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Research compliance fundamentals and risks

by Donnetta Horseman, Gabriella Neff, and Dawn N.L. Pittinger

Research is fundamentally different from other operational activities of a healthcare organization and, at times, can be overwhelming. Research compliance and the regulatory environment surrounding research are increasingly complex and apply when conducting research in a healthcare setting. This article outlines the various compliance issues and regulations specific to research.

Human subject research and protection

The Nuremberg Code of 1947 initially created human subjects research protections in response to the horrific and cruel experiments in Nazi concentration camps during World War II. The subsequent Declaration of Helsinki[1] (1964) and *The Belmont Report*[2] (1979) further strengthened protections and established the three fundamental ethical principles for research involving human subjects:

1. *Respect for persons* – respecting the autonomy of and equally protecting all individuals, including persons with diminished autonomy;
2. *Beneficence* – protecting subjects from harm by maximizing possible benefits and minimizing potential harms; and
3. *Justice* – individuals should be equitably represented in research by fair distribution of the risks and benefits.

The International Conference on Harmonization and Good Clinical Practice was established in 1976 to further protect human subjects by establishing international ethical and scientific quality standards for designing, conducting, recording, and reporting clinical trials involving human subjects.

The U.S. Department of Health and Human Services (HHS) regulates human research supported by federal funds

and the use of investigational drugs, biologics, and devices. HHS Office of Human Research Protection was created in 2000 to lead HHS efforts to protect human subjects and provide oversight of the "Common Rule," which is the short name for "The Federal Policy for the Protection of Human Subjects." The Common Rule represents the accumulation of all human research protection principles. Compliance with these standards provides assurance that the rights, safety, and well-being of trial subjects are protected and that clinical trial data is credible.[3]

FDA regulations

Over the years, regulations relating protecting the US public evolved simultaneously with human subjects' protections. The Food and Drug Administration (FDA) was established in 1906 to enforce food, drug, and cosmetic protections for the US public. But as science and clinical trials advanced, new ethical and regulatory challenges were discovered, requiring updates to clinical trials' ethical and legal framework.[4]

Following World War II, medical research expanded, as did new ethical concerns surrounding protecting research subjects in clinical trials—particularly after the Nuremberg experiments. In 1947, a randomized controlled trial to treat pulmonary tuberculosis with streptomycin was conducted in Britain and triggered ethical concerns around placebo versus active treatments.[5]

In the late 1950s, thalidomide was given to pregnant women to treat nausea. It was discovered to cause severe birth defects and infant deaths within a few years and was banned in Europe. As a result of this tragedy, the US and countries worldwide adopted requirements for systematic testing of pharmaceutical products for developmental and reproductive toxicity before marketing. Consequently, in 1962, the Kefauver–Harris Amendments were passed, strengthening the FDA's controls over drug trials and changing how new drugs are approved and regulated.

And finally, in 1980, the FDA transferred under the purview of HHS, where it currently has oversight of the protection of human subjects, institutional review boards (IRBs), investigational drugs, investigational devices, biologics, the safety of the nation's food supply, cosmetics, and products that emit radiation. Understanding of and compliance with these regulations is necessary to ensure that clinical trials are conducted appropriately, and human subjects are protected.[6]

Animal use and welfare

HHS Office of Laboratory Animal Welfare (OLAW) oversees the care and use of animals in research in any public or private organization, business, or agency. No substitute exists to match the complexity of the human structure or function. Without an existing replacement, animals will play a critical role in helping researchers test potential new drugs and medical treatments for effectiveness and safety.

Animals are used in scientific research because they are biologically similar to humans. In fact, mice share more than 92% of human DNA. In addition, animals are susceptible to many health problems like humans—such as cancer, diabetes, and heart disease. Studying animals throughout their life span and across several generations can be vital in understanding how a disease progresses and how to treat it.

Any institution using animal research requires an Institutional Animal Care and Use Committee (IACUC), which oversees the use of vertebrate animals in research, teaching, and testing committees. OLAW has embraced the three Rs (replacement, reduction, and refinement) as guiding principles of animal research to give researchers practical and ethical methods for using animals in research:[7]

- **Replacement** refers to achieving a research goal or objective without conducting animal experiments. Methods are employed whereby animals are replaced with suitable alternatives.
- **Reduction** refers to using methods that allow researchers to obtain comparable levels of information using fewer animals.
- **Refinement** refers to practices that reduce or eliminate the animals' pain, stress, and discomfort during experimental procedures and with the animals' daily social and physical environments.