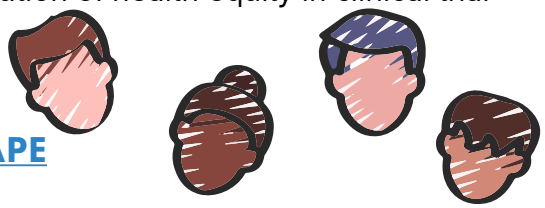
Exploring the Evolution of Health Equity in Clinical Trial Regulations

The regulatory landscape for clinical trials in the United States has evolved significantly over many years, showcasing a commitment to ongoing improvement, and establishing comprehensive laws and regulations to shape the field. Globally, expectations and standards for the medical community are consistently raised, striking a delicate balance between the necessity for increased regulations and the imperative for advancements in medical research.

Nevertheless, the prevalence of medical mistrust is both real and understandable, stemming from the historical track record of the U.S. and unethical events within medical research, particularly impacting marginalized groups. In this eBook, we provide a deep dive into the evolution of health equity in clinical trial regulations.



FOSTERING A MORE INCLUSIVE CLINICAL TRIAL LANDSCAPE

Trust in clinical research is paramount; the healthcare/pharmaceutical industry has struggled in the past but has recently begun focusing on initiatives to restore trust, such as increased transparency, fostering diverse staff, utilizing digital marketing techniques, and strengthening community relations. Improving standards in clinical research directly contributes to higher-quality care by improving study outcomes and producing more reliable data.

By implementing culturally relevant marketing and transparent practices, companies enhance study demographics, fostering patient trust and contributing to a more representative sample – ultimately aligning with evolving regulatory standards for elevated patient care. Below, we explore the historical trajectory of clinical trial regulations, offering essential context for recent updates enacted into law last year.

HISTORICAL ADVANCEMENTS IN CLINICAL TRIAL REGULATIONS

Starting with the landmark Drug Importation Act of 1848 through the 2022 Food and Drug Omnibus Reform Act (FDORA), the advancements in clinical trial regulation has continued to focus on improved ethical standards and transparency. Major events in clinical research like the 1932-72 Tuskegee Study, the 1947 Nuremberg Code, and the 1962 Kefauver-Harris Amendment are all associated with terrible conduct by the research community. These regulations, however, have also laid the groundwork for major protections for patients/participants, driving the concept of informed consent, the idea of beneficence, and the need for proof of efficacy and safety.

Government intervention has often been vital to curbing poor behavior, i.e., the National Research Act of 1974 and the Belmont Report of 1979, providing the necessary protections for study participants' trust and well-being. It's difficult to think of where medical research would be without the FDA and DHHS stepping in to enact initiatives like the 1997 ICH E6 Good Clinical Practice (GCP) guidelines and the 2007 FDA Amendments Act, which helped to increase participant confidence and the reliability of the results reported.

These historical efforts have resulted in a much safer and more productive research environment. However, it can't be denied that with regulation comes potential hurdles to innovation. Therefore, it's critical to

understand when regulations or legislation are necessary and when they become a hindrance.

Much like many of the examples cited above, we are long overdue for the regulations introduced by the 2022 Food and Drug Omnibus Reform Act (FDORA), which emphasizes modernization, diversity, and flexibility in clinical trials. FDORA introduces critical updates, focusing on two vital aspects: Clinical Trial Diversity and Clinical Trial Flexibility.

1) CLINICAL TRIAL DIVERSITY:

The focus of this portion of the legislation is to introduce a mandate for all Phase 3 and/or pivotal studies to create and maintain a Diversity Action Plan, requiring a strategic approach to enhance diversity. Plans encompassing enrollment goals and strategies are submitted with the study protocol. The FDA may waive the requirement based on disease prevalence or impracticality. Guidance on Diversity Action Plans ensures a standardized approach and promotes consistency and transparency. Public workshops and annual reports are integral components, soliciting input, fostering communication, and monitoring progress.

This appears to be building off earlier legislation that passed in 2012 (FDASIA). There is an interesting opportunity here to take this one step further and mandate demographic analysis to be prominently displayed on clinicaltrials.gov and/or when submitting the final paper to PubMed (both of which are already mandated by the FDA – 2007 FDA Amendment, and 2008 NIH public access policy).

