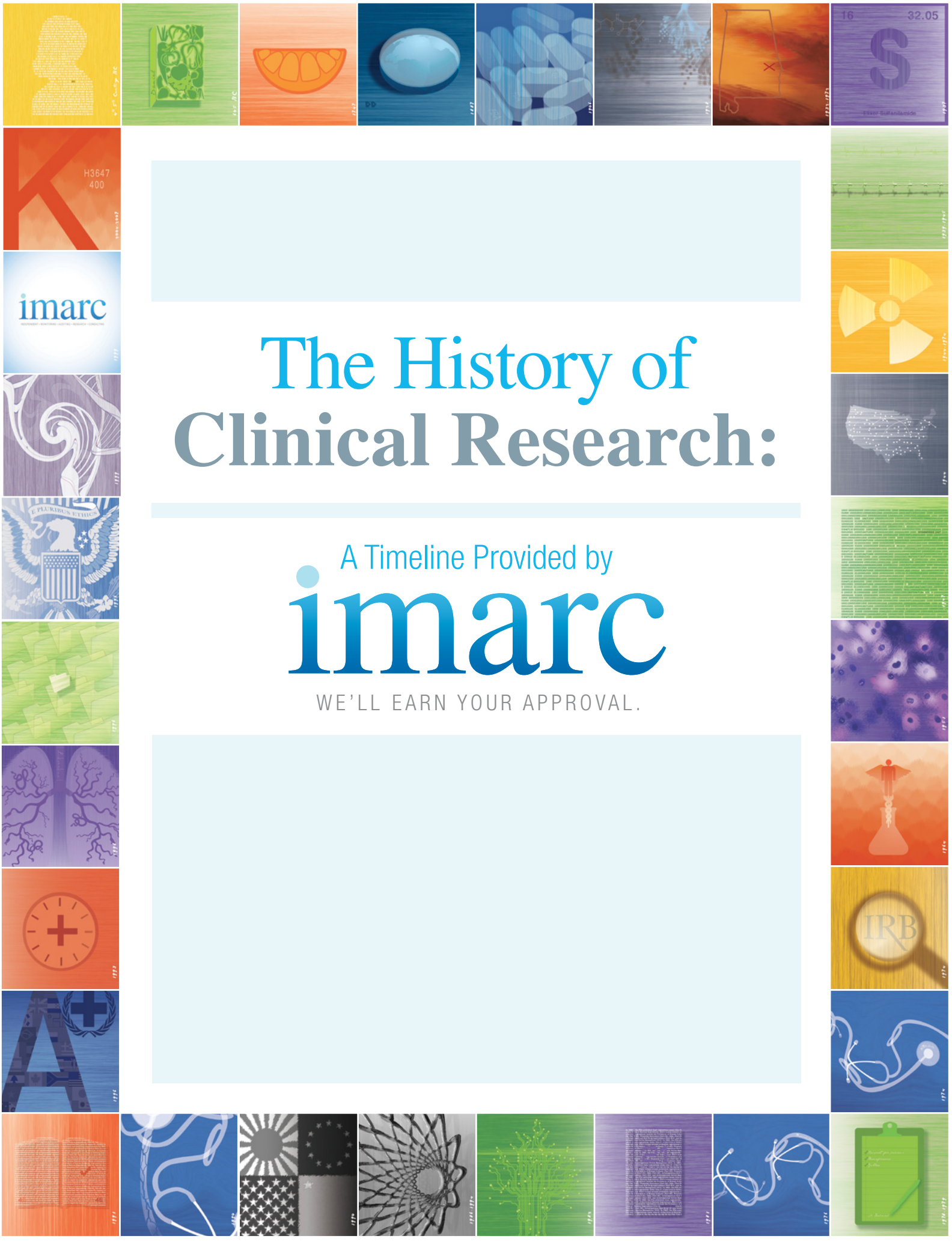



# The History of Clinical Research:

A Timeline Provided by

imarc

WE'LL EARN YOUR APPROVAL.

# Introduction

As research professionals involved in clinical trials, we have been charged with the immense responsibility of protecting human subjects, but as history has taught us, unethical practice and disregard for the well-being of human subjects has occurred and continues to occur. IMARC commissioned this piece of art to pay tribute to those who courageously participated in clinical research, both willingly and unwillingly, to recognize the good that has come out of the atrocities, to highlight some major achievements that would not have been possible without clinical trials, and to serve as a reminder to all of us that as we write our chapter in clinical research history, we do so ethically, with a strong regulatory foundation, and always—always—with an eye on human subject protection above all else.

Sandra Maddock
CEO, President
IMARC Research


# 605 BC

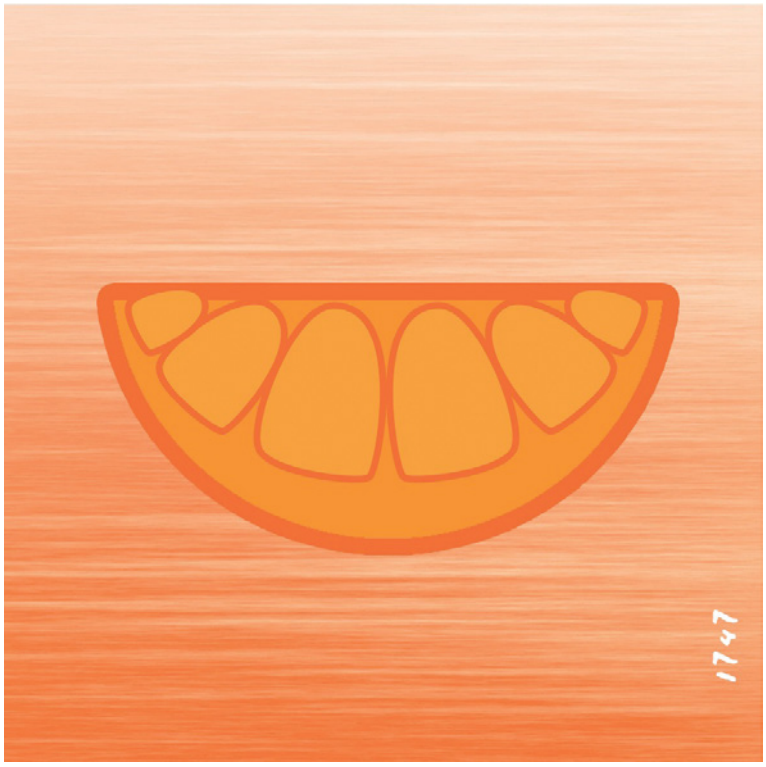
## Book of Daniel

In one of the earliest recorded examples of classical experimental design in history, Daniel sought to test the effects and benefits of a vegetarian diet. For ten days he ate only vegetables while the other subjects enjoyed the King's meat and wine. After the ten days, they assessed who was healthier – in this case Daniel.

