ELSEVIER

Urologic Oncology: Seminars and Original Investigations 30 (2012) S28–S32

UROLOGIC ONCOLOGY

Article

A clinical trial primer: Historical perspective and modern implementation☆

Lawrence I. Karsh, M.D., F.A.C.S., C.P.I.*

The Urology Center of Colorado, Denver, CO 80211, USA

Abstract

The structure of modern clinical trials is designed to protect patient safety while generating safety and efficacy data. Safety is the primary concern, and United States regulations are shaped by a series of responses to incidents, including notable safety lapses and unethical trials. These regulations focus on 3 essential components, defined by the 1979 Belmont Report: respect for persons, beneficence, and justice. Further, the international community has formally outlined good clinical practice (GCP), which mandates that trials are designed to produce meaningful data, conform to international ethics regulations, and provide assurances that data are reported in a credible and reliable manner. The Food and Drug Administration (FDA) and federal government have outlined the necessary components of clinical trials in the Code of Federal Regulations (CFR). These include institutional review boards (IRBs), standard operating procedures (SOPs), sites, sponsors, investigators, and patients. The investigator is the center of the trial and is required to sign an agreement with the federal government to uphold the CFR. Investigator duties include making sure that investigator and support staff having appropriate qualifications, delegating duties, monitoring the study for compliance and record keeping, providing care, and accepting accountability for the trial, among other duties. Physicians, who already have significant time demands, need a well-trained staff, including clinical coordinators, to adequately meet these duties. Despite these requirements, trials can have significant benefits for investigators, practices, and patients, foremost of which is the ability to provide cutting edge care. However, the clinical trial process requires routine evaluation and continual performance improvement in order to ensure that patients not only receive excellent care, but also do so in the safest possible manner.

Keywords: Clinical trials; Compliance; FDA; GCP

How we got here: The evolution of United States regulations

The structure of modern clinical trials began after World War II, but was shaped by several notable events prior to this. In 1937, 107 people, many children, died as a result of the Elixir Sulfanilidamide tragedy [1,2]. In order to increase the popularity of sulfanilidamide, a Tennessee company created a liquid formulation in which the sulfanilidamide had been diluted with diethylene glycol—the main component of antifreeze—that caused vascular nephropathy [2]. The toxicity of the inactive ingredients was not tested, as it was not required by existing regulations. As a direct result of the event, the FDA established the 1938 Federal Food, Drug, and Cosmetic Act, which required drug manufacturers to send new drug application (NDA) reports to the FDA, showing drug safety. It also banned false labeling and dangerous ingredients, requiring manufacturers to disclose all active ingredients [3]. Prescriptions were required for certain medications, although it would take the 1951 Durham-Humphrey Amendment to create the category of prescription drugs. Most importantly, the 1938 act was the first to require scientific tests when manufacturing a drug.

This was not the first drug regulatory act on the books. Previously, the 1906 Pure Food and Drug Act was designed to eliminate adulterated and misbranded food and drugs [3]. While the legislation had been under consideration for some time, the 1906 publication of Upton Sinclair's *The Jungle*, an exposé of the Chicago meatpacking industry, generated

Disclosure/Conflict of Interest Statement: L.I. Karsh is a consultant for Amgen, Dendreon, Bayer, Allergan, Spectrum, Janssen and Astellas/Medivation.

☆ LIK serves on advisory boards for Amgen, Johnson and Johnson, Pfizer, Sanofi Aventis, and Spectrum, and as a speaker for Allergan, Amgen, Dendreon, Ferring, GlaxoSmithKline, and Pfizer.

* Corresponding author. Tel.: +1-303-825-8822; fax: +1-303-825-4022.

E-mail address: larrykarsh@gmail.com (L.I. Karsh).