2) CLINICAL TRIAL FLEXIBILITY:

The other key focus of this legislation is the modernization of clinical trials, specifically adding provisions on clinical trial flexibility for an evolving research landscape. Draft guidance on decentralized clinical studies and the use of digital health technologies reflects a commitment to innovation while maintaining rigorous oversight. Collaboration with foreign regulators underscores the global nature of clinical research and the importance of harmonized standards.

LOOKING AHEAD

The Food and Drug Omnibus Reform Act (FDORA) represents a milestone in the ongoing journey to enhance ethical conduct, transparency, and inclusivity of clinical trials. Its provisions for diversity action plans and flexible trial designs underscore a commitment to adapting to the evolving landscape of clinical research.

As the FDA actively implements FDORA's provisions, it will be critical for leadership to work with experts to stay informed of the latest guidance and help create and enhance existing community relations and marketing efforts while building out digital and analytic capabilities to meet the needs of the changing landscape. The legacy of FDORA and the DEPICT Act extends beyond the legislation itself, encompassing collaborative efforts by researchers, regulators, and the public to advance the ethical and scientific foundations of clinical research.

To chat more about health equity in clinical trials, connect with our team today.

Evolution of Health Equity in Clinical Trial Regulations

1848 Drug Importation Act:

The Introduction of U.S. federal regulation with the Drug Importation Act helped to set a standard for study participants and ensure that imported drugs were safe. It's generally regarded as the first legislative act introduced to regulate the drug industry and was implemented to appoint examiners to assess the purity of drugs imported into the U.S.

1932-1973 Tuskegee Study:

The Tuskegee Study of Untreated Syphilis studied 600 black men, 399 men with syphilis and 201 men as unaffected controls. Without consent, researchers provided no treatment for syphilis to observe the natural progression of the virus. Participants were actively mislead by researchers. In fact, in 1943, penicillin was confirmed to cure the virus, yet no patient was notified and the study continued for another 30 years. The study was finally shut down due to an article being written bringing these issues to light, spurring immense public outcry. By this time, 128 participants had already died due to the disease, and 40 spouses and 19 children had contracted it as well. Congressional hearings led to paid settlements to the families of participants, and new federal guidelines were later issued to protect participants' rights. This study and the conduct of the Researchers involved the emphasized the importance of informed consent and the ethical treatment of all participants.

1947 Nuremberg Code:

The Nuremberg Code established ethical standards for human experimentation, emphasizing the need for participant consent and the assurance of benefit. The Nuremberg Code was meant to establish a globally recognized code of conduct that all researchers should employ in response to the scientific atrocities committed by the Nazi regime during WWII. The 10 principles in the document, such as an experiment needing to be for the good of society, have significantly impacted global human rights law and medical ethics. Although it was never officially adopted as law, it has had a significant impact since its creation.

1962 Kefauver-Harris Amendment:

The Kefauver-Harris Amendment was introduced in 1962 in response to the Thalidomide tragedy, requiring proof of efficacy, safety, and consent in clinical trials. Thalidomide was developed in the 1950s in West Germany and was ultimately marketed as a sedative and even a morning sickness remedy during pregnancy. It was marketed as safe and effective but was later found to cause significant congenital abnormalities in over 10,000 children. This issue led to global reform in the form of the Kefauver-Harris Amendment, highlighting the importance of rigorous testing and the need for stringent regulations on the marketing and dispensing of medications. It also highlights the importance of representation in clinical trials and the need for testing in a given population before approvals are granted.

1974 National Research Act:

In response to unethical trials like Tuskegee, the National Research Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Basic ethical principles for biomedical and behavioral research studies were outlined to ensure the fair and informed treatment and participation of the subjects. This law has helped to ensure that research trials that operate without informed consent, like Tuskegee, do not happen again.

1979 Belmont Report:

The Belmont Report outlined ethical principles and guidelines for the protection of human subjects in research. Created by the committee established by the National Research Act of 1974, the report establishes 3 main concepts: Respect for Persons. Beneficence, and Justice. While it was not codified as law in the U.S., it has been noted as the inspiration for several portions of the CFR.