# 500 BC

## The Hippocratic Oath

Hippocrates, "the father of Western Medicine," is believed to have created the oath that bears his name over 2,400 years ago. By taking it, physicians and other healthcare professionals swear to practice medicine justly and ethically. The responsibility of practicing medicine ethically carries over to clinical research, where the protection of human subjects is paramount.




# 1747

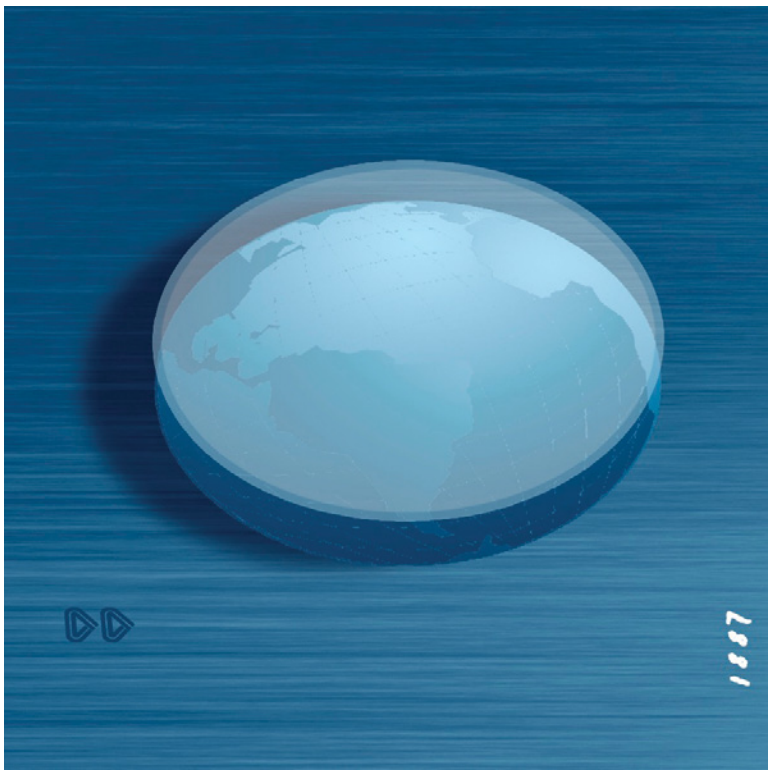
## James Lind's Scurvy Experiment

In one of the first clinical experiments in the history of medicine, Scottish physician in the British Navy James Lind tested his theory that citric acids could prevent and cure scurvy, a huge problem among sailors at the time. As a result of scurvy, sailors suffered poor wound healing, skin changes, and loosening of teeth. With no way to treat scurvy, many sailors died at sea. During Lind's 'trial' twelve affected soldiers were divided into six groups, with each group receiving a different supplement in addition to their regular diet. Cider, sulfuric acid, vinegar, seawater, oranges and lemons, and a spicy paste with barley water were all tested. The group receiving the citrus fruit saw positive effects and began recovering immediately.

# 1887

## National Institute of Health (NIH) Founded

Originally named the Hygienic Laboratory, the National Institute of Health was founded by Joseph J. Kinyoun. Today the NIH is the largest source of funding for medical research in the world, investing $30.9 billion annually to support scientific discovery.




# 1906

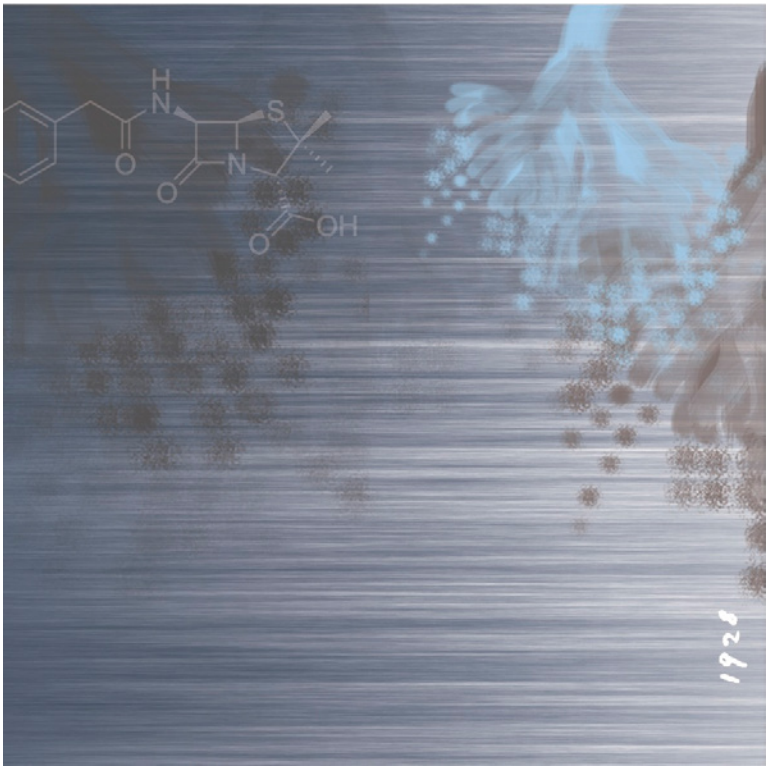
## FDA Pure Food and Drug Act

President Theodore Roosevelt signed the FDA Pure Food and Drug Act into law, which regulated that products could not be sold for indications outside the labeling and prohibited interstate transportation of unlawful food and drugs.

