ETHICS IN CLINICAL RESEARCH:

The Nursing Perspective

Strict codes and regulations governing clinical research are in place to protect patients; nurses must strike a balance between providing optimal care to patients and advancing medical knowledge.

On May 4 of this year, Ellen Roche inhaled a gram of hexamethonium; on June 2, the previously healthy 24-year-old died. Researchers at Johns Hopkins University in Baltimore had prescribed the experimental agent as part of a clinical trial that sought to determine the causes of asthma (hexamethonium is a ganglionic blocking agent that was used to prevent constricted airways from opening, mimicking asthma, though it’s not approved for use as an inhalant). As reported in the New York Times and elsewhere, it was determined several weeks after her death that the drug destroyed Ms. Roche’s lung tissue.

Consequently, on July 19 the Office for Human Research Protections, a federal agency, suspended all research using humans at Hopkins—the recipient of more federal funding for research than any other university (upwards of $300 million annually)—charging its ethics committee with failure to protect its subjects. It had come to light that the trial’s lead investigator, Alkis Togias, failed to report to Hopkins’s internal review board a previous subject’s adverse reaction to hexamethonium; neither did he inform participants that the agent was experimental. But the review board may also have been at fault; it approved hexamethonium for use in the asthma study, despite evidence dating from the 1950s that showed possible lung damage caused by hexamethonium when used to treat hypertension. On July 23, having reached an agreement with Hopkins officials that stipulated “corrective action”—including the continued suspension of more than 2,000 studies that had undergone insufficient review (as well as the discontinuation of Togias’s research, though he remains employed by the university)—the Office for Human Research Protections resolved that the university may resume its research on humans.

That a formerly healthy young woman died after inhaling an experimental drug given to her by researchers led to a flurry of media attention that spotlighted what the public has seen, increasingly in recent years, as faulty: the ethical conduct of researchers.

Such cases may exacerbate the unfavorable view many people have of clinical trials and research as exemplifying the medical establishment’s interest in experimentation for the sake of science rather than the sake of public health. Although ethical conduct in clinical trials and research is of concern to all health care professionals, it’s the nurse, especially, who must maintain a balance between patient safety and risk. And trying to maintain such a balance often leads to personal and professional dilemmas.

Clinical trials offer exciting opportunities for nurses to expand their scope of practice and they often serve as the best opportunity for patients to receive state-of-the-art treatment. But an understanding of the complex rules, regulations, and issues governing trials and research, such as the meaning and importance of informed consent, research protocol, and how an institutional review board (IRB) functions, is absolutely essential to providing nursing care in a clinical trial. This article discusses the ethical implications of caring for research patients and offers a historical perspective on research and the development of the regulations governing it.

HISTORICAL PERSPECTIVES

The idea that human subjects involved in clinical trials and research should have rights was documented as long ago as the early 1800s. In 1833, the American
physician William Beaumont created guidelines by which ethically sound clinical studies could be conducted. He stipulated absolutely that the patient must be fully informed before providing consent and that he should have the right to withdraw from the study at any time. The Nazis. The importance and necessity of vigilant oversight to ensure ethical treatment of patients involved in research became apparent during the Nuremberg trials, in which Nazi physicians were tried for atrocities committed against concentration camp prisoners during World War II. Some of the "experiments" involved amputation, sterilization, euthanasia, and exposure to poisons, disease, and untested drugs, and most were conducted without any form of anesthesia on patients who were not permitted to decline participation. Not only scientists, but high government, military, and Nazi party officials performed many of the experiments, as was the case in the Dachau hypothermia experiments, which were directed by Sigmund Rascher, who was neither a physician nor a scientist. The experiments on the prisoners did not follow proper protocols, which resulted in questionable conclusions, the scientific value of which is still debated, and many subjects died or suffered permanent physical or psychological damage. In response to the horrors that came to light during the trials, the Nuremberg Code was developed to define the ethical conduct of research. (See Significant Research Documents, page 28.)

Once the Nuremberg Code was in place, scientists and physicians assumed that all investigators would conduct research and trials ethically. However, by the 1960s issues not covered by the code had arisen. Documents such as the Declaration of Helsinki, completