How Are Drugs Approved?
Part 2: Ethical Foundations of Clinical Research

ABSTRACT

In the United States, the U.S. Food and Drug Administration (FDA) evaluates and approves drugs through a process that includes clinical research. The purpose of clinical research is to diminish uncertainty by acquiring knowledge. For drug development, the goal is to approve drugs that are safe and effective. Because of the uncertainty, however, participation in clinical research entails some degree of risk. Ethical principles provide the framework on which studies can be designed and conducted and which appropriately balance benefits and risks for research participants. As part of a broad overview of the drug development process, this article reviews the ethical foundations of clinical research.

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The U.S. Food and Drug Administration (FDA) evaluates and approves drugs through a process that includes clinical research. The purpose of clinical research is to diminish uncertainty by acquiring knowledge (Tannert, Elvers, & Jandrig, 2007). For drug development, the clinical research goal is to approve drugs that are safe and effective; however, participation in clinical research entails some degree of risk. Ethical principles provide the framework on which studies can be designed and conducted and which appropriately balance benefits and risks for research participants (Brody, McCullough, & Sharp, 2005). Ethics and research have genuine implications for nursing practice (Karigan, 2001; Mitchell, 2002). As part of a broad overview of the drug development process, the first article of this series described the historical evolution of the FDA (Howland, 2008), this article reviews the ethical foundations of clinical research, and the third article will focus on the stages of drug development.

NAZI MEDICINE: A TURNING POINT IN RESEARCH ETHICS

Historically, ethical standards for using and protecting human participants in clinical research have evolved in accord with changing moral values, social customs, and professional practices (Emanuel & Grady, 2006). Before the 20th century, little distinction was made between experimentation and therapy. "Researchers" were usually physicians who did, and were trusted to do, what they thought was best for their patients. There were no specific codes of ethics, laws, or regulations that governed the conduct of research. Checks on questionable or unethical practices were usually left to the anecdotal observations and judgment of individual peers (Benedek, 2005; Numbers, 1979). For example, one of the earliest statements about human experimentation was made by French physiologist Claude Bernard in 1865:

> It is our duty and our right to perform an experiment on man whenever it can save his life, cure him or gain him some personal benefit. The principle of medical and surgical morality, therefore, consists in never performing on man an experiment which might be harmful to him to any extent, even though the result might be highly advantageous to science, i.e., to the health of others…. Christian morals forbid only one thing, doing ill to one's neighbor. So, among the experiments that may be tried on man, those that can only harm are forbidden, those that are innocent are permissible, and those that may do good are obligatory. (as cited in Numbers, 1979, p. 135)

Unfortunately, major transformations of research practices and the development of more authoritative ethical guidelines sometimes have occurred only when egregious examples of negligent, willful, or even malicious behaviors have come to light (Emanuel & Grady, 2006). Such research abuses typically involved children, prisoners, or other vulnerable populations (Arboleda-Florez, 2005; Diekema, 2006; Schuklenk, 2000). Partly in response to human inoculation experiments with gonococcal infections conducted during the latter half of the 19th century, a regulation was passed in 1900 by the Prussian Ministry of Education, covering the Prussian region of Germany where much of this research was done (Benedek, 2005):

> The directors of clinics, outpatient departments and other medical facilities are advised that medical interventions for purposes other than diagnosis, treatment and immunization are prohibited even when other circumstances for legitimate and ethical permission are present when: 1) It pertains to a person who is still a minor, or for other reasons is not competent; 2) The person in question has not given her consent to the intervention unequivocally; 3) When the explanation does not provide adequate understanding of the possible injurious consequences of the intervention. (pp. 69-70)

Coincidentally, sulfanilamide was the first drug found that could treat gonorrhea, and it was a contaminated "elixir" formulation of this antibacterial agent that killed more than 100 people and led to a major change in FDA oversight of drug safety in 1938 (Howland, 2008). In 1931, following the deaths of 77 children in experiments with antituberculosis vaccinations, the Reich Health Council in Germany issued its "Regulations on New Therapy and Human Experimentation." Among the provisions of this German national policy were that "innovative therapy may be carried out only after the subject or his legal representative has unambiguously consented to the procedure in the light of relevant information being provided in advance" (Weindling, 2001, p. 41).