# 1928

## Sir Alexander Fleming Discovers Penicillin

Alexander Fleming's cluttered and untidy lab yielded one of the most important discoveries in the history of medicine as penicillin was identified on mold growing on a stack of staphylococci cultures. Soon thereafter, penicillin was recognized as one of the most efficacious life-saving drugs in the world, forever changing the treatment of bacterial infections.




# 1932-1972

## The Tuskegee Syphilis Study

For 40 years, impoverished syphilis-positive African Americans were lied to and misled in the name of science. The US Public Health Service conducted studies on 600 (including 201 control) subjects to study the effects of syphilis. Subjects did not provide informed consent and were denied access to Penicillin, a proven treatment for syphilis. Many died as a result, infected others with the disease, and passed congenital syphilis to their children.

# 1937

## Elixir Sulfanilamide Disaster

S. E. Massengill Co.'s work to market Sulfanilamide towards children became one of the deadliest mass poisonings of the 20th century. Chief chemist, Harold Cole Watkins, liquefied the drug by dissolving it in the toxic compound diethylene glycol, but failed to test the compound for toxicity since this was not a requirement at the time. Over 100 patients died after consuming Elixir Sulfanilamide. Watkins died while awaiting trial and it is believed that he committed suicide. S.E. Massengill paid a minimal fine for mislabeling the compound as an elixir even though it contained no alcohol. This was the only penalty the company was subject to under the 1906 Federal Food and Drugs Act.


# 1938

## Federal Food, Drug and Cosmetic Act

Following the Elixir Sulfanilamide disaster, the U.S. Congress passed the 1938 Federal Food, Drug and Cosmetic Act, which required proof of safety before the release of a new drug. The 1938 law changed the drug focus of the FDA from that of a policing agency primarily concerned with the confiscation of adulterated drugs, to a regulatory agency increasingly involved with overseeing the evaluation of new drugs.

This law, though extensively amended in subsequent years, remains the central foundation of FDA regulatory authority to this day.

This act mandated that safety be demonstrated prior to market approval, and required that drugs be labeled with adequate directions for safe use.

# 1939-1945

## World War II Experiments

A series of grotesque medical experiments were conducted by the German Nazi Party on large numbers of concentration camp prisoners during World War II as part of the Holocaust. Prisoners were subjected to hazardous experiments with the goal of developing new weapons, to aid in treating injured German soldiers, and to advance their eugenic racial ideologies. These experiments often resulted in death, disfigurement, or permanent disability.

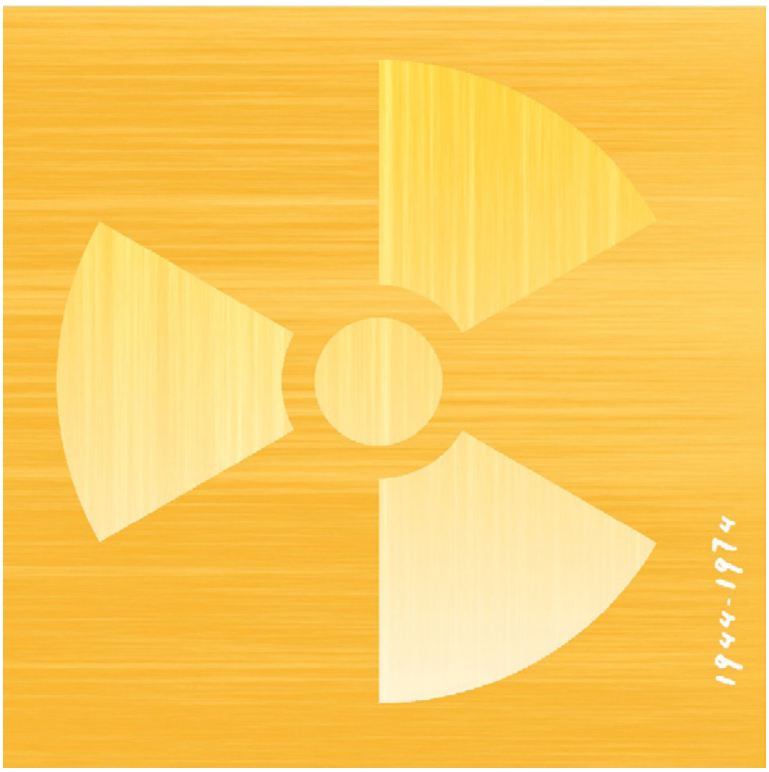

# 1944
## Multicenter Studies

Conducting large trials at multiple sites represented a significant change in how studies were conducted. For the first time, trials were conducted at different sites using the same protocol, with all the centers' results assessed together. This finally allowed for larger numbers of participants and a wider range of population groups to be studied, which strengthens research trial designs and analyses.

Today most large trials are conducted at multiple clinical research centers. Our monitors at IMARC can attest to this, as the majority of our monitored studies take place at numerous sites across the country.

# 1944-1974
## Human Radiation Experiments

During the Cold War, thousands of U.S. citizens became the innocent and unknowing victims of over 4,000 secret experiments sponsored by the U.S. government aimed at determining the effects of atomic radiation on the human body, often using doses likely to harm the subjects. The majority of victims included vulnerable groups such as prisoners, pregnant women, children, and impoverished or disabled patients.

