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Ethics, Human Rights, and Clinical Research

Editors' note: This article is the eleventh in a multipart series designed to improve the knowledge base of readers, particularly novices, in the area of clinical research. A better understanding of these principles should help in reading and understanding the application of published studies. It should also help those involved in beginning their own research projects.

Ethical treatment of human subjects is fundamental to the conduct of research. Although respect for the rights of others has long been ingrained in health professionals, it was not until the mid 20th century that principles of conducting research with respect to human subjects and their rights were defined. Many principles and guidelines are in place today to protect subjects and assure that research is conducted in a way that prevents harm. Federal and international regulations ensure that research studies have institutional review board (IRB) review by an independent panel not involved with the research. The panel protects patient rights, analyzes the validity and methodology of the research, ensures subjects have been provided informed consent, and scrutinizes for compliance with federal regulations. This article discusses historical context, ethical principles, and legal guidelines to protect human subjects; the institutional review process; informed consent; multi-site studies; and guidelines for emergency research.

Historical Overview

Requirements of informed consent are derived from a 1914 New York legal case, *Schloendorff vs. Society of New York*, for which Supreme Court Justice Cardozo ruled, "Every human being of adult years and sound mind is entitled to determine what is to be done to his body."[1] This law still exists; however, "consent" in practice and research has often been ignored or misinterpreted. Not until after World War II, when Nazi physicians were charged with murder for atrocities against other human beings, did violations of informed consent received widespread attention. In 1947, the Nuremburg Code was written and used for judgment of war criminals at the Nuremburg trials.

The Nuremberg Code is a cornerstone for human experimentation and research ethics. The summarized principles include voluntary and informed consent, autonomy in decision making, risk/benefit and avoidance of harm, and benefit to society.[2] Consent is a process designed to ensure that the researcher respects the subject's self-determination and ability to make free choices. Failure to obtain consent, or any violations of the consent principle, regardless of whether harm results, is viewed as battery and negligence.[3] Consent is held to be invalid if any information deemed necessary or important to the subject's decision-making process is withheld. Key components of the consent include knowledge of risk and benefits, duration of study, right to refuse, right to withdraw with impunity, and where and by whom the study is being conducted. The researcher is responsibility for demonstrating the subject's grasp of the material before giving consent.[3]

Although the Nuremberg Code served as a basis for ethical principles, it was ignored by researchers who believed it was developed to convict those physicians who committed war crimes. Others believed the Nuremburg Code to be incomplete, which led to the Declaration of Helsinki by the World Medical Association in 1964. The declaration reinforced the principles of the Nuremburg Code and further addressed privacy, parameters for consent, competency, vulnerable populations and those at risk, and accuracy of published results. The declaration provided the "how to" for conducting ethical research and placed responsibility for subject welfare in the hands of the researcher. Subsequent to the Declaration of Helsinki, biomedical journals adopted its provisions and today uniformly require that research be performed in accordance with the Declaration.[4,5]

In the 1966 *New England Journal of Medicine* article entitled "Ethics and Clinical Research," Dr. Henry Beecher cited 22 representative examples from over 200 experiments on humans conducted by unnamed, well-respected investigators from leading institutions, in which basic, accepted standards of human subject treatment were disregarded and the results had been published in respected journals.[6] One example cited by Beecher included increasing carbon dioxide levels in surgical patients and observing life-threatening arrhythmias.[6] Another study included injecting chronically ill patients, without patient knowledge or consent, with cancer cells and observing the course of the disease.[6,7]

After Beecher's publication, the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) altered their investigator guidelines to require peer-reviewed superintendence and evidence of informed consent in all human experiments.[7] In 1966, the US Public Health Service mandated that all federally funded research

involving human subjects be reviewed by a committee of institutional associates.[8,9]

In 1974, the National Research Act (Pub. L. 93-348) was signed into law, creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report, "Ethical Principles and Guidelines," summarizes the Commission's work and includes respect for persons, beneficence, justice, application of the general principles in informed consent, assessment of risk and benefit, and selection of subjects.[10] **Respect for persons** acknowledges that each individual should be treated as an autonomous agent and that those with diminished autonomy are entitled to protection.[10] **Beneficence** refers to respecting a subject's decisions and protecting a subject from harm. This includes maximizing benefits and minimizing harm, actual or potential. **Justice** incorporates fairness of distribution so that no one is denied a benefit unless there is good cause. An investigator's number one responsibility is to design and implement research based on these three principles. Application of these three briefly described principles is evidenced in the areas of informed consent, risk/benefit assessment, and selection of subjects for research.[10]

Regulatory Standards

Federal law requires the Department of Health and Human Services (DHHS) to issue regulations for the protection of human subjects of research and to implement a program of instruction and guidance in ethical issues associated with research. These regulations are codified at Title 45, Part 46 of the Code of Federal Regulations, Protection of Human Subjects, 45 CFR 46.[11]

The Council for International Organizations of Medical Services publication "International Ethical Guidelines for Biomedical Research Involving Human Subjects" provides guidelines for international studies, and the Tri-Council Policy Statement "Ethical Conduct for Research Involving Humans" describes the policies of the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, and the Social Sciences and Humanities Research Council of Canada.[12,13]

Institutional Review Approval

All research involving human subjects is required by federal regulation to be submitted for IRB review. Each institution has individualized forms that incorporate criteria and guidelines for review and approval as established by the DHHS Office for Protection for Research Risks and published in the Code of Federal Regulations.