In the wake of the horrendous Nazi Germany "medical science" experiments conducted on prisoners during World War II, the International Military Tribunal issued a code of ethics at the conclusion of the Nuremberg Medical Trial (Weindling, 2001). Known as the *Nuremberg Code* (1949), this represented the first international code of research ethics and outlines 10 basic principles of human research. Also in response to the Nazi-era medical atrocities, the

International Code of Medical Ethics of the World Medical Association (WMA) was issued in 1949. It stated that "a physician shall always bear in mind the obligation to respect human life" (Duties of Physicians to Patients, ¶1), that the health of the patient will be the physician's first consideration, and that "a physician shall act in the patient's best interest when providing medical care" (Duties of Physicians to Patients, ¶2) that might weaken the patient's physical and mental condition. The code also included the *Declaration of Geneva,* which was previously adopted by the WMA in 1948 and was intended as a modern revision of the Hippocratic Oath.

In the United States in 1953, the National Institutes of Health (NIH) clinical research center formulated an agency policy that ethical responsibility for medical experiments lies with the study's principal investigators. As part of the landmark Kefauver-Harris Drug Amendments legislation (passed in 1962 in response to the thalidomide tragedy in Western Europe), the FDA issued a formal regulation in 1963 that, for the first time, required clinical investigators to certify informed consent of participants in drug efficacy and safety studies.

The WMA developed the *Declaration of Helsinki* in 1964 as a set of ethical principles for the medical community regarding human experimentation. It is an important document in the history of research ethics as it is the first significant effort of the international medical community to regulate research itself, and it is widely regarded as the cornerstone document of human research ethics that forms the basis of most later documents. The *Declaration of Helsinki* further developed, combined, and expanded on the principles of the *Nuremberg Code* and the *International Code of Medical Ethics* to more specifically address various aspects of clinical research. It was originally adopted in 1964 and has undergone five revisions and two clarifications (most recently in 2004), growing in length from 11 to 32 paragraphs.

BEECHER, TUSKEGEE, AND THE BELMONT REPORT

In 1966, the *New England Journal of Medicine* published a seminal paper in which Henry Beecher described 22 examples of unethical medical experiments performed on human beings and urged appropriate reform of research practices. Interestingly, Beecher had conducted clinical studies of lysergic acid diethylamide (LSD) in the 1950s. These studies were later considered abusive and unethical, although Beecher did not cite his LSD work in the 1966 article (Mashour, 2007).

The 1966 article was highly influential; its publication generated considerable discussion, debate, and controversy among medical professionals, researchers, the public, and government officials (Freidenfelds, 2007). Consequently, the U.S. Surgeon General issued an official policy statement ("Clinical Research and Investigation Involving Human Beings") (Freidenfelds, 2007) in 1966. This policy formally required that all federally funded research and research training grants involving human participants be reviewed and approved by local review boards. This is the origin of what is now known as the Institutional Review Board (IRB) system. Specific requirements of the function of IRBs and the elements of informed consent were then defined by FDA regulations.

Another critical event was the highly publicized exposé in 1972 of the U.S. Public Health Service (USPHS) Syphilis Study at Tuskegee (McCallum, Arekere, Green, Katz, & Rivers, 2006). From 1932 to 1972, the USPHS conducted an experiment involving the observation of the course of untreated syphilis among 399 African American share croppers in Alabama (R.M. White, 2000). Disclosure of the Tuskegee Study had prominent and long-lasting effects on the conduct and oversight of human research. The most significant consequence was enactment of the National Research Act (NRA) in 1974, which required the U.S. Department of Health, Education, and Welfare (DHEW; now the U.S. Department of Health and Human Services [USDHHS]) to incorporate existing research policies into specific regulations ("Regulations for the Protection of Human Subjects of Biomedical and Behavioral Research"). The specific regulations are outlined in the *Code of Federal Regulations* (CFR), *Title 45, Part 46* (known as 45 CFR 46) (2005). The provisions of Subpart A 45 CFR 46 broadly govern the ethical conduct of research, including the protection of human participants, informed consent, and IRB guidelines. Additional subparts to 45 CFR 46 created special protections for pregnant women and fetuses (Subpart B, 1974), prisoners (Subpart C, 1978), and children (Subpart C, 1983).