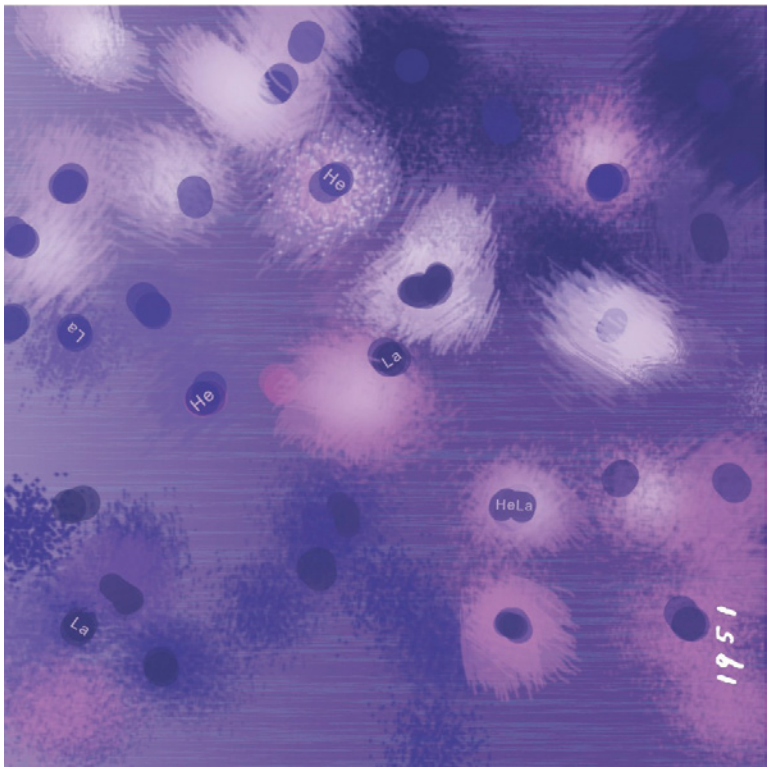



# 1947
## Nuremberg Code

During the Nuremberg Trials, 23 members of the German Nazi Party were tried for crimes against humanity for the atrocious experiments conducted on unwilling prisoners of war. The resulting verdict contained a set of ten ethical principles for human experimentation. This Code established the requirements for informed consent, absence of coercion, properly formulated scientific experimentation, and beneficence towards experiment participants.

# 1951
## Henrietta Lacks

Henrietta Lacks' contribution to medical science is enormous, yet she never knew or intended it to happen. During treatment for cervical cancer, cells were taken from her tumor without her knowledge. Researcher George Otto Gey took these cells and noticed that, remarkably, the cells could be kept alive in culture. Her cells would eventually become the HeLa (He for Henrietta and La for Lacks) immortal cell line, commonly used in biomedical research. Since the extraction of Henrietta's cells, some 20 tons of cells have been grown from the HeLa line and distributed to researchers across the world. These cells were used to test the first polio vaccine in the 1950's and have since been used for AIDS and cancer research, as well as many other scientific pursuits.




# 1960's

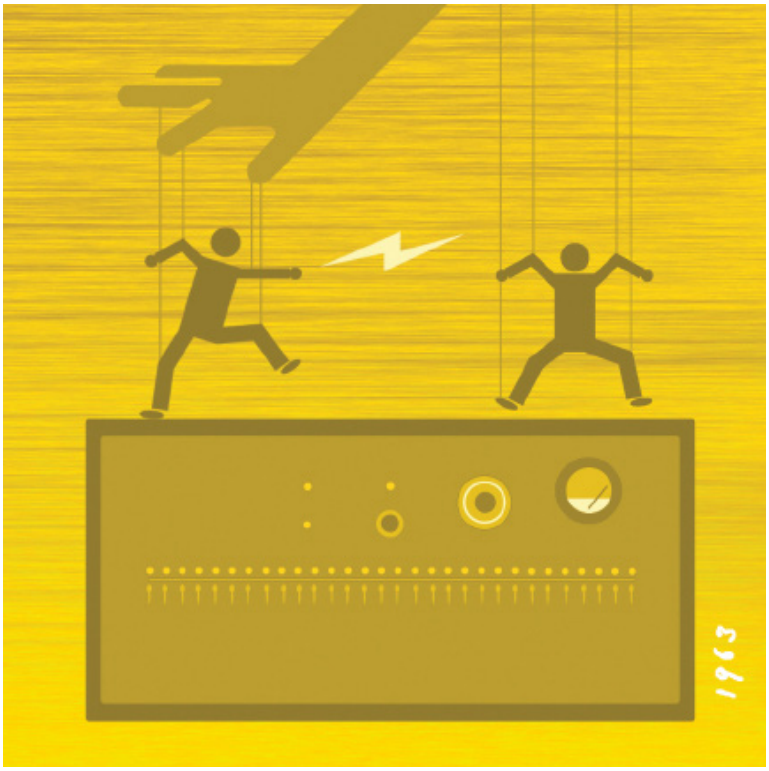
## Harvard Psilocybin Experiments

In the early 1960's, as Harvard was formulating its own policies regarding human research, two of its professors, Timothy Leary and Richard Alpert gave the psychedelic drug psilocybin to students and prisoners as part of a hypothesis that the then-legal drug could alter behavior in dramatic and beneficial ways. Due to the controversy surrounding an article published in the *Crimson* in 1962, Leary and Alpert were dismissed by the university.

# 1962

## Kefauver-Harris Drug Amendment

In addition to demonstrating safety, manufacturers were now required to provide proof of effectiveness of their drugs prior to approval and to disclose accurate information about their side effects. This prohibits cheaper generic drugs from being marketed as expensive new "breakthrough" medications.




