About FDA

FDA and Clinical Drug Trials: A Short History

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The function of the controlled clinical trial is not the "discovery" of a new drug or therapy. Discoveries are made in the animal laboratory, by chance observation, or at the bedside by an acute clinician. The function of the formal controlled clinical trial is to separate the relative handful of discoveries which prove to be true advances in therapy from a legion of false leads and unverifiable clinical impressions, and to delineate in a scientific way the extent of and the limitations which attend the effectiveness of drugs.

William Thomas Beaver [2]

Overview

The U.S. Food and Drug Administration has evolved as one of the world's foremost institutional authorities for conducting and evaluating controlled clinical drug trials.

Ancient civilizations relied on medical observation to identify herbs, drugs and therapies that worked, and those that did not. Beginning in the early twentieth century, therapeutic reformers in the United States and in other places began to develop the concept of the "well-controlled" therapeutic drug trial. This concept, included, for example, laboratory analysis followed by clinical study. As medical historians have pointed out, however, these early reformers' therapeutic vision often far exceeded their clinical and experimental grasp. [3] In 1938, a newly enacted U.S. Food, Drug, and Cosmetic Act subjected new drugs to pre-market safety evaluation for the first time. This required FDA regulators to review both pre-clinical and clinical test results for new drugs. Although the law did not specify the kinds of tests that were required for approval, the new authority allowed drug officials to block the marketing of a new drug formally or delay it by requiring additional data. The act also gave regulators limited powers of negotiation over scientific study and approval requirements with the pharmaceutical industry and the medical profession. A worldwide drug disaster in 1961 resulted in the enactment of the 1962 Drug Amendments, which explicitly stated that the FDA would rely on scientific testing and that new drug approvals would be based not only upon proof of safety, but also on "substantial evidence" of a drug's efficacy [i.e. the impact of a drug in a clinical trial setting]. Increasingly, responsibility for testing standards previously established as voluntary by the American Medical Association's (AMA) Council on Drugs, the U.S. Pharmacopeia and the National Formulary were taken up by the FDA. Since 1962, FDA has overseen substantial refinements to the broad legal requirement that post-1962 new drugs be approved on the basis of "adequate and well-controlled" studies. [4]

Medical Observation As Precursor to Clinical Trials

Clinical trials are prospective, organized, systematic exposures of patients to an intervention of some kind (drug, surgical procedure, dietary change). The earliest recorded therapeutic investigations, however, lacked the rigor of a modern clinical trial. Based largely on observations and tested through time by trial and error, ancient medicine such as that practiced by the Egyptians, Babylonians, and Hebrews was closely allied with religion. Nonetheless, some of these early medical investigations did yield some important successes in fields such as minor surgery and orthopedics. The Hebrews, in particular, excelled in public hygiene, but even their public health strictures, so effective in preventing epidemic disease, were observational and experiential rather than experimental. [5]

The Babylonians reportedly exhibited their sick in a public place so that onlookers could freely offer their therapeutic advice based on previous and personal experience. [6] The first mention of a paid experimental subject came from Diarist Samuel Pepys who documented an experiment involving a

paid subject in a diary entry for November 21, 1667. He noted that the local college had hired a "poor and debauched man" to have some sheep blood "let into his body." Although there had been plenty of consternation beforehand, the man apparently suffered no ill effects.

One of the most memorable successes from an early but earnest clinical trial was actually more of an anomaly rather than a harbinger of great progress in medical experimentation. British naval surgeon James Lind (1716-1794), who had learned of the death of three quarters of a ships' crew during a long voyage around the world, planned a comparative trial of several popularly suggested "cures" for the scurvy on his next voyage. Twelve men with similar cases of scurvy ate a common diet and slept together. Six pairs, however, were given different "treatments" for their malady. Two were given a quart of cider daily; two an "elixir;" two seawater; two a remedy suggested by the ship's surgeon (horseradish, mustard and garlic); two vinegar; and the final two were given "oranges and lemons" daily. One man who received the oranges and lemons recovered within six days, while the other recovered sufficiently that he "was appointed nurse to the rest of the sick." At first Lind questioned his own experimental results, but by the time he published them (1753 and 1757) they were recognized as important. Nonetheless, the British Navy did not supply citrus to its ships until 1795. [7]

Although simple observation may provide a starting point for medical study, however, experience has shown that it is rarely efficient at advancing medical knowledge. As one early proponent of planned experimentation in the form of clinical trials remarked, "when we are reduced to [mere] observation, science crawls." [8] A modern drug regulator is more explicit, acknowledging that modern retrospective [studies], epidemiologic analyses, and astute observations are all instructive. Although clinical trials are not the only way to find things out, the clinical trial is unique. "It is under the investigator's control, subject not to data availability or chance but to his ability to ask good questions and design means of answering them." [9]