The NRA also authorized formation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This Commission, meeting from 1974 to 1978, issued seminal reports on the following topics: research on fetuses (1975), research with prisoners (1976), research with children (1977), psychosurgery (1977), disclosure of research information (1977), research in-

volving individuals with mental illness (1978), ethical guidelines for delivery of health services by DHEW (1978), IRBs (1978), and implications of advances in biomedical and behavioral research (1978), as well as *The Belmont Report* (1979). Specific information about all of these reports can be accessed online from The President's Council on Bioethics Web site: http://www.bioethics.gov.

In developing these reports, the Commission's fundamental purpose was to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human participants and to develop guidelines that should be followed to ensure such research is conducted in accordance with those principles. The Commission contemplated the following issues:

- The boundaries between biomedical and behavioral research and the accepted and routine practice of medicine.
- The role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human participants.
- Appropriate guidelines for the selection of human participants in such research.
- The nature and definition of informed consent in various research settings.

The Belmont Report, issued in 1979, was the defining culmination of the Commission's work. It is a statement of basic ethical principles and guidelines that should be used to resolve ethical problems surrounding the conduct of human participants research. The report explains the unifying ethical principles forming the basis for the Commission's other reports and the ensuing regulations that incorporate its recommendations. The three fundamental ethical principles for all human participants are respect for persons, beneficence, and justice (*The Belmont Report,* 1979; Whitney, 2001a, 2001b). The report is an important historical document in biomedical ethics, and it remains an essential reference document for IRBs that review clinical research proposals involving human participants to ensure the research meets the ethical foundations of the 45 CFR 46 regulations.

RESEARCH ETHICS SINCE *THE BELMONT REPORT*

The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research was formed in 1978. This congressionally mandated Commission succeeded the NRA Commission. Meeting from 1980 to 1983, it issued key reports on the following topics: defining death (1981), protection of human participants (1981), whistle blowing in biomedical research (1981), an IRB guidebook (1981), compensation for research injuries (1982), social and ethical issues of human genetic engineering (1982), health care decisions (1982), foregoing life-sustaining treatment (1983), screening and counseling for genetic conditions (1983), and securing access to health care (1983). The Ethics Advisory Board (a separate Presidential bioethics commission) issued a single report on human embryo research (*DHEW Support of Research Involving Human In Vitro Fertilization and Embryo Transfer: Report and Conclusions*) in 1979 (The President's Council on Bioethics, n.d.).

FDA regulations related to the protection of human participants (21 CFR 50) and IRBs (21 CFR 56) were revised in 1981 to correspond to existing USDHHS ethical regulations (45 CFR 46). In 1991, the USDHHS and 14 other federal departments and agencies adopted a uniform set of rules for the protection of human participants, identical to Subpart A of 45 CFR 46 of the USDHHS regulations. This uniform set of regulations is the *Federal Policy for the Protection of Human Subjects,* informally known as the "Common Rule."

A final report of the Advisory Committee on Human Radiation Experiments (created in 1994) was issued in 1995. The purpose of the Advisory Committee was to investigate reports of possibly unethical radiation experiments funded by the government during the Cold War era. This extensive report describes the history of standards for conducting human radiation research, describes the history of human radiation experiments through representative case studies, assesses whether current protections for human participants are better than those during the 1944-1974 period, and recommends the changes that should be instituted in current policies governing human participant research on the basis of these findings. The Office of Human Radiation Experiments in the Department of Energy, established in 1994, leads an ongoing effort to investigate and report on radiation research.