# 1963

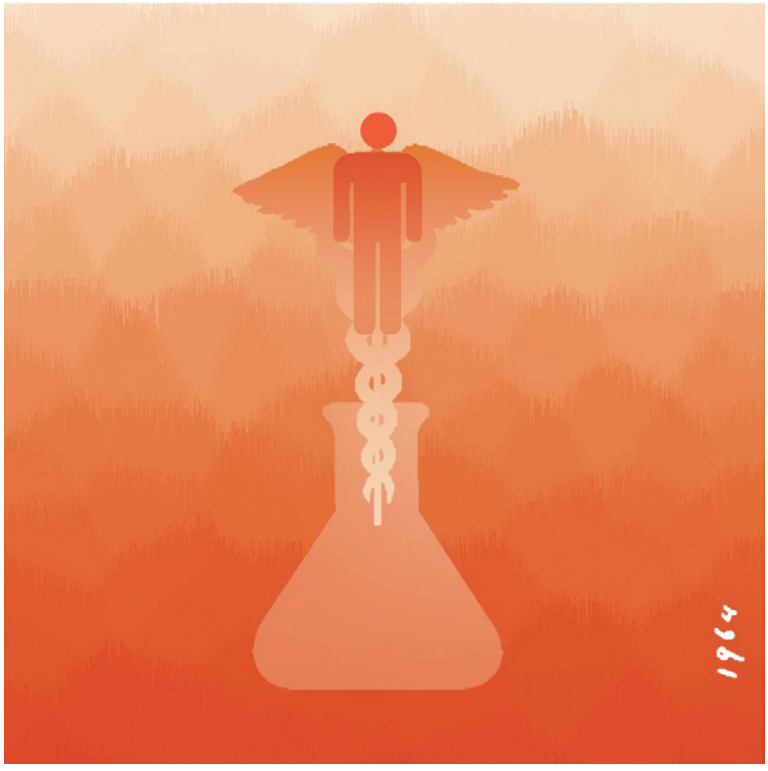
## The Milgram Experiment

In one of the most well-known studies on obedience, the experimenter assigned participants to “teach” someone posing as a learner and instructed them to deliver increasingly intense electric shocks when the learner answered questions incorrectly. Although the shocks weren’t real, participants experienced intense distress believing they were causing someone physical harm.

# 1964

## Declaration of Helsinki

The Declaration expands on the ten principles necessary for ethical human experimentation set forth in the Nuremberg Code. Developed by the World Medical Association, the Declaration of Helsinki is generally regarded as the cornerstone document of human research ethics. Since its inception in June 1964, it has undergone six revisions, the most recent coming in 2008. The focus of the Declaration is on respect for the subject, the subject’s right to self-determination and their right to make informed decisions regarding research participation. It stands as a clear and powerful statement that the rights of the human subject shall never be compromised for the sake of science.




# 1974

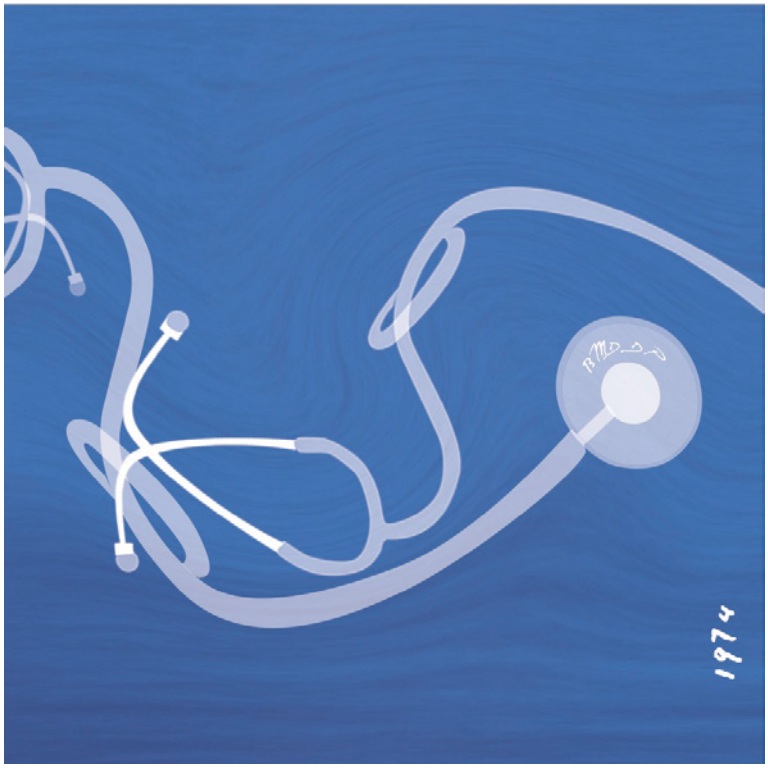
## The National Research Act

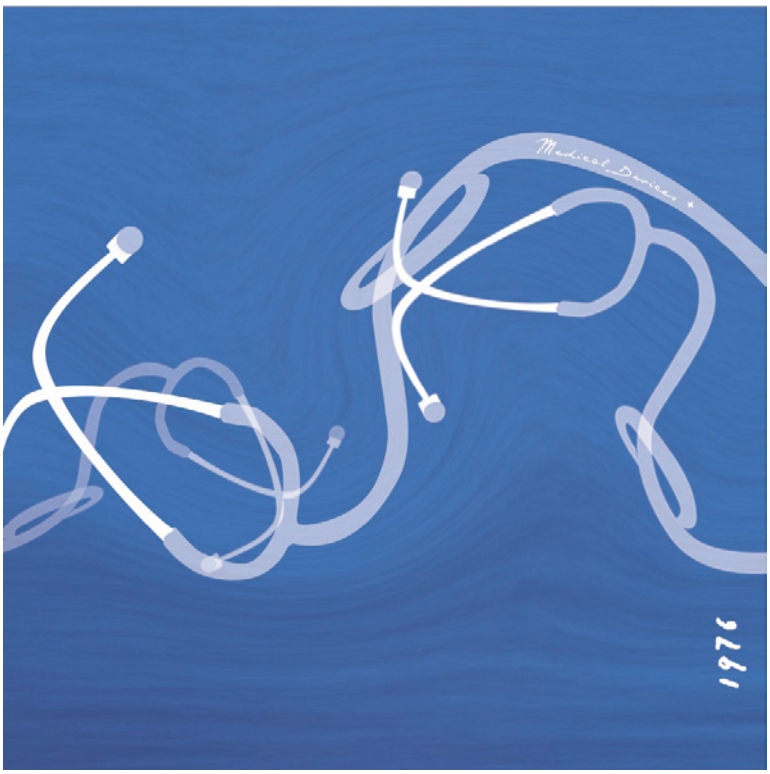
President Richard Nixon signed the National Research Act into law in response primarily to the Tuskegee Syphilis Study. The act requires that all research using human subjects be reviewed by an Institutional Review Board as another step to ensure protection of human subjects.

# 1974

## FDA Bureau of Medical Devices and Diagnostic Products

Advances in technology led to a significant growth in the medical device field, yet the industry was still operating based on device regulations from the Federal Food, Drug and Cosmetic Act of 1938. Clearly, updated regulations were needed. In February 1974, the FDA created the Bureau of Medical Devices and Diagnostic Products to meet this need.






