eli Lilly & Company. (Lilly terminates its funding of the Center in 2000 when the Hastings Center Report publishes a special issue, "Prozac, Alienation, and the Self," with articles critical of Prozac, a Lilly drug, and pharmaceutical company marketing practices.)
- 1971 Georgetown University opens Kennedy Institute of Ethics, a university-based bioethics institute.
- 1971 FDA requires "institutional review committees" for clinical research under INDs.
- 1972 Peter J. Buxton, a law student and former public health worker, exposes the Tuskegee Study of Untreated Syphilis in the Negro Male to Jean Heller, an Associated Press reporter, who publishes an expose'. Thousands of physicians had been aware of the study previously. The study is terminated the following year. (The study began in 1932. Penicillin was accepted for treatment of

syphilis in 1943 and became widely available in 1951; it was withheld from the subjects. Between 1932 and 1974, 13 papers about the study were published in medical journals.)

- 1972 American Hospital Association adopts "The Patient's Bill of Rights."
- 1972 National Institutes of Health forms Office for Protection from Research Risks to develop, implement and oversee compliance with Public Health Service "Policy on Humane Care and Use of Laboratory Animals."
- 1972 Division of Biological Standards, with responsibility for regulating biologics, is transferred from NIH to FDA.
- 1973 NIH sponsors multicenter kidney transplant histocompatibility study with two sites using electronic data capture (EDC) through teleprinter terminals connected via dial-up telephone lines to a mainframe computer.
- 1974 City of Philadelphia closes the clinical research program at Holmesburg Prison where, for 25 years, physician Albert M. Kligman conducted ethically-deficient experiments on prisoners under the auspices of the University of Pennsylvania.
- 1974 45 CFR 46 Subpart B adds special protections for pregnant women and fetuses in clinical research.
- 1974 National Research Act requires institutional review boards for Department of Health, Education, and Welfare-funded biomedical and behavioral research involving human subjects, and calls for the formation of National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which issues the Belmont Report in 1978.
- 1974 Family Educational Rights and Privacy Act protects student privacy.
- 1974 Public Responsibility in Medicine and Research/Applied Research Ethics National Association (PRIM&R/ARENA) founded.
- 1975 World Medical Association's Declaration of Tokyo expands on the Declaration of Helsinki with additional subject protections, including ethics boards with the authority to comment and provide guidance, but without the authority held by institutional review boards in the U.S. to approve or disapprove studies.
- 1975 A.H. Robins Co. recalls Dalkon Shield contraceptive device after four years on the market for causing severe pelvic infections.
- 1976 Medical Device Amendments to Federal Food, Drug, and Cosmetic Act extend full FDA regulatory authority to medical devices, including the requirement for approval prior to marketing.
- 1976 California Medical Experimentation Act includes Experimental Subject's Bill of Rights.
- 1976 Association of Clinical Research Professionals (ACRP) founded.
- 1978 National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issues Belmont Report, requiring respect for persons, beneficence and justice in clinical research.
- 1977 FDA Bioresearch Monitoring Program is created to ensure quality and integrity of data, and safety, rights and welfare of human research subjects.
- 1978 45 CFR 46 Subpart C adds special protections for prisoners in clinical research.
- 1978 Society for Clinical Trials (SCT) is established.
- 1979 Institute of Clinical Research (ICR) founded in the UK.