The IRB committee's main responsibility is to protect the rights and welfare of human subjects and to the evaluate risks/benefits and ethical components of the proposal. The committee is composed of at least five people from diverse backgrounds. At least one member must be from outside the institution where the IRB is reviewed. Under 45 CFR 46, 111, IRBs are responsible for determining that risks to subjects are minimized and reasonable in relation to anticipated benefits, selection of subjects is equitable, privacy and confidentiality of subjects are protected, and appropriate safeguards exist to protect vulnerable populations.[14]

Research must be categorized as exempt, expedited, or full review according to federal criteria. Exempt and expedited reviews are for studies having minimal risk. Six categories of research may be considered exempt. One example includes "research conducted in a commonly accepted education setting, involving usual education practice." Expedited refers to several types of research authorized by 45 CFR 46.110. and 21 CFR 56.110, such as collection of blood samples by finger stick, heel stick, or ear stick, from healthy, nonpregnant adults who weigh at least 110 pounds, or prospective collection of biological specimens for research purposes by noninvasive means.[15] Exempt and expedited reviews do not apply for certain populations of people, such as prisoners or pregnant women. The classification of exempt or expedited is to be made by the appropriate IRB. The investigator may not make this determination independent of the IRB.

The purpose of the Health Insurance Portability and Accountability Act of 1996 is to regulate the sharing of medical information. This act stipulates requirements related to exempt studies. Studies classified as exempt are limited to studies with de-identified data, studies with a limited data set, and studies with health records of decedents. Studies not qualifying for exempt or expedited status must be submitted for full review. Full board review implies that there is more than a minimal risk to subjects or that the study involves a vulnerable population.

Before submitting for IRB review, the researcher is advised to visit the IRB office and discuss the process, including deadlines, guidelines, and expected time for review decision. An instruction packet may be obtained from the IRB office with instructions and guidelines for submitting for review. The packet includes information relating to type of review categories, submission requirements, responsibilities of the principal investigators (PI), guidelines for research involving health care data, and IRB forms for informed consent, for summary safeguards, for study amendments, and for reporting of adverse events.

In most institutions that provide IRB review, investigators are required to take a human subjects protection test, usually accessed through the IRB institution. Alternative training can be accessed at the NIH website and at the Office of Research Integrity (ORI), DHHS.[16-18] The ORI programs cover topics such as data acquisition, conflicts of interest, human subjects, animal welfare, research misconduct, publication practices, responsible authorship, and peer review.[18] The Collaborative Institutional Training Initiative is another online resource for education of human subjects' protection and the responsible conduct of research.[19,20]

The PI, as leader of the research team, is responsible for ethical conduct of the research, maintaining IRB records, advertisement and recruiting of subjects, reporting deviations from protocol, ascertaining the need for protocol amendments, reporting adverse effects, and other responsibilities spelled out in the IRB Instruction Packet. Changes

in research protocol must be reported to the IRB. IRB approval is good for 1 year, at which time a status report is submitted by the PI each year. Continued approval may be granted if needed and appropriate. All research documentation is subject to federal audit.

Sometimes local IRB review is not possible, as may be the case when an air medical transport program is not affiliated with an institution that has IRB review. In this situation, the review may need to be performed in a place other than where the research is conducted. An independent or nonlocal IRB may review studies that are not performed on-site as long as the 21 CFR parts 50 and 56 requirements are met.[21] Guidelines for nonlocal IRB review are outlined in FDA guidelines 21 CFR parts 50 and 56.[22]

Multi-site Studies

Multi-site studies offer multiple advantages for research. Such studies enhance generalization by providing access to a larger number of subjects with geographical representation and may accrue more subjects for studies involving those with rare conditions or traits.[23] These studies, however, pose a number of well-documented challenges, including differences in IRB requirements, lack of standardized forms, influence of institutional culture, regional thinking, varied experiences of investigators meeting the requirements, and requests of the various geographical review boards.[24] Other issues include increased expense, plus varied and prolonged time for review at each of the various sites.[23-26]

Given the obstacles to multi-site research, a number of investigators have identified strategies to navigate the process and still maintain the integrity of human ethics. Dewa and Durbin[27] cite a summary of challenges, solutions, benefits, and requirements for multi-site success that are categorized as communication, contribution, compatibility, consensus, credit, and commitment. Communication, education, and standardization of forms were additional strategies to multi-site success.[23,28]

Cooperative research, involving research at more than one site, is sanctioned by 45 CFR 46.114. Models include a joint review agreement in which an institution may rely on a central institution for IRB review entirely or use a model with certain sections of an IRB review divided among the different institutions. The study is coordinated at each site by a project coordinator and, as with any study, the final responsibility belongs to the PI. When funds are allocated to an institution, the awarded institution lists each of the cooperating institutions and their respective IRBs.