# 1976
## Medical Device Amendments

President Gerald Ford signed this amendment into law to increase FDA's authority over the production of medical devices. This created the current classification of devices with 3 classes based on risk, each having different regulatory pathways, and required devices to be proven safe and effective before they can be marketed.

# 1979
## The Belmont Report

Developed primarily in response to the Tuskegee Syphilis Study, The Belmont Report explains the three unifying ethical principles to guide human research: Respect for persons, Beneficence, and Justice. The Belmont Report has become the primary ethical framework for protecting human research subjects in the United States.


# 1981

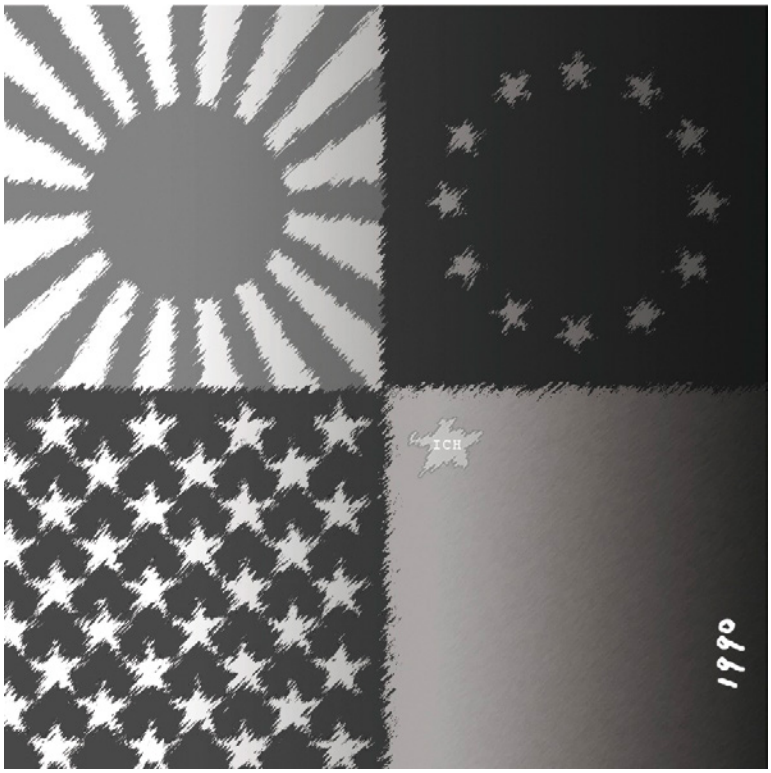
## FDA Regulations Title 21

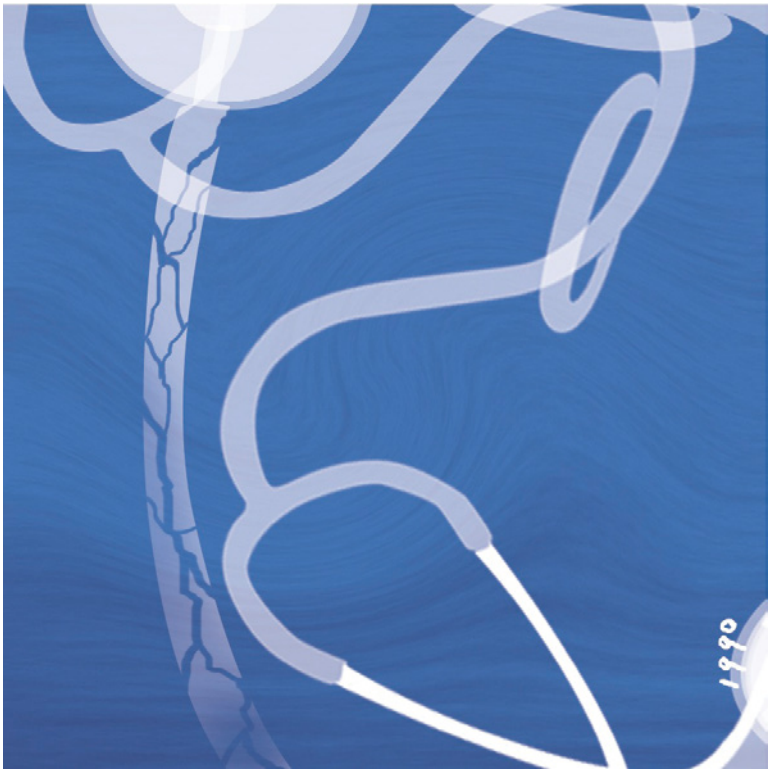
In follow-up to the Belmont Report, FDA and the Department of Health and Human Services formally revised regulations for human subject protections by creating Title 21, which includes regulations for the Protection of Human Subjects (Part 50), Financial Disclosure (Part 54), IRBs (Part 56), Investigational New Drug Applications (Part 312), Investigational Device Exemptions (Part 812), and Electronic Records (Part 11).

# 1990

## International Conference on Harmonization Guidelines

Many European nations along with Japan and the United States began creating plans for global harmonization of regulatory requirements to reduce duplicate, time-consuming, and expensive procedures needed to market products internationally, while maintaining safeguards on quality, safety, and efficacy. This need led to the creation of the ICH guidelines in April of 1990.