1078-1439/$ – see front matter
doi:10.1016/j.urolonc.2011.05.012

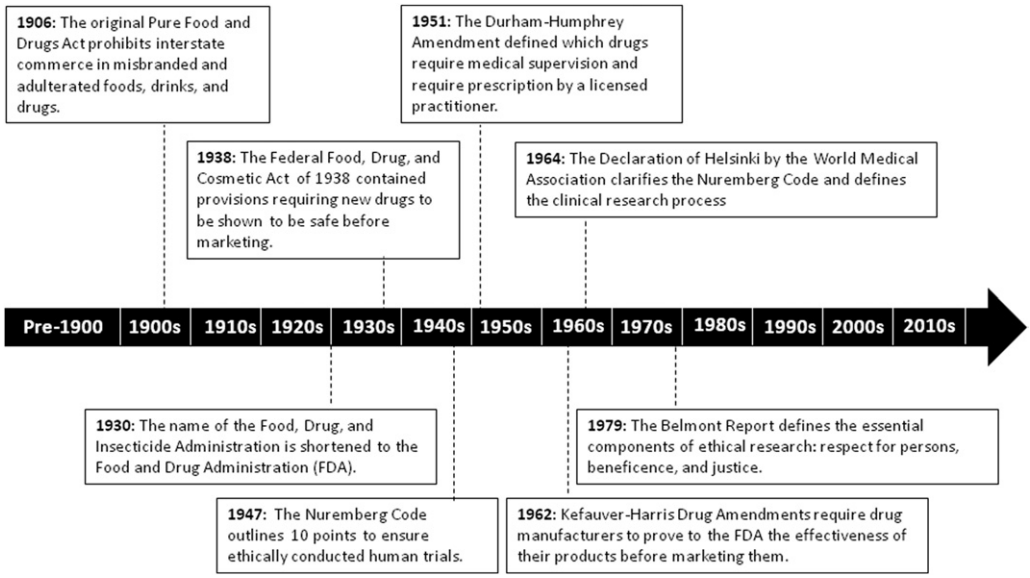

Fig. 1. The foundations of modern clinical trial regulations [21].

public support for the measure [4]. The act was regulated by the Bureau of Chemistry in the Department of Agriculture, which became the FDA in 1930 [3]. The act did not regulate drug safety or advertisement.

While the 1938 Federal Food, Drug, and Cosmetic Act significantly affected the way pharmaceuticals were dispensed, it did not require proof of efficacy, nor did it standardize clinical testing. The FDA did not review an NDA until the drug was marketed, and drugs were automatically approved if the FDA had not completed its NDA review within 60 days [3]. It would take another 23 years before significant changes would be made in the drug review process.

In the interim, another tragedy shaped human clinical trials. The 1947 Nuremberg Code was drafted in response to experiments conducted by Nazi scientists [5]. The code outlined 10 principles for conducting human clinical trials. These included voluntary consent, ensuring that experiments are useful and necessary, conducting animal experiments before using human subjects, allowing subjects to stop at any time, and the use of qualified scientists to conduct the research [5]. These became the backbone of research ethics and the protection of human subjects.

It would take yet another tragedy to move the industry forward. The first "thalidomide baby" was born in Germany in 1957, although it was several years before the connection between thalidomide and birth defects was made. This tragedy was largely confined to Europe, where an estimated 8,000 deformed babies were born as a result of thalidomide [3]. In the United States, thalidomide was denied US approval—based on one FDA reviewer's objections that its sponsor failed to show the product's pharmacologic and toxicologic characteristics [1]. Accordingly, there were only 17 cases of thalidomide malformations in the United States, and the reviewer, Dr. Frances Kelsey, received the President's Award for Distinguished Federal Civilian Service from President Kennedy [6]. The tragedy, though, spurred the 1962 Kefauver-Harris Amendment [7]. The act required "substantial evidence" of safety and efficacy for new drugs before they come to market [1]. It also regulated drug marketing and placed it under control of the FDA, established good manufacturing practices, and allowed the FDA to verify those practices. It introduced informed consent requirements and established the current format of clinical testing [1].

This was soon followed by the 1964 Declaration of Helsinki, which along with the 1947 Nuremberg Code forms the basis of protection of subject rights. The World Medical Association, an organization created in 1947 to ensure ethical behavior and care by physicians, developed the declaration, which clarified and interpreted the Nuremberg Code [8]. In addition to acknowledging the importance of clinical research, it defined the process. This included the formal outline of an experimental protocol, including ethical statements, ethical review by an independent outside body, engaging in human research only when the risks involved have been assessed, conducting trials in which there is a likely or potential benefit, the use of informed volunteers who consent to the study, and safeguards for the integrity of the subjects [8]. The Declaration of Helsinki is periodically updated, with the last version (the eighth revision) released in 2008 [9].

While there were codes to foster the ethical study of human subjects in the United States, these codes were not followed in the case of the Tuskegee Syphilis Experiment, a study conducted among rural African-American men in Alabama between 1932 and 1972. The men, who were infected with syphilis, were given free medical care—but they were not told they had syphilis nor were they treated for it [10]. Public awareness of this study, along with sev-