The Human Embryo Research Panel, formed by the NIH, issued a report in 1994 (The President's Council on Bioethics, n.d.) that classified human embryo research into three categories (acceptable, needing additional review, unacceptable); it also drafted guidelines for the review and conduct of acceptable research. The National Bioethics Advisory Commission, meeting from 1996 to 2001, issued a series of ethical and policy reports on the following

topics: human cloning (1997), research involving individuals with mental disorders that may affect their capacity for decision making (1998), research involving human biological materials (1999), ethical issues in human stem cell research (1999), ethical and policy issues in international research (2001), and ethical and policy issues in research involving human participants (2001).

FDA regulations were revised in 1996 to allow exception from informed consent requirements for research studies involving emergency research. In 1996, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) developed its guideline (E6) for good clinical practices. The ICH E6 is an international ethical and scientific quality standard for designing, conducting, recording, and reporting research studies that involve human participants, providing a unified standard for the European Union, Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in those jurisdictions. Compliance with ICH E6 ensures clinical trials are accurate and credible and that the rights, safety, and well-being of research participants are protected.

Although the guidelines were codified in 1996, their development was based on many of the important ethical documents described above. With the Modernization Act of 1997, the FDA (n.d.) formally required that biomedical research be conducted in accordance with specific regulatory guidelines based on ICH E6 (good clinical practice). The World Health Organization (2000) published its *Operational Guidelines for Ethics Committees that Review Biomedical Research*, which suggested the role, constituents, and requirements for ethics committees. This was intended to facilitate and support ethical review in countries around the world, including cross-national clinical research studies.

In 2000, the USDHHS began to require that all federally funded investigators complete documented training in the responsible conduct of research, including training in the ethical use of human participants. Such training also extended to members of ethical review committees. This policy was formulated partly in response to several highly publicized events, including the deaths of several clinical trial participants and the temporary suspension of several prominent research programs because of apparent lax IRB oversight discovered during NIH and FDA audits (Fost & Levine, 2007; Kahn & Mastroianni, 2001; Karigan, 2001).

The FDA amended its regulations for new products in 2002 so certain human drugs and biologics intended to reduce or prevent serious or life-threatening conditions could be approved on the basis of evidence of effectiveness from appropriate animal studies when human efficacy studies are not ethical or feasible. This action was part of the federal government's broad bioterrorism-preparedness program, in recognition of the need for adequate medical responses to protect or treat individuals exposed to lethal or permanently disabling toxic substances or organisms. This rule would apply when adequate and well-controlled clinical studies in human beings cannot be ethically conducted because the studies would involve administering a potentially lethal or permanently disabling toxic substance or organism to healthy volunteers. Products used to reduce or prevent the toxicity of chemical, biological, radiological, or nuclear substances may be approved for use in human beings on the basis of evidence of effectiveness derived only from appropriate animal studies and additional supporting data, but they would still be evaluated for safety under preexisting requirements for establishing the safety of new products.

CONCLUSION

Science and ethics are entwined, especially so in clinical research (Dawson & Yentis, 2007). Although ethical considerations should necessarily guide the scientific process, this has not always happened. Ethical standards must continue to evolve to keep pace with scientific advances. The President's Council on Bioethics, created in 2001, is an ongoing council charged with advising the President on bioethical issues that may emerge as a consequence of advances in biomedical science and technology. So far, it has published reports on the following topics: human cloning and dignity (2002), biotechnology and the pursuit of happiness (2003), being human (2003), monitoring stem cell research (2004), reproduction and the regulation of new biotechnologies (2004), alternative sources of pluripotent stem cells (2005), and ethical caregiving in our aging society (2005).

Human genetics research is one of the most important contemporary bioethical topics. The Ethical, Legal and Social Implications Research Program is the largest bioethics initiative funded by the federal government. Since 1989, it has been studying the ethical, legal, and social implications of human genome research, currently focusing on four areas: the use and interpretation of genetic information, clinical integration of genetic technologies, issues surrounding genetics research, and public and

professional education and training on those issues. Nurses have an important stake in these contemporary topics (Mitchell, 2002; G.B. White, 2000), justifying the need for continuing education in clinical research ethics (Jeffers, 2002). After describing the historical evolution of the FDA and reviewing the ethical foundations of clinical research, this series will conclude with an article covering the stages of drug development.

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