1980-81 Food and Drug Association (FDA) and Department of Health and Human Services (DHHS) Regulations:

The FDA and DHHS incorporated regulations based on the Belmont Report, shaping the practice of clinical research. Many see these regulations as giving teeth to institutional review boards and incorporating many of the ideals of the Belmont report into Federally backed regulation. FDA regulations on informed consent (21 CFR part 50) and IRB standards (21 CFR part 56) were adopted in 1981 (subsequently amended and federal policy was finalized in 1988). This helps solidify standards for what and how researchers should be communicating with participants before they enroll in a study, as well as establishing entities that monitor these entities before, during, and after the study to ensure compliance.

Evolution of Health Equity in Clinical Trial Regulations Continued

1997 International Council for Harmonization (ICH) E6 Good Clinical Practice:

The International Conference of Harmonization published guidelines for Good Clinical Practice, setting international standards to ensure the protection/rights of study participants and the production of accurate/reliable data. These guidelines helped to lay the foundation for modern clinical trial regulations and standards. Even though the FDA has its standards (which are very similar), companies often follow ICH guidelines as they are generally more detailed, and compliance expedites trial acceptance more broadly internationally. Major topics covered by this guidance include clinical trial design and execution, document creation and regulation (ICF, IB, PA, etc.); data quality, documentation, and record maintenance/retention, etc.

2007 FDA Amendments Act:

The FDA Amendments Act (FDAAA) helped mandate the registration and results reporting of outcomes from clinical trials to ensure greater standardization, including establishing ClinicalTrials.gov and enhancing commitment to transparency. The amendment also mandated the release of medical devices and prescription Drug User Fee Rates, IT initiatives, and hiring practices. It also focuses on providing additional protections and guidance for pediatric trials, establishes the Reagan-Udall Foundation, and issues further guidance on conflict of interest.

2010-14 Affordable Care Act (ACA):

The Affordable Care Act (ACA) includes provisions to ensure that individuals enrolled in clinical trials receive coverage for routine clinical care, prohibiting insurers from denying or limiting coverage. The law aims to increase access/participation and applies to all "approved" clinical trials (phase I-IV) relating to preventing, detecting, or treating life-threatening diseases. The trial must be either federally funded, conducted under an IND application, or exempt from such an IND application. Insurers are required to cover routine patient costs, and discrimination based on trial participation is prohibited. This has resulted in a greater accessibility of medication, diagnostic services, and general medical care.

2012 Food and Drug Administration Safety and Innovation Act FDASIA:

The Food and Drug Administration Safety and Innovation Act (FDASIA)'s significant contributions focused on stakeholder engagement, issued guidance on supply chain monitoring/reliability, introduced the "breakthrough therapy" designation, continued existing user fee programs and created new programs for generic drugs and biosimilar products. The "breakthrough therapy" designation empowered the FDA to expedite the review of new drugs for severe or life-threatening diseases that show a potential for significant improvement over existing therapies. Both programs collaborated with key stakeholders to improve the regulatory framework and with it the insights from patients and their advocates.

2014 FDA Action Plan (Section 907 of FDASIA):

Following FDASIA, the FDA Action Plan aimed to enhance the collection and availability of demographic subgroup data, improving transparency and reliability. The focus of this update was a commitment to increase the participation of underrepresented populations. After this action plan was instated, representation of minority groups has been growing, making new therapies and medicines more accessible for all patients.

2018 Risk-Based Approach to Quality Management:

Focusing on quality throughout the entire clinical trial lifecycle, focusing on building out a robust Quality Management System (QMS), ensuring the QMS is commensurate with the level of risk in the study. The focus of this update was to increase efficiency, ensure participant safety, and maintain the integrity of trial data. This new roadmap provided enhanced transparency in the FDA inspection process, making the standard investigation more manageable and standard between trials.

2022 FDORA:

The Food and Drug Omnibus Reform Act, enacted in 2022, focuses on modernizing clinical trials with provisions for diversity action plans and flexible trial designs. Diversity has become an even more integral component of trials, and researchers are now required to submit a diversity action plan to the FDA. Regulation pathways have also been increasingly optimized, such as the modernization of fast trial approval.