1 Lessons from a Horse Named Jim and Other Events in History Affecting the Regulation of Clinical Research

In this Chapter

- Milestones in the history of food and drug safety – from the first food laws to the founding of the FDA to the Privacy Rule

"It had become clear to me that medicine could hardly hope to become a science until . . . qualified men could give themselves to uninterrupted study and investigation. I knew nothing of the cost of research; I did not realize its enormous difficulty; the only thing I saw was the overwhelming and universal need and the infinite promise, world-wide, universal, and eternal."

John D. Rockefeller (1839–1937), American Industrialist and Philanthropist

A Clinical Trials Manual From The Duke Clinical Research Institute: Lessons From A Horse Named Jim, 2nd edition. By Margaret B. Liu and Kate Davis. Published 2010 by Blackwell Publishing

The First Clinical Trial?

The Book of Daniel in the Bible describes a comparative trial – in which Daniel experiments with feeding youthful palace servants legumes and porridge rather than the rich meats eaten by the king and his court.

The Result?

"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." (Daniel 1:15 KJV)

From the earliest days of civilization, people have been concerned about the quality, safety, and integrity of foods and medicines. The first known English food law was enacted in 1202 when King John of England proclaimed the **Assize of Bread**, a law prohibiting the adulteration of bread with ingredients such as ground peas or beans.[1] One of the earliest food and drug laws in U.S. history was enacted in 1785, when the state of Massachusetts passed the first general food adulteration law regulating food quality, quantity, and branding.

Since then, many events, often accompanied by tragic outcomes, have raised additional concerns related to food and drug safety. This has led in turn to the creation and adoption of regulations that affect the way we investigate and manufacture new products, including medicines and medical devices. The following are only some of the events and subsequent laws or responses, largely drawn from events in the past 150 years of American history that have shaped and defined how we conduct clinical research of investigational products in the U.S. today, as well as how we currently bring these products to market.

The Jungle by Upton Sinclair

Published in 1906, this novel described the lives of people working in Chicago stockyards and slaughterhouses. Sinclair wrote about poisoned rats being ground up in meat, the slaughter of diseased animals, and chemicals used to disguise the smell of rotten meat. The description of meat factories as unsanitary and rat-infested outraged the public. When the sales of American meat dropped dramatically, meat packing companies lobbied the U.S. federal government to pass legislation for improved meat inspection and certification. Their efforts contributed to the passage of the **Meat Inspection Act** and the **Food and Drugs Act** of 1906.[2]

1848 The first U.S. *federal* regulation dates to this year, when American soldiers died as a result of ingesting adulterated quinine during the Mexican War. In response to these deaths, Congress passed the **Drug Importation Act**, requiring U.S. Customs to perform inspections aimed at stopping the importation of adulterated drugs from overseas.

1901 A horse named Jim was used to prepare an antitoxin for diphtheria. After 13 children who received the antitoxin died, authorities discovered that the horse had developed tetanus, thereby contaminating the antitoxin. This tragedy prompted Congress to pass the **Biologics Control Act of 1902**, giving the government regulatory power over antitoxin and vaccine development.

1906 In the early 1900s, the federal government completed a study about the effect of colored dyes and chemical preservatives on digestion and health. Study results, which showed that certain food preservatives and dyes were poisonous, drew widespread attention and public support for a federal food and drug law and resulted in the **Food and Drugs Act** of 1906. The original **Food and Drugs Act** prohibited interstate commerce of misbranded or adulterated food, drugs, and drinks. The Act also mandated truth-in-labeling, authorizing the federal government (enforced by the Bureau of Chemistry) to monitor food purity and the safety of

medicines. Unfortunately, truth-in-labeling did not prevent companies from making false health claims about their products.

1931 As part of a Congressional effort to provide more thorough regulation of food and drug marketing, the Bureau of Chemistry was reorganized and renamed the Food, Drug, and Insecticide Administration in 1927. A few years later in 1931, it was again renamed, this time to its current title of the **U.S. Food and Drug Administration (FDA)**.

