



REMINGTON-DAVIS

Professional Clinical Research

The History of *Clinical Research*

A journey through the pivotal moments, ethical turning points,
and scientific advances that shaped modern clinical research.



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Clinical research, as we know it today, is the result of centuries of scientific innovation, ethical evolution, and regulatory refinement. It's a field marked by extraordinary breakthroughs and also sobering lessons that have refined how we protect participants' rights, safety, and dignity.



Origins and Early Experiments

Ancient Medical Practices and Observations (Babylonians, Book of Daniel)

The earliest seeds of clinical inquiry were planted long before modern medicine. As early as 605 BC, the Book of Daniel describes what is recognized as one of the first comparative clinical experiments. Daniel and his companions, opting for a vegetarian diet instead of the king's rich foods, were observed over ten days to assess health outcomes, laying an ancient anecdotal foundation for hypothesis-driven experimentation.

Ambroise Paré and Battlefield Medicine

In the 16th century, French military surgeon Ambroise Paré challenged conventional wound care by replacing boiling oil cauterization with a soothing mixture of egg yolk, rose oil, and turpentine. His battlefield observations revealed that less invasive care tended to yield better outcomes — an early example of observational research that emphasized patient welfare.

James Lind and the First Controlled Trial (1747)

James Lind's 1747 experiment aboard the HMS Salisbury is often heralded as the first clinical trial. Suffering from rampant scurvy, Lind, a medical officer in the British Navy, divided twelve patients (sailors in this case) into groups receiving different treatments; only those given citrus fruits recovered. Lind's systematic approach introduced key elements of controlled study design and comparative trial analysis.



Scientific Advancements in the 19th and 20th Century

Introduction of Placebo and Blinding (Austin Flint, 1863)

In 1863, American physician Austin Flint conducted one of the earliest placebo-controlled clinical trials, testing the efficacy of a herbal remedy for rheumatism against a dummy treatment. His work demonstrated the value of blinding and the placebo effect, laying the groundwork for modern trial methodology.

Statistical Approaches and Study Designs

The emergence of biostatistics in the early 20th century revolutionized clinical trials and expanded the professional general knowledge of how to design studies that produce valid, unbiased data. Randomization, pioneered by Ronald Fisher, became instrumental in eliminating bias — a principle that helped form the foundation of the double-blind controlled trial. This approach was notably applied by the U.K.'s Tuberculosis Trials Committee, which conducted some of the earliest large-scale randomized controlled trials to evaluate new tuberculosis treatments. Multi-center studies, first conducted in the 1940s, further advanced the field by allowing larger, more diverse patient populations to be studied at the same time.

Rise of Institutional Oversight

Following numerous ethical failures, institutional oversight mechanisms like institutional review boards (IRBs) became standard by the 1970s, safeguarding participant welfare and ensuring ethical compliance in medical research.



Ethics and Regulatory Frameworks

WWII's Aftermath and the Nuremberg Code

The atrocities committed during Nazi medical experiments during WWII led directly to the 1947 Nuremberg Code, which introduced core principles: voluntary informed consent, scientific necessity, and participant welfare. These became foundational ethical standards for research worldwide.

Declaration of Helsinki and Belmont Report

In 1964, the Declaration of Helsinki further established globally recognized ethical guidelines, emphasizing participant autonomy and scientific rigor. This marked a moment where physicians established clearer responsibilities to protect participants and uphold scientific integrity. In the U.S., the 1979 Belmont Report articulated the principles of Respect for Persons, Beneficence, and Justice following revelations from the Tuskegee Syphilis Study, when African American participants were misled and denied care.

Dr. Louis Lasagna and the Rise of Modern Ethical Standards

A pioneering clinical pharmacologist and advocate for patient rights, Dr. Louis Lasagna is recognized as a key figure in shaping the ethical and methodological frameworks of modern clinical trials. In the mid-20th century, Lasagna emerged as a thought leader in the movement to formalize informed consent and improve the scientific integrity of human research.

In 1964, he authored a widely adopted revision of the Hippocratic Oath, emphasizing the ethical obligations of physicians to respect patient autonomy—years before formal federal regulations were in place. He also advocated for placebo-controlled trials, helping to validate the use of controls and blinding in drug development. His influence extended to the FDA, where he served as an advisor amid development of stronger regulatory frameworks after the thalidomide crisis.

Lasagna's contributions bridged ethics and science, helping to lay the groundwork for Good Clinical Practice (GCP) standards. He is also remembered for "Lasagna's Law," an observation of the difficulty of enrolling enough participants in trials despite early assumptions of abundance.

The Tuskegee Syphilis Study

From 1932 to 1972, the U.S. Public Health Service conducted the Tuskegee Syphilis Study in rural Alabama, observing the natural progression of untreated syphilis in 399 African American men — all without their informed consent. The men were misled into believing they were receiving free medical care, when in fact treatment was deliberately withheld, even after penicillin became the standard cure in the 1940s. Participants were never told they had syphilis and were subjected to painful procedures under false pretenses. When the study was finally exposed by the press in 1972, it triggered national outrage, congressional hearings, and a deep reckoning with the systemic racism embedded in public health research.

The Thalidomide Tragedy and the Birth of Modern Drug Regulation

The thalidomide tragedy of the early 1960s profoundly shaped modern drug regulation. Prescribed widely in Europe for morning sickness, thalidomide caused severe birth defects in over 10,000 infants. While never approved in the U.S., the near-miss prompted swift legislative action. In 1962, the Kefauver–Harris Amendments were passed, requiring proof of safety and efficacy before drug approval and mandating informed consent for clinical trial participants.