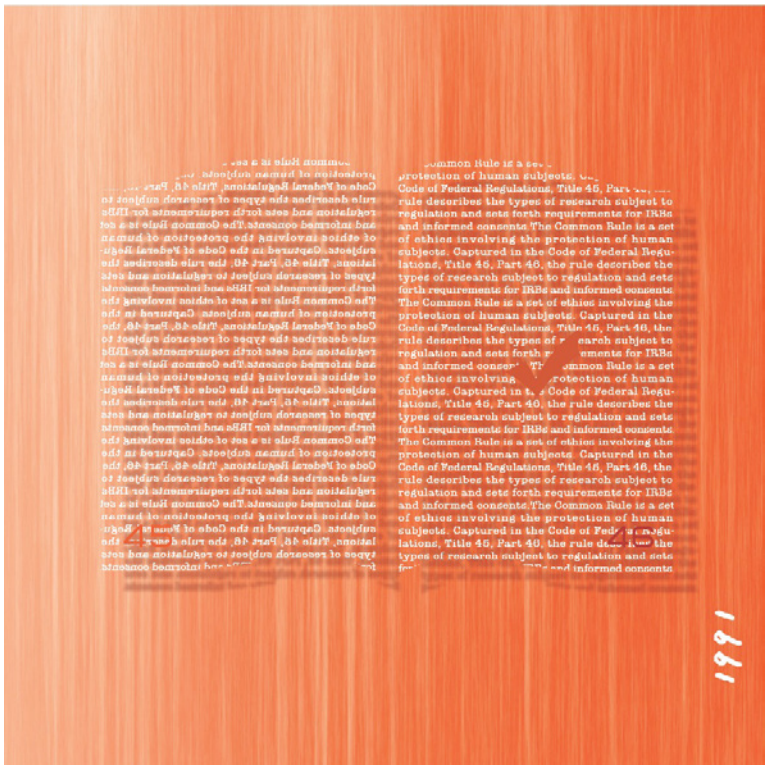


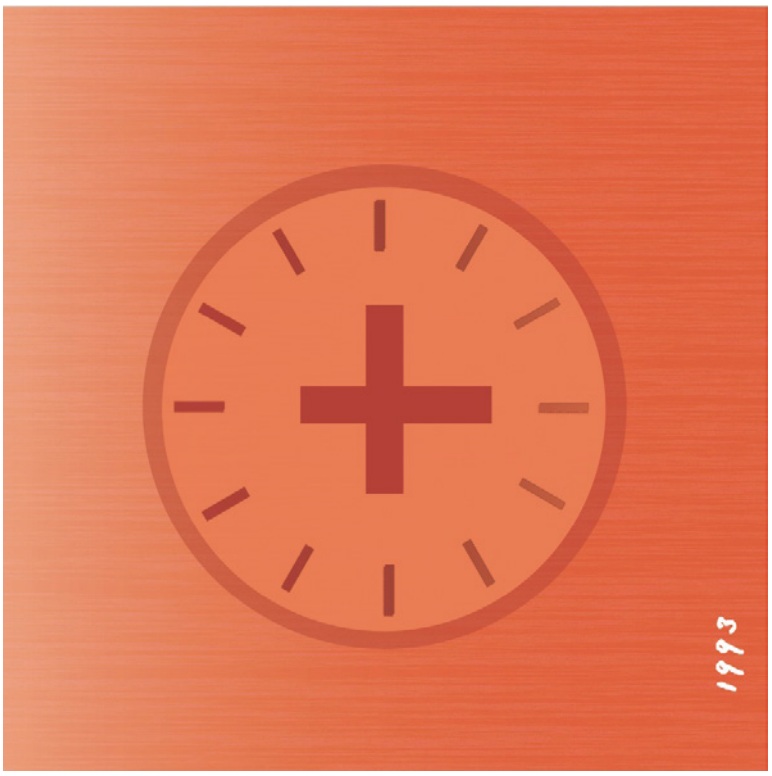

# 1990
## The Safe Medical Devices Act

An extension of the Medical Device Reporting Legislation, the Safe Medical Devices Act brought about requirements for hospitals and health professionals to report incidents to the FDA and manufacturers when devices cause serious injury or death. The act authorized the FDA to order device product recalls and take other actions. This reinforced the importance of protecting patients' health from defective or risky devices.

# 1991
## The Common Rule

The Common Rule is yet another set of ethics involving the protection of human subjects. Captured in the Code of Federal Regulations, Title 45, Part 46, the rule describes the types of research subject to regulation. The rule also sets forth requirements for the Institutional Review Board's oversight of clinical trials and details protection of human subjects regarding informed consent.



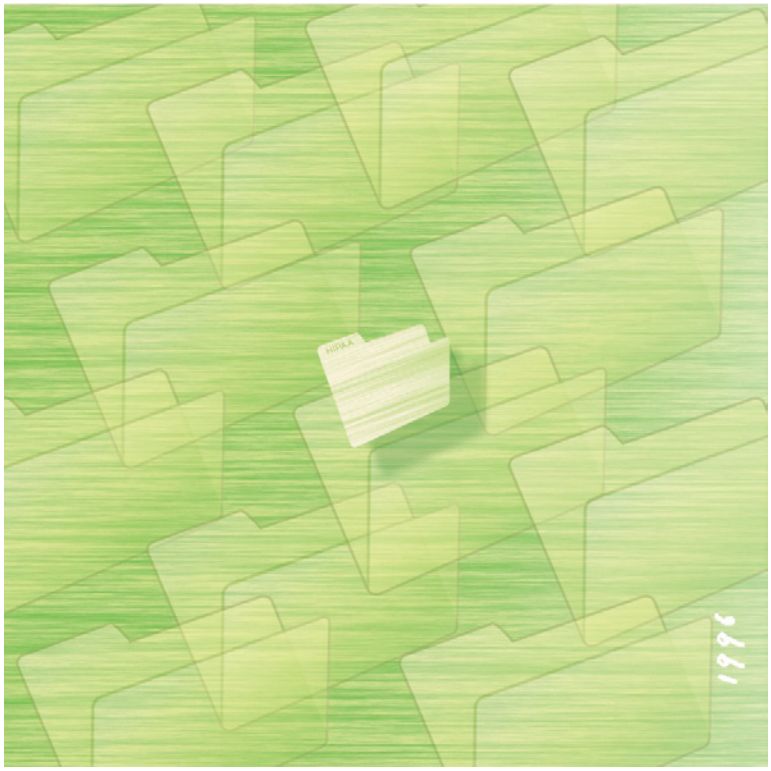



# 1993
## MedWatch

MedWatch was launched by the FDA as a system designed to collect health professionals' reports of adverse events involving medical products. When safety hazards are detected, the FDA issues medical product safety alerts or orders product recalls, withdrawals, or labeling changes to protect the public health.