Evolution of Clinical Trial Concept in America

According to medical historian Harry Marks, the modern controlled clinical trial is largely an American invention as statistically-based clinical trials became a critically important part of evidence-based medicine in the U.S. following WWII. [10] Certainly clinical trials in this country have evolved in pursuit of a larger therapeutic goal -- to see that the physicians use the best possible therapies available. It is interesting to note that in the late 19th century, U.S. antivivisectionists protested against the use of human beings as subjects in medical experiments. In their quest to protect animals, they viewed both animals and human beings as equally vulnerable, and feared that the replacement of the family physician by a "scientist at the bedside" would inspire non-therapeutic experimentation. It was the antivivisectionist and playwright George Bernard Shaw, in fact, who first used the term "human guinea pig." [11]

Nonetheless, as early as the late nineteenth and early twentieth century, interest in clinical objectivity grew, spurred on not only by astounding successes in laboratory science and clinical medicine abroad (e.g. discovery of microbes, pasteurization of milk, development of anthrax and rabies vaccines) but because of the sorry state of therapeutics at the time in America. In 1880, patent medicines – a misnomer because nothing but the label and the bottle were actually patented or trademarked – constituted 28% of marketed drugs. By 1900, however, they represented 72% of drug sales and products with inert ingredients were promoted as vigorously, if not more so, than drugs with active ingredients. It was popular to blame both the gullible physician and the ignorant laymen for being equally taken in by the advertising excesses of the era. [12]

The American Medical Association (AMA) began to push for federal evaluation of new medical products hoping to make a dent in the patent medicine industry, but it was unsuccessful. In 1905, the AMA formed its own Council on Pharmacy and Chemistry which levied a fee on manufacturers to evaluate their drugs for quality (ingredient testing) and safety. Drugs accepted by the Council could carry the AMA's Seal of Acceptance and only products with the seal had access to the advertising pages of the *Journal of the American Medical Association* (JAMA). The AMA's Chemical Laboratory tested commercial statements about the composition and purity of drugs in their labs, while the Council on Pharmacy and Chemistry followed up with safety evaluations and rudimentary

efficacy evaluations designed to eliminate exaggerated or misleading therapeutic claims. [13] Although the Council eagerly sought evidence that drugs had an effect on the cause or course of a disease, the Seal was awarded to drugs that merely provided symptomatic relief. Although the Council would have liked to rely upon clinical studies to supplement laboratory studies submitted by drug manufacturers, they lacked the necessary funding to support such studies and the AMA did not authorize the Council to require them. Instead of relying on the anecdotal information provided by private practitioners, however, the Council relied heavily on the opinions and recommendations of Council members who were well-respected medical specialists and scientists, a progressive practice for the era. Once their evaluations became a regular feature in the Journal of the American Medical Association (JAMA) the Council began to make inroads against the commercialism that physicians had felt were "debauching" medical journals and "tainting" medical textbooks. The AMA's drug certification program remained in place until 1955.

Clinical Trials and the 1906 Pure Food and Drugs Act

While the AMA Council on Pharmacy and Chemistry held out a carrot of certification to ethical drug products that met their standards, the first federal food and drug statute, the 1906 Pure Food and Drugs Act, wielded little in the way of a stick. The AMA had been unsuccessful in getting any kind of drug review in the new law and the statute merely provided a legal definition for the terms "adulterated" and "misbranded" as they related to both food and drug products and prescribed legal penalties for each offense. The law did empower the Bureau of Chemistry (forerunner of the U.S. Food and Drug Administration) to seize adulterated and misbranded products that moved in interstate commerce, but it simply adopted the drug standards as published in the U.S. Pharmacopeia and the National Formulary. The law also prohibited "false and misleading" statements on product labels. In the case of drugs, the law listed eleven so-called "dangerous ingredients" including opium (and its derivatives) and alcohol which, if they were present in the product, had to be listed on the drug label. This listing requirement alone inspired many manufacturers to abandon use of many dangerous ingredients following passage of the 1906 Act. But efforts to prohibit false therapeutic claims on drug labels were defeated both by the Supreme Court and the U.S. Congress.