The FDA's Formation and Role

U.S. federal regulation of drugs began in earnest with the 1906 Pure Food and Drug Act, but the 1938 Federal Food, Drug, and Cosmetic Act (prompted by the Elixir Sulfanilamide disaster) required proof of safety before new drugs could reach the market. The 1962 Kefauver–Harris Amendments further required drug efficacy data and rigorous oversight, firmly establishing the FDA as the primary regulator of clinical trials.



The Modern Clinical Trial Era

Emergence of Contract Research Organizations (CROs)

As clinical trials grew increasingly complex in the late 20th century, contract research organizations (CROs) emerged to manage studies on behalf of sponsors. These organizations brought specialized expertise in trial logistics, monitoring, and regulatory compliance — helping trials scale globally while maintaining quality.

International Collaboration and Multicenter Trials

By the 1990s, global harmonization efforts such as the International Conference on Harmonization (ICH) helped align regulatory standards across nations, reducing duplication and facilitating approvals for international clinical trials. Today, most large-scale clinical trials involve multiple sites across continents to support diverse participant representation and expedited enrollment.

Technological Advancements in Data Management

Digital technologies have transformed data collection and analysis. eSource platforms allow direct electronic capture of patient data, reducing transcription errors and improving data integrity. Wearable devices, remote monitoring tools, and integrated data systems continue to enhance both the precision and efficiency in clinical research.





Global Perspectives

The Evolution of Clinical Research in India

India emerged as a major player in global research in the early 2000s. Its large, diverse population, skilled medical professionals, and cost advantages make it an attractive destination for global sponsors. Regulatory reforms in recent years strengthened ethical protections and further aligned practices with international standards.

Ethical Principles in Different Regions

While ethical principles such as informed consent, participant safety, and scientific integrity guide clinical research worldwide, different regions bring unique legal and cultural considerations to their frameworks.

In the European Union, the General Data Protection Regulation (GDPR) and the EU Clinical Trials Regulation (EU CTR 536/2014) establish strict standards for data privacy, informed consent, and trial oversight. GDPR requires participants' explicit consent for data use and gives individuals broad rights over their personal information. The EU CTR, fully implemented in 2022, streamlines multi-country trial approvals through a centralized system, while maintaining high ethical and scientific standards across all member states.

In Japan, the Ethical Guidelines for Medical and Biological Research Involving Human Subjects integrate international standards with local cultural practices. Family involvement is often part of the consent process, especially for elderly or critically ill patients. Ethical review boards emphasize transparency and conflict-of-interest disclosures, with oversight provided by Japan's Pharmaceutical and Medical Device Agency (PMDA),



COVID-19's Impact



The COVID-19 pandemic permanently changed clinical trial operations. In early 2020, lockdowns and travel restrictions halted many site-based studies, forcing rapid adoption of decentralized and hybrid trial designs. Technologies like telemedicine, eConsent, and remote monitoring allowed trials to continue despite physical distancing requirements.

Simultaneously, regulatory agencies like the FDA issued emergency guidance to accommodate virtual visits, flexible data collection, and safety assessments. Remarkably, vaccine trials for the Pfizer-BioNTech and Moderna COVID-19 vaccines progressed from Phase I to Emergency Use Authorization within a year, demonstrating new levels of public-private collaboration, scientific and bureaucratic agility, and regulatory adaptability.

The pandemic also drove long-term adoption of digital health platforms and heightened public awareness of research's role in public health, increasing trust and participation rates.



Strengthening Diversity in Clinical Studies

FDA Guidance on Diversity and Inclusion

The FDA first issued formal guidance in 2016, encouraging sponsors to collect race and ethnicity data and proactively plan for more representative enrollment. This marked a pivotal moment in modern regulatory oversight, emphasizing that trial data lacking adequate demographic representation may be insufficient to support broad safety and efficacy claims.

In 2020 and 2022, the FDA expanded these expectations with detailed recommendations for race and ethnicity diversity plans. Sponsors are now expected to:

- Set enrollment targets based on disease prevalence across subpopulations
- Design protocols that reduce barriers to participation
- Implement outreach strategies to engage underserved communities
- Monitor enrollment progress and address shortfalls proactively

Legislative Mandates and Enforcement

In 2022, these diversity efforts advanced from guidance to mandate with the passage of the Food and Drug Omnibus Reform Act (FDORA). Under FDORA, most Phase III and pivotal trials submitted for FDA review must include formal diversity action plans as part of their submission packages. Failure to meet enrollment targets may trigger post-approval requirements or additional studies.

This U.S. framework complements growing international guidance that increasingly calls for demographic representation to be factored into trial approval decisions worldwide.



Summary and Future Directions

Ongoing Challenges and Innovations

Even with modern advances, research faces persistent challenges: patient recruitment remains one of the largest bottlenecks, with dropout rates jeopardizing timelines and budgets. Decentralized and hybrid models introduced new ways to reduce participant burden and improve engagement.

The Role of AI and Big Data

Artificial intelligence (AI) and big data analytics are poised to explore the next frontier of clinical trials. Predictive modeling, real-time data monitoring, and adaptive trial designs promise to increase efficiency, identify safety signals earlier, and deliver more personalized treatment strategies.

Clinical Research at RDI

The evolution of clinical research reflects science's long and fascinating journey and important lessons learned along the way. With each advancement in trial design, ethical conduct, technology, and regulation, the field continues to improve how we generate knowledge and safeguard the wellbeing of participants.

We've witnessed many of these shifts in this history of clinical trials firsthand and continue to adapt as new methodologies and innovations emerge. From progressive regulatory frameworks to the adoption of hybrid trial models and digital tools, we remain committed to applying these advancements in ways that support sound science and positive patient experiences.

While the field will always change and adapt, the underlying mission remains the same: **to conduct high-quality research that expands scientific and medical understanding, contributing to better care for patients today and in the future.**

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