# 1996
## Health Insurance Portability and Accountability Act

The Health Insurance Portability and Accountability Act requires that patients be informed of how their protected health information will be stored and kept private when they participate in a research trial. President Bill Clinton signed this act into law in 1992, but the final HIPAA rule did not go into effect until 1996.




# 1996

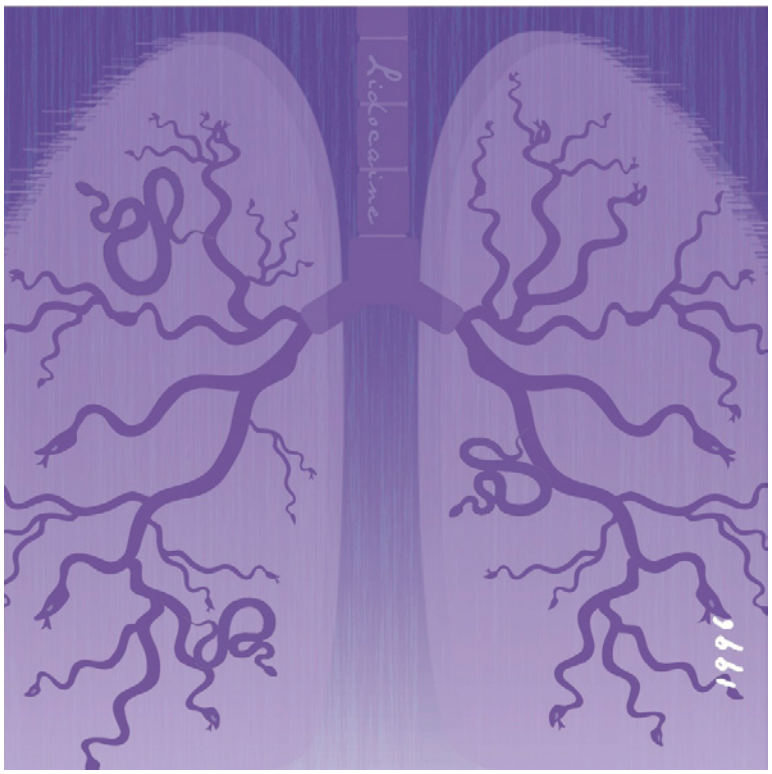
## National Bioethics Advisory Commission

Created by President Clinton, the National Bioethics Advisory Commission was created to explore ethical issues in science and medicine and advise the President on bioethical issues. The commission examined topics including cloning, human stem cell research, and research involving human subjects.

# 1996

## The World Health Organization Guidelines for Good Clinical Practice

The guideline addresses justifications for a trial and protocol; protection of subjects; responsibilities of investigators, sponsors and monitors; assurance of data integrity and product accountability; and roles of regulatory authorities.




# 1996

## Hoiyan (Nicole) Wan

Nineteen-year-old Nicole Wan participated in a minimal risk smoking and air pollution research study where she underwent a bronchoscopy to obtain some of her lung cells. Ms. Wan received four times the maximum tolerated dose of lidocaine administered by an inexperienced intern. She died two days later from complications. The attending physician was found guilty of failing to clearly state the maximum dosages in the study's protocol, violating the stated guidelines, and failing to properly monitor the young woman's condition after the procedure.

# 1999

## IMARC Research, Inc.

Sandra Maddock founded IMARC Research, Inc. in 1999 to deliver the highest-quality clinical research monitoring, auditing, training, development and consulting services for companies seeking to correctly follow the guidelines for legal and ethical trials.


# 1999

## Jesse Gelsinger

Jesse Gelsinger suffered from a rare x-linked genetic disease of the liver but did not suffer effects at the time he enrolled in a gene therapy study at a University to help others. The eighteen-year-old died four days after the research procedure. The University failed to report patients had experienced serious side effects, the informed consent did not disclose known deaths during animal trials, and the co-investigator and University had a financial interest in the trial. Additionally, Jesse's high ammonia levels should have excluded him from participating in the study in the first place.

# 2004-2007

## Ketek

The antibiotic Ketek won FDA approval in 2004; since then, Ketek has been linked to dozens of cases of severe liver injury, including a link to four deaths. It has been the subject of a series of increasingly urgent safety warnings and sparked two Congressional investigations of the FDA's acceptance of fraudulent safety data and inappropriate trial methods when it reviewed the drug for approval.


# 2010

## PIP Breast Implant Scandal

Over a 20-year period, Poly Implant Prosthese produced more than 2 million sets of breast implants using a cheaper, industrial-grade silicone not approved for medical use. The implants ruptured at a rate that was double the industry average, and the silicone caused inflammation, possible scarring and other harmful long-term effects.

## Conclusion

Ensuring accurate and credible data from clinical trials and protection of human subjects are the roles of every individual on the research team. The price for compromise is high; history provides an array of haunting reminders of our failure to uphold our obligation to ethical excellence in our work. Even more sobering is the realization that even today, research professionals sometimes fail to protect innocent people from harm and research misconduct.

Advances in the field of medicine are dependent on the quality of research that is conducted. **IMARC Research has assisted the research community in navigating the challenges of conducting safe, compliant clinical trials for more than a decade.** We are committed to not only facilitating a well-controlled study, but we are also armed with the knowledge that on the other side of those investigational products are real people; patients who are taking a risk to help the research and medical community and protecting them is our biggest responsibility.

## Sandra Maddock, CEO and President

Under Sandra Maddock's leadership, IMARC Research was founded in 1999 to deliver the highest-qualityclinical research monitoring, auditing, training/development and consulting services.

**Sandra offers IMARC partners years of expertise covering:**
coronary and peripheral stents, angioplasty balloons, combination products, thrombolytics, chemotherapy agents, endovascular grafts for treatment of thoracic and abdominal aortic aneurysms, wound care, and dura mater replacement grafts. Whether serving as a global auditor for a device study across the U.S., Japan and Germany, or working with U.S. sites establishing GCP Compliance in preparation for an FDA Inspection, Sandra's hands-on approach has become her trademark.

A special thank you to Nicolette Capuano,Owner / Principal Designer at Nicolette Atelier, ltd who was able to capture the history of clinical research through her exquisite artwork.

To learn more about IMARC Research,
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