During the 1920's, 30's and 40's medical researchers began to conduct "cooperative investigations" designed to overcome errors attributed to individual observers working in relative isolation and replace them with standardized evaluations of therapeutic research in hundreds of patients. [14] Therapeutic experimentation, however, did not begin to gain a true foothold in modern medicine until the U.S. legal system stopped equating experimentation with medical malpractice. As late as 1934, state courts seemed to uphold traditional views that the doctor was bound to act within accepted methods of clinical practice and that patients had not consented for their physician to deviate from these methods. [15] In a landmark state Supreme Court decision in 1935, however, the state of Michigan seemed to recognize and authorize controlled clinical investigations as a part of medical practice without subjecting the researcher to strict liability (without fault) for any injury so long as the patient consented to the experiment and it did not "vary too radically" from accepted methods of procedure. [16] In particular, the Michigan Supreme Court accepted that experimentation was necessary not just to treat the individual, but also to help medicine progress. "We recognize," noted the Court, "the fact that if the general practice of medicine and surgery is to progress, there must be a certain amount of experimentation carried on."

By 1937, it had become clear to regulators and to an increasing number of outside organizations, including the AMA, that the original 1906 "Wiley" Act had become outdated. Breakthrough drugs such as the first sulfa drug, sulfanilamide, new drugs including amphetamines and barbiturates, and biologics such as insulin were coming onto the market and beginning to transform medicine entirely. Clinical trials and human experimentation were becoming increasingly more important in medical research. Moreover, turn-of-the-century patent medicines with inert ingredients and quirky but quaint labels were becoming a true public health danger when patients relied on them rather than seeking out effective new therapies. The case of Banbar, in particular, convinced regulators early in the 1930's that the 1906 law's recognition of the rights of proprietors was becoming an increasing impediment to efforts to insure drug safety.

Soon after the 1906 Act had been enacted, a dispute arose over the meaning and enforcement of

the drug labeling provisions of the law. The Supreme Court ruled in *U.S. v. Johnson* in 1911, that the new law did not prohibit false therapeutic claims – the product involved was labeled Dr. Johnson's Cure for Cancer – it just prohibited "false and misleading" label claims regarding the ingredients or identity of the drug. In 1912, Congress quickly enacted the Sherley Amendment, a compromise that merely prohibited false therapeutic claims "intended to defraud" the consumer. Proving that a proprietor knew that his drug was worthless in order to demonstrate fraud under the statute, however, could be a daunting task. To cite a single example: an old patent medicine maker created a "cure" for diabetes which he marketed as Banbar. Its active ingredients included milk sugar and equisetum (horsetail). The product was particularly dangerous since diabetics were rejecting insulin injections in favor of Banbar (the hormone insulin had been isolated in 1922 and was a lifesaving therapy for diabetics). FDA seized the product in the mid-1930s, charging the proprietor with fraud under the Sherley Amendment. In his defense, the proprietor submitted testimonial letters written to him thanking him for the product. His lawyer argued that it was obvious, since these sincere people took the trouble to write him and thank him, that he had no idea that the product might not be effective much less dangerous. Government officials selected a representative group of testimonial letters and matched them side-by-side with death certificates from the same individuals indicating that they had died from diabetes. Although the public health threat was obvious, the court ruled that the proprietor had not intended to defraud his customers and the product remained on the market until Congress enacted a new food and drug statute without this so-called "fraud joker" in 1938. Banbar, in particular, gave drug regulators their first direct experience interpreting drug data obtained not from direct clinical trials, but from both uncontrolled trials and "historical" data, one of three types of clinical trial data eventually recognized as acceptable under law in 1970. [17]

Most consumers were unaware of Banbar, but in 1937, a broader drug disaster did capture public attention and first drew the federal government into playing a limited, but soon growing role in the evaluation of new drugs, including the conduct of clinical trials for new drugs. In 1937 a drug company developed a liquid preparation of the first "wonder drug" sulfanilamide, used to fight streptococcal infections (i.e. strep throat). The product was not tested in animals or humans prior to marketing. The solvent used to suspend the active drug, diethylene glycol, was a poison (chemically related to anti-freeze). It required the entire field force of the FDA to retrieve all available bottles of Elixir Sulfanilamide when the company's own recall efforts proved inadequate to the task. FDA officials soon discovered that adequate records had not been kept by either physicians or pharmacists documenting prescriptions written and filled for the poisonous product. FDA, however, was only empowered to act against the deadly product because it was misbranded – it contained no alcohol whereas the term "elixir" implied that it did contain alcohol.