- 1980 Controlled Clinical Trials, later renamed Contemporary Clinical Trials, publishes first issue.
- 1981 FDA issues regulations covering protection of human subjects, informed consent, and standards for institutional review boards.
- 1981 Title 45, Code of Federal Regulations, Part 46: Protection of Human Subjects establishes regulations for research supported by Department of Health and Human Services.
- 1982 Council for the International Organization of Medical Sciences (CIOMS) publishes "International Ethics Guidelines for Biomedical Research Involving Human Subjects," including cross-cultural guidance for conducting research in developing countries.
- 1983 Orphan Drug Act provides tax benefits and exclusive marketing rights to developers of drugs that treat rare diseases.
- 1983 45 CFR 46 Subpart D adds special protections for children in clinical research.
- 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act) expands the categories of drugs, e.g., generics, eligible for Accelerated New Drug Applications (ANDAs) and adds up to five years of patent protection for drugs to offset the time required for FDA approval.
- 1985 FDA issues IND amendments clarifying requirements for clinical research with biological products, e.g., gene therapy.
- 1986 1863 False Claims Act is amended to reward and protect whistleblowers, and otherwise strengthen the ability to impose civil liability for submitting a false or fraudulent claim for payment to the United States government, e.g., for double-billing a clinical trial sponsor and Medicare for clinical trial costs.
- 1986 U.S. Representative Edward Markey issues report titled "American Nuclear Pigs: Three Decades of Radiation Experiments on U.S. Citizens," describing numerous government experiments that intentionally released radioactive materials into the environment in the 1940s through 1970s.
- 1987 FDA issues 21 CFR 312.34 regulations for Treatment INDs, allowing use of investigational new drugs showing promise in clinical testing for treating serious or immediately life-threatening conditions.
- 1988 French government enacts "la Loi Huriet" (the Huriet Law) to protect healthy human research subjects.
- 1989 "Stark I" law, part of the Omnibus Budget Reconciliation Act of 1989, prohibits physician referral of Medicare patients to clinical laboratories in which the physician or member of his/her family has a financial relationship.
- 1990 Safe Medical Devices Act requires medical device tracing, registries and post-marketing surveillance.
- 1991 Department of Health & Human Services and 15 other government departments and agencies (not including FDA) adopt the "Common Rule" (45 CFR 46) governing conduct of clinical research. FDA regulations 21 CFR 50 and 21 CFR 56 are somewhat different.
- 1992 Generic Drug Enforcement Act imposes debarment and other penalties for criminal convictions related to NDAs for generic and branded drugs.
- 1992 Prescription Drug User Fee Act requires pharmaceutical companies to pay fees on certain NDAs and supplements, establishments and products, to fund 700

- additional FDA staff.
- 1992 FDA issues regulations for accelerated approval and a "parallel-track" mechanism so that patients with AIDS, whose condition prevents them from participating in controlled clinical trials, can receive investigational drugs shown in preliminary studies to be potentially useful.
 - 1992 FDA bans silicone breast implants.
 - 1993 Albuquerque Tribune reveals that government-sponsored researchers injected plutonium into unknowing subjects to study the effects of the atomic bomb.
 - 1993 National Academy of Sciences publishes report estimating that over 60,000 servicemen were used in chemical research during World War II.
 - 1993 "Stark II" law, part of the Omnibus Budget Reconciliation Act of 1993, expands Stark I's laboratory referral prohibition to include a number of "designated health services" and Medicaid services, including physical and occupational therapy; radiology; durable medical equipment, parenteral/enteral and prosthetic items; home health services; outpatient prescription drugs and hospital services.
 - 1993 National Institutes of Health Revitalization Act mandates inclusion of women and minorities in federally-funded, population-based studies.
 - 1994 Advisory Committee on Human Radiation Experiments is created, leading to formation of National Bioethics Advisory Commission in 1995.
 - 1994 Dietary Supplement and Health Education Act exempts dietary supplements and herbal remedies from FDA oversight.
 - 1995 Medicare agrees to cover costs related to clinical trials involving marketed medical devices under investigational device exemptions.
 - 1995 Based on findings of the Advisory Committee on Human Radiation Experiments, which was formed in 1994 due to articles published by Eileen Welsome in the Albuquerque Tribune in 1993, National Bioethics Advisory Commission is created to advise the President on bioethics issues.
 - 1995 On behalf of the American people, President Bill Clinton apologizes to survivors of human radiation experiments conducted by U.S. government.
 - 1997 FDA Modernization Act offers marketing incentives for pediatric studies, implements risk-based regulation of medical devices, authorizes a public registry of clinical trials (www.clinicaltrials.gov), and expands access to investigational therapies and diagnostics.
 - 1997 On behalf of the American people, President Bill Clinton apologizes to surviving Tuskegee experimental subjects.
 - 1998 FDA requires financial disclosure by clinical investigators.
 - 1998 FDA requires efficacy and safety data by demographic subgroup (e.g., gender, race and age) in new drug applications, as well as enrollment data for demographic subgroups, in annual IND reports.
 - 1998 Protection of Pupil Rights Amendment protects student privacy in surveys.
 - 1999 Jesse Gelsinger dies in gene transfer experiment that would not have benefited his health.
 - 2000 World Medical Association, in a meeting in Edinburgh, expands on the Declarations of Helsinki and Tokyo by prohibiting the use of placebo controls when there is a known effective treatment. Subsequent clarification removes

- the prohibition.
- 2000 National Coverage Decision provides for Medicare coverage of "routine" costs of "qualifying" clinical trials.
 - 2001 Health Insurance Portability and Accountability Act requires privacy and security for personal health information.
 - 2000 Department of Health and Human Services transfers Office for Protection from Research Risks from National Institutes of Health to Office of the Secretary, and renames it the Office for Human Research Protections
 - 2001 Clinical Trials Directive (European Union Directive 2001/20/EC) simplifies and harmonizes ("approximates") administrative provisions governing clinical trials in the European Union.
 - 2001 Association for the Accreditation of Human Research Protections Programs (AAHRPP) is established.
 - 2001 After Ellen Roche dies during an asthma drug study, Office for Human Research Protections suspends all Federally-funded clinical research at Johns Hopkins University School of Medicine and affiliated institutions. At the time, Johns Hopkins University was the leading recipient of Federal research funding.
 - 2001 In the cases of Ericka Grimes and Myron Higgins v. Kennedy Krieger Institute, relating to a research study on the prevention of lead poisoning among inner-city children, Maryland Court of Appeals rules that parents cannot consent to participation by their children "in nontherapeutic research or studies in which there is any risk of injury or damage to the health of the subject."
 - 2002 Medical Device User Fee and Modernization Act authorizes user fees for FDA premarket reviews.
 - 2002 Best Pharmaceuticals for Children Act provides six-month patent extension for manufacturers who conduct pediatric trials.
 - 2002 Pharmaceutical Research and Manufacturers Association (PhRMA) adopts "Principles on Conduct of Clinical Trials."
 - 2002 Animal Efficacy Rule authorizes FDA to approve drugs based on animal test results if human testing is not practical because the drugs prevent or ameliorate "serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances."
 - 2003 Pediatric Research Equity Act gives FDA authority to require pediatric studies of pharmaceutical products.
 - 2003 National Coverage Decision states that Medicare/Medicaid will cover certain costs associated with device trials.
 - 2003 American Association for Cancer Research removes the name of Cornelius P. Rhoads from its annual award given to young cancer investigators, because it came to its notice that at least 13 Puerto Rican subjects had died in the 1930s after Dr. Rhoads injected them with cancer cells. Dr. Rhoades also made highly racist remarks about the inhabitants of Puerto Rico.
 - 2003 Wolfgang Weyers writes "The Abuse of Man: An Illustrated History of Dubious Medical Experimentation," a comprehensive history of clinical research.
 - 2003 In Diaz v. Hillsborough County Hospital Authority lawsuit, class action plaintiffs settles case for \$3.8 million in damages for "dignitary harm" that involves no physical harm.

- 2004 Pharmaceutical Research and Manufacturers Association (PhRMA) updates its clinical research principles to include timely communication of clinical trial results, whether those results are positive or negative.
- 2005 International Committee of Medical Journal Editors (ICMJE) requires registration of clinical trials prior to publication.
- 2005 World Health Organization (WHO) specifies "Minimal Registration Data Set" for registering clinical trials.
- 2005 Journal of Clinical Research Best Practices publishes first issue.

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