Informed Consent

Informed consent is a process of human subject protection. The basic premise of consent is that subjects are autonomous and have a right to self-determination. This requires that subjects have the mental ability and are legally competent to make an informed choice. Another premise of consent is that of volunteerism, which implies that after being fully informed, subjects choose to participate, without coercion.[29] Special considerations are present for vulnerable populations. When children are research subjects, federal law requires parental signature and in some cases voluntary assent by the child.[30]

Administration of the consent form involves a verbal explanation of the study, including purpose, number of participants, study procedure, risks and benefits of participation, confidentiality, cost or compensations, the voluntary nature of participation, which addresses the subject's right to refuse participation or to withdraw without penalty, and contact information for the researcher. The consent form should: (1) be written at a reading level that potential subjects will be able to understand (typically sixth to eight grade); (2) provide simple definitions, avoiding use of jargon; and (3) use subject headings and an easy-to-read font.[31] The researcher is responsible for assuring that the subject is competent, understands the study content presented in the consent form, and is not under any undue stress that might influence participation. A subject's signature is obtained to document verification of the explanation. A number of issues plague the informed consent process even in the presence of best intentions. Subjects may be poorly educated, have a grave illness that clouds the consequences of participation, or feel a need to please a researcher. Throughout the consent process, all measures must be taken to assure respect for person, beneficence, and justice.

Table 1. Emergency Exception to Informed Consent

Excerpts from 21CFR 50.24
• Subject is in life-threatening situation
• Subject is unable to consent because of condition
• No time to contact subject's legally authorized representative
• Available treatments are untested or deemed unsatisfactory
• Possibility must exist that subject will benefit from treatment
• Prior community consultation and public disclosure of study protocol

Data from Title 21, Part 50, Section 24. Exception from informed consent requirements for emergency research. Available at http://www.cfsan.fda.gov/-lrd/cfr50.html. *Accessed November 1, 2007.*

Guidelines for Emergency Research

In 1966, a Waiver of Informed Consent Guidelines for emergency research was established under federal rule (21CFR 50.24). The federal guidelines commonly referred to as Final Rule outline qualifying criteria for subjects (Table 1) and include required provisions for community consultation and public disclosure of proposed emergency research.[32] An example of community consultation and disclosure includes researchers holding town hall meetings to discuss the meaning of exemption of consent for emergency research and information regarding study protocols.[32] However, because the term "community" may be interpreted with different meanings, it is recommended that the definition and plan for public disclosure of study information be discussed with the IRB before implementation.[33] The reference list contains a number of examples of

research in emergency patients and of study experience with 21 CFR 50.24.[33-37]

IRB hesitancy to approve emergency research requiring waiver of consent and inconsistencies in the public disclosure process prompted a committee of the American Hospital Association to develop and publish, in 2007, "Recommendations for Implementation of Community Consultation and Public Disclosure Under the Food and Drug Administration's "Exception From Informed Consent Requirements for Emergency Research.""[38,39] The recommendations categorizing subjects according to risk are endorsed by the American College of Emergency Physicians and the Society for Academic Emergency Medicine. The guidelines give examples to help IRBs become familiar with the process of implementing and reviewing studies with exception to informed consent and propose that trials of interventions approved by the FDA should require different levels of community consultation and public disclosure than studies of unapproved interventions.[38]

Summary

Despite the safeguards imposed by the IRB and the consent process, the prospective researcher still may have problems with ethical considerations. There are many motives for performing clinical research, which run the gamut from patient-care concerns, such as inadequate standard therapy, to those less pure, such as reimbursement and academic standing. It is imperative that the rights and welfare of study populations be observed and guarded strictly. This means that all studies must be reviewed by an appropriate IRB before initiation of the study. Failure to do so not only may compromise the ethical integrity of the study but also may prevent the investigator from publishing their findings.

Although emergency research may present challenges, recently published guidelines give direction for emergency research requiring waiver of informed consent. Knowledge of the guidelines and federal regulations will assist the researcher to know the expectations necessary to prepare for an IRB review. Ongoing dialog with an IRB representative is helpful to explain and clarify the study and assure that questions are answered before IRB submission.

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