Clinical Trials and the 1938 Food, Drug, and Cosmetic Act

Congress reacted to the tragedy, which killed over 100 people, by enacting a new federal food and drug statute, the 1938 Food, Drug, and Cosmetic Act. A new provision in the act-- requiring drug sponsors to submit safety data to FDA officials for evaluation prior to marketing -- appeared with relatively little discussion following on the heels of the Elixir Sulfanilamide disaster. "Instead of going to market based on their own assessment of the drug, sponsors had to notify the FDA of their intent to market the drug by submitting an NDA (New Drug Application)," explains Dr. Robert Temple, currently head of FDA's Office of Medical Policy. Although the new law did not specify any particular testing method(s), the law did require that drugs be studied by "adequate tests by all methods reasonably applicable to show whether or not the drug is safe." Sponsors were required to demonstrate to FDA that they had carried out all reasonably applicable studies to demonstrate safety and that the drug was "safe for use under the conditions prescribed, recommended or suggested in the proposed labeling thereof." [18] In the future, FDA could use these new tools not only to ban Banbar, but to try and prevent drug disasters rather than merely react to them.

Under the law, there was no true requirement for FDA "approval" or "clearance" of a new drug. Rather, it was presumed that most drugs would be marketed and therefore the default position was "approval." [19] Under the 1938 Act, the government had sixty days (could be extended to 180 days) to complete its safety evaluation. Form 356, the New Drug Application (NDA), required information about all clinical investigations, a full list of the drug's components and composition,

methods of manufacture including facilities and controls, and copies of both the packaging and labeling of the new drug. If a company had not received a regulatory response at the end of 60 days it could proceed with marketing its new drug.

Regulators adopted many of the standards and rules of evidence first advocated by turn-of-the-century therapeutic reformers. [20] Laboratory analysis akin to that originally conducted by the AMA's Chemical Laboratory initially screened most new drugs, companies were required to conduct safety studies, and an increasing number of drugs would soon be studied in the kind of clinical (cooperative) drug trials that the AMA's Council on Pharmacy and Chemistry had advocated, but not conducted, earlier in the century. [21] Animal studies were not required under the 1938 Act to precede human drug trials, but such studies, including animal autopsies, could be requested by regulators as part of the agency's drug safety review. FDA also began to employ the practice, similar to that of the Council, of consulting expert academic specialists, often before making a final decision on drug approvals. [22]

FDA's statutory authority over products increased as a result of egregious public health disasters, but the associated scientific methodology to evaluate safety and efficacy did not accelerate in tandem. Regulatory work under the new drug safety provisions of the Act was fairly limited, although the new law did sanction factory inspections for the first time and officials were able to eliminate many worthless products submitted for approval to treat serious diseases (i.e. cancer and diabetes) by holding them to be "unsafe" under the statute. [23] Regulators could deny an application if the sponsor's drug application did not include "adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended or suggested in the proposed labeling thereof." [24] Occasionally, in interpreting this provision, agency officials recommended labeling changes, including warnings, to sponsors and to the U.S.P., but FDA itself lacked authority under the 1938 Act to determine the text and layout of drug labels. [25] Larger efforts to improve drug testing, prescribing patterns, and patient use and compliance, however, were left to the practice of medicine and medicine's scientific and professional authorities.

Although FDA had authority under the 1938 Act to establish rules governing the use of investigational drugs, FDA did not employ this authority to regulate clinical trials and clinical trial methodology until 1961. [26] Even though physicians at elite university clinics and members from the AMA Council on Pharmacy and Chemistry all agreed on the importance of standardized drug testing through clinical trials, FDA did not have the authority to require them under the 1938 statute. [27] FDA scientists, however, did begin to exert some influence on the conduct of clinical trials and move in the direction of standardization on the eve of WWII, when they published an article in JAMA on experimental design, proper clinical trial methods, and methods of data analysis. [28] Their article, however, was published as a Report under the auspices of the AMA's Council on Pharmacy and Chemistry and was accompanied by a disclaimer to the effect that the "outline" presented in the report was "offered as an objective, a pattern, and not a regulation." During WWII, the agency actively promoted drug testing standards in the face of increased wartime expenditures for drug trials designed to answer important questions about the safety and use of many new drugs for the war effort. [29] An important breakthrough in clinical trial design followed from the shortages of a new drug, streptomycin, shortly after the war.

Following war trials of penicillin, British epidemiologist and biostatistician, A. Bradford Hill, was faced with the task of testing a promising antibiotic, streptomycin, against tuberculosis. Researchers in the United States studying the same drug had ample supplies and led to more effective treatment for patient subjects but produced less conclusive clinical trial data. [30] Hill and his colleagues, however, were faced with a severe shortage of the streptomycin drug they were studying. In post-war Britain, the central government could not afford to purchase more of the drug. Scarcity and expense, therefore, justified their decision to formally but randomly assign patients to control groups and treatment groups. This eliminated a well-known form of treatment "bias" in which physicians are known to select their healthier patients for experimental treatment leaving sicker patients in the control group. Hill's study was a true randomized study. It was not, however, "double blinded" – another way of insuring the objectivity of a trial by neutralizing the power of "suggestion."

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