1932 The **Tuskegee Study of Untreated Syphilis in the Negro Male** was initiated under the auspices of the U.S. Public Health Service. Research subjects, many of them poor African-American sharecroppers, included 399 men with latent syphilis and 201 without the disease who served as controls. The men were told that they were being treated for "bad blood" and were not told the purpose of the study. When penicillin became available in the 1950s, treatment was not offered to the men with syphilis. It was not until 1972 – 40 years after this study began – that it became widely known that the study followed the untreated course of syphilis and that subjects were deprived of effective treatment in order not to interrupt the project.[3]

1937 Sulfanilamide, introduced in 1935, was very effective in treating bacterial infections, but the pills were barely palatable. To make the drug easier for patients, especially children, to swallow, a chemist created a liquid solution in which the sulfanilamide was dissolved. Soon after this sulfanilamide product came on the market, there were reports of 107 deaths after patients, mostly children, ingested the medication labeled "elixir of sulfanilamide." It was then discovered that it was not an elixir (by definition an alcohol solution), but a diethylene glycol (antifreeze) solution. The FDA successfully removed the product from the market, not because it proved fatal, but only because it was mislabeled. This incident highlighted the need for assuring drug safety before marketing.[4]

1938 The following year, Congress passed the **Food, Drug, and Cosmetic Act of 1938**. The Act expanded the FDA's role, requiring proof of *safety* of new drugs before marketing, and extended the FDA's control to include cosmetics and medical devices.

1940–45 At the end of World War II, the international community became aware that Nazi medical personnel had conducted medical experiments on non-German civilians and prisoners of war in concentration camps such as Auschwitz and Dachau. These experiments, which were done without the consent of the subjects and had

The Nuremberg Code

1. Voluntary consent is absolutely essential
2. Results must be for the good of society and otherwise unobtainable
3. Trials must be based on animal experiments and knowledge of the natural history of the disease or condition
4. Trials must avoid unnecessary physical and mental suffering
5. Trials must not be conducted if injury or death is expected
6. Risks must be less than the importance of the problem
7. Subjects must be protected from harm or injury
8. Trials must be conducted by qualified people
9. Subjects have the freedom to stop at any time
10. Investigators have an obligation to stop if harm occurs

A Trial Account by Douglas O. Linder

"No trial provides a better basis for understanding the nature and causes of evil than do the Nuremberg trials from 1945 to 1949. Those who come to the trials expecting to find sadistic monsters are generally disappointed. What is shocking about Nuremberg is the ordinariness of the defendants: men who may be good fathers, kind to animals, even unassuming – yet committed unspeakable crimes."[6]

no potential benefit to individual participants, included sterilization and euthanasia, as well as exposure to temperature extremes, simulations of high altitude (with reduced air pressure/oxygen), bacteria, and untested drugs.

1946–47 In 1946, the U.S. convened the Doctors' Trial in Nuremberg, Germany, to try 20 German physicians (as well as three other Nazi officials) accused of participating in the Nazi program to euthanize persons deemed "unworthy of life" (the mentally ill, mentally retarded, or physically disabled) or of conducting experiments on concentration camp prisoners without their consent. During the trial, ten ethical standards were drafted as a method for judging the physicians and scientists who had conducted abusive and sadistic biomedical experiments. These principles, known as the **Nuremberg Code**, became the prototype for future codes intended to assure that research in human subjects would be conducted in an ethical manner. (See the Nuremberg Code in Appendix A.)

> After almost 140 days of proceedings, a verdict was handed down in the Doctors' Trial. A total of 85 witnesses testified and almost 1,500 documents were introduced as evidence. Sixteen of the 23 defendants were found guilty, and seven were executed.[5]

1957–62 Even after the announcement of the Nuremberg Code standards, it remained a common practice for drug manufacturers to send samples of unapproved drugs to physicians for *ad hoc* testing on patients; the physicians would then report the results of these informal tests to the drug manufacturers. Unfortunately patients did not know they were being used as test subjects, but the U.S. government was apprehensive about interfering with the doctor–patient relationship.

One tragic result of this practice occurred in the late 1950s to early 1960s with the drug thalidomide, used in Europe to bring a quick, natural sleep for millions of people, and to give pregnant women relief from morning sickness. The German manufacturer claimed it was non-addictive, caused no hang-over, and was safe for pregnant women. By 1957, thalidomide was sold over-the-counter in Germany and by 1960 it was sold throughout Europe, South America, Canada, and other countries.[7]

To introduce it into the United States, a U.S.-based pharmaceutical company submitted an application to the FDA to market thalidomide. Frances Oldham Kelsey, the FDA medical officer assigned to the case, requested more data to support the drug's

safety. Kelsey was concerned that the chronic toxicity studies had not been conducted for sufficiently long periods, the absorption and excretion data were inadequate, and the clinical reports were not based on the results of well-designed, well-executed studies. Late in 1960, the *British Medical Journal* published a letter regarding cases of peripheral neuritis (painful tingling of the arms and feet) in patients taking thalidomide over a long period of time. Kelsey suspected that a drug that could damage nerves could also affect a developing fetus. Her suspicions were confirmed when European physicians began reporting a growing number of women giving birth to deformed babies. By late 1961, a German pediatrician determined the cause of the deformities to be thalidomide. German health authorities pulled the drug from the market and other countries followed. The U.S. pharmaceutical company withdrew its application to the FDA.[8]

An estimated 10,000 babies in Europe and Africa were born with birth defects, including phocomelia (a defective development of the arms and/or legs in which the hands and feet are attached close to the body) to mothers taking thalidomide. While never approved for marketing in the U.S., thalidomide was being used extensively in research in American women. Until this time, there was no requirement to notify the FDA regarding the investigational use of drugs. Therefore, when the FDA approximated the number of U.S. physicians using thalidomide, the estimate of 40–50 fell far short of the more than 1000 physicians actually using the drug in an investigational setting.

1962 Faced with the devastating effects of physicians prescribing untested thalidomide as well as other informal drug testing practices, Congress passed the **Kefauver-Harris Amendment** to the Food, Drug, and Cosmetic Act. It required manufacturers to provide proof of *efficacy* (effectiveness) and greater proof of safety before marketing a new drug, and required assurances of consent from research subjects. The new laws did not eliminate all problems associated with drug testing, but did put a great deal of pressure on manufacturers to obtain data in a more ethical manner.

1964 The World Medical Association (WMA), made up of and funded by voluntary national medical associations representing physicians from countries around the world, identified a need for worldwide recommendations to guide physicians conducting biomedical research involving human subjects. This idea, first

Frances Oldham Kelsey

"Although pressured by the manufacturer to quickly approve a drug already in widespread use throughout the rest of the world, Kelsey held her ground. When she repeatedly asked for more data and effectively forestalled the approval of thalidomide, Kelsey did more than keep a dangerous drug off the market. She set into motion a series of events that would forever change the way drugs are tested, evaluated, and introduced in America."[9]

Thalidomide Use Today

- In 1998 the FDA approved the use of thalidomide for the treatment of the painful and disfiguring skin lesions of erythema nodosum leprosum, a complication of Hansen disease, commonly known as leprosy.
- In 2006, the FDA approved the use of thalidomide in combination with dexamethasone in the treatment of multiple myeloma. Thalidomide has been shown to slow the growth of myeloma cells and inhibit the growth of new blood vessels that feed the cancer cells.
- The use of thalidomide is carefully supervised to ensure that it is not administered to pregnant women. Clinical trials are still being done to see if thalidomide is useful in the treatment of other diseases.

Declaration of Helsinki: Basic principles in the original declaration

The declaration provided guidelines for the ethical treatment of human research subjects:

- Research must be based on animal experiments
- Research must be conducted only by qualified persons
- Research must be of importance when compared to risks
- Risk and benefits must be assessed before research is conducted
- Subjects must be volunteers and informed

Notable Revisions of the Declaration of Helsinki

1975 – Independent Committee Review of informed consent emphasized

1983 – Obtain consent from minors when possible

1989 – Independent Committee Review clarified

1996 – New sentence regarding use of placebo in studies where no proven diagnostic or therapeutic method exists

2000 – 32 Basic Principles; research with cognitively impaired subjects expanded

2002 – Clarification regarding placebo use in the absence of existing proven therapy

2004 – Statement that subjects should have access to the best proven practice/ treatment at the conclusion of a study

2008 – Revised statements about vulnerable populations; reworded statement regarding access to post-study intervention; provided clarification regarding when use of placebo is ethical; requires all clinical trials to be registered in a public database.

brought to the attention of its Medical Ethics Committee in 1953, was inspired in part by the horrors revealed during the Nuremberg Trials. Years of discussion, research, and revisions finally resulted in the adoption of a document, known as the **Declaration of Helsinki**, at the WMA's 18th Medical Assembly in Helsinki, Finland.[10] The Declaration of Helsinki is prefaced by a binding statement for physicians: "The health of my patient will be my first consideration." The declaration, subsequently amended several times by the WMA, provides guidelines for the ethical treatment of human subjects (see Appendix A). The Helsinki declaration provides a clear distinction between situations where a subject benefits from research participation and one where benefit is not expected, and its basic elements are incorporated into the U.S. Code of Federal Regulations.

1966 In spite of the Nuremberg Code and the Declaration of Helsinki, ethical breaches in human research continued to occur. A series of these breaches, including hepatitis studies involving cognitively impaired, institutionalized children, and studies in which live cancer cells were injected into patients without their permission, were documented in a medical journal by Dr. Henry Beecher in 1966.[11]

1972 The **Tuskegee Study of Untreated Syphilis in the Negro Male** was exposed in a front-page New York Times article and led to a public outcry. The study ended when it became widely known that subjects had been misled and were deprived of effective treatment with penicillin.[12]

1974 In response to the Tuskegee Study and other unethical trials, the **National Research Act** was signed into law, creating the *National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research*. This committee was created to identify the basic ethical principles on which clinical research should be based. Over the next 5 years, several reports were commissioned to identify principles related to research on fetuses, research involving prisoners, research involving children, institutional review boards, and research involving mentally infirm subjects.

1976 The **Medical Device Amendments** to the Food, Drug, and Cosmetic Act provides exemption from premarket notification, premarket approval, and other controls of the Food, Drug and Cosmetic Act in order to encourage the discovery and development of useful medical devices.

1979 The *National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research* issued the **Belmont Report**, a statement of basic ethical principles and guidelines for the protection of human research subjects (see Appendix A). The Belmont Report is a timeless document that contains guiding principles, provides an analytical framework, and helps resolve ethical problems related to clinical research. Three basic principles were identified: 1) *respect for persons*, including respect for the decisions of autonomous individuals and protection of those with diminished autonomy; 2) *beneficence*, or an obligation to do no harm, maximizing possible benefits and minimizing possible harm; and 3) *justice*, the fair and equal distribution of clinical research burdens and benefits.[13]

1980–81 The FDA and Department of Health and Human Services (DHHS) incorporated the principles set forth in the Belmont Report into laws regarding clinical research. The basic regulations governing the practice of clinical research for investigational drugs were issued in Title 21 of the **Code of Federal Regulations** (CFR). Protection of human research subjects is dealt with in 21 CFR Part 50; 21 CFR Part 56 addresses Institutional Review Boards (IRBs); and 21 CFR Part 312 lists regulations pertaining to an investigational new drug application, general responsibilities of investigators, the control of investigational drugs, record keeping and retention, and assurance of IRB reviews. Some components of 21 CFR were written as early as 1975 and it has continued to be revised and amended.

1983 The **Orphan Drug Act** was passed, enabling the FDA to promote research into, and approval and marketing, of otherwise unprofitable drugs needed to treat rare diseases.

1988 **The Food and Drug Administration Act** made the FDA an agency of the DHHS, with a Commissioner of Food and Drugs appointed by the President of the United States.

1990 Congress passed the **Safe Medical Devices Act**, requiring medical device users such as hospitals and nursing homes to report promptly to the FDA any incidents that reasonably suggest that a medical device caused or contributed to the death, serious illness,

Dr. Henry Knowles Beecher

Beecher was a world-renowned anesthesiologist who made many scientific contributions in his field and developed techniques for quantifying subjective clinical responses such as pain, thirst, and mood. Beecher pioneered the recognition of the placebo effect and was an early advocate for double-blind controlled studies. His 1966 exposé provided 22 examples of unethical research occurring at prestigious institutions by highly funded investigators. Beecher was appalled by the universal nature of these ethical violations and even more outraged by the complacency within the medical community.

The Belmont Report was created in 1979 and gets its name from the Belmont Conference Center, located in the state of Maryland, where the document was drafted. It identifies three fundamental ethical principles for all human subject research – **respect for persons**, **beneficence**, and **justice** – and forms the basis for human research regulations in place today.

or injury of a patient. Device users were also required to establish methods for tracing and locating patients depending on such devices.

1990 In the late 1980s, increasing concern about ethical standards for research at an international level precipitated interest in harmonizing research requirements among nations. This movement was formalized when representatives from Europe, Japan, and the United states met at the **International Conference on Harmonisation** *of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)*. A committee of representatives from participating countries was formed to make recommendations for greater standardization in clinical research, with the goal of reducing or eliminating duplication of testing in various countries. Their objectives included better use of human, animal, and material resources. A secondary aim was the elimination of delays in global drug development while maintaining safeguards on quality, safety, efficacy, and regulatory obligations to protect public health.

1997 The FDA published **ICH E6 Good Clinical Practice: Consolidated Guidance** in the *Federal Register*. Although it is not a regulation, it is an effective guideline that helps ensure the proper conduct of clinical research. When studies in other countries are conducted under these ICH Good Clinical Practice (GCP) guidelines, the data collected may be accepted by the FDA to support an application for marketing a product in the United States.

1997–98 In an effort to increase the number of new drugs and biological products for use in children, the FDA established the **Pediatric Rule**, requiring manufacturers of selected new and previously marketed drug and biological products to conduct additional studies to assess safety and efficacy in children before the product could be marketed.

Also during this time, Congress passed the **Food and Drug Administration Modernization Act (FDAMA) of 1997**, which included a provision to extend marketing exclusivity of a drug for an additional 6 months in exchange for the manufacturer conducting pediatric drug studies. Market exclusivity prevents a competitor from marketing a generic drug during the applicable time period of exclusivity. Until this time, manufacturers had been required to either test drugs in children or include disclaimers for use in children on the drug labels. Many manufacturers took the path of writing pediatric disclaimers rather than conducting trials. This led to a lack of information regarding dosing, safety, and efficacy of drugs used in children, with the ultimate result that 75% of all drugs prescribed for

children had not been tested in that population.[14] The goal of this provision of FDAMA was to provide an incentive for manufacturers to conduct pediatric clinical trials.[15]

1999 An 18-year-old subject in a clinical trial, Jesse Gelsinger, died from multiple-organ failure triggered by the infusion of genetically altered cold viruses intended to treat an inherited liver disorder. Although Gelsinger was fairly healthy when he began the study, he did have ornithine transcarboxylase deficiency (OTCD), a rare but serious disease in which a genetic defect prevents the liver from making an enzyme that breaks down ammonia. Gelsinger volunteered to participate in the study to help scientists identify a cure for his disease; four days after receiving the gene therapy, Gelsinger died. Subsequent investigation into his death revealed irregularities in the informed consent process; in particular, information from pre-clinical trials of the therapy regarding the death of monkeys due to liver failure was not made known to potential subjects. Gelsinger also had an elevated ammonia level at the time of study entry, which some say should have excluded him from study participation. A federal panel charged with overseeing safety in gene transfer trials – the Recombinant DNA Advisory Committee (RAC) – recommended a series of changes to ensure patient protection and fully informed consent in gene therapy trials. One step was the development of a database that would allow gene researchers and the FDA to compare research results.[16]

Another step was to rename the **Office for Human Research Protection (OHRP)**, formerly the Office for Protection from Research Risks (OPRR), and transfer it from the NIH to the Office of the Assistant Secretary of the DHHS. This organizational change expanded the OHRP's role and elevated its stature and effectiveness, placing even stronger emphasis on the protection of human subjects.

2000 The *Standards for Privacy of Individually Identifiable Health Information*, known as the "**Privacy Rule**," was issued by DHHS to implement the requirements of the *Health Insurance Portability and Accountability Act* (**HIPAA**) of 1996. The Privacy Rule established a set of national standards for the protection of health information, its goal being to assure the protection of individuals' health information while allowing the flow of health information needed to provide and promote high-quality health care.[17]

What does the HIPAA Privacy Rule do?

- Gives patients more control over their health information
- Sets boundaries on the use and release of health records
- Establishes safeguards to be used by health care providers and others
- Strikes a balance when public responsibility supports disclosure of some health information, for example, to protect public health
- Enables patients to find out how their health information may be used
- Generally limits the release of information to the minimum information needed for the purpose of the disclosure
- Generally gives patients the right to examine and obtain a copy of their own health records and to request corrections to their health records[18]

What information is protected?

- Information in medical/health care records/case notes
- Conversations between doctors, nurses, and other health care providers regarding an individual's care or treatment
- Information in the health insurers' computer systems
- Billing information at hospitals and clinics

2001 The ***Association for the Accreditation of Human Research Protection Programs (AAHRPP)*** was established in response to public concern about the quality of research and the protection of human subjects. AAHRPP established a program to provide accreditation for institutions that meet established criteria for ethically sound research and the protection of human subjects.

2002 The **Best Pharmaceuticals for Children Act** authorized government spending for pediatric trials to improve the safety and efficacy of patented and off-patent medicines for children. It continued the exclusivity provisions for pediatric drugs as mandated earlier under the FDAMA of 1997.

2003 After lawsuits resulted in a temporary suspension of the *Pediatric Rule* in 2002, the **Pediatric Research Equity Act** was enacted, reinstating provisions of the *Pediatric Rule*, and requiring manufacturers to include pediatric trials in the drug development process for certain drug and biologic products.

2005 In an effort to ensure honest reporting of clinical trials, the International Committee of Medical Journal Editors (ICMJE) initiated a policy requiring investigators to enter clinical trial information in a public registry before beginning patient enrollment. The aim of this policy was to ensure that information about clinical trials was publicly available, thereby preventing selective reporting of positive study results.

2007 The **Food and Drug Administration Amendments Act of 2007** amends the Public Health Service Act to mandate registration and results reporting of applicable clinical trials on *www.ClinicalTrials.gov*, an on-line data bank established in 1999, and to make study results more readily accessible to the public. This legislation also includes a requirement that if an applicable clinical trial is funded by a grant from the Department of Health and Human Services, progress reports must include certification that the responsible party has made all required submissions for the applicable trial to www.ClinicalTrials.gov.[19]

2008 The **NIH Public Access Policy**, enacted as section 218 of the Consolidated Appropriations Act of 2008, requires all investigators who receive NIH funding to submit final peer-reviewed manuscripts accepted for journal publication to PubMed Central, a publicly available Web forum. To provide the public with access to the results of NIH funded research, manuscripts must be available at the PubMed Central Web site within 12 months of publication.[20]

More Scandals and Tragedies

In 2005 South Korean scientist Hwang Woo-Suk faked stem cell research and paid junior colleagues to donate eggs for research.

In 2006 in the UK, a phase I trial of an anti-inflammatory monoclonal antibody (TGN1412) targeted to treat inflammatory diseases such as rheumatoid arthritis and chronic lymphocytic leukemia resulted in severe adverse reactions in all six normal volunteers who received the active drug.

This brief overview documents the origin and implementation of many laws and regulations governing clinical research and human subject protection. However, many of these rules have been created in response to isolated and often tragic events, rather than being based on a prospective plan. While much progress has been made, health care providers and regulators of clinical trials continue to face ethical issues in conducting clinical research. Current challenges include how to manage genetic testing, confidentiality in an electronic era, gene therapy, and stem cell research. The conduct of clinical trials will undoubtedly continue to change as the landscape of science and technology shifts and new events unfold to shape the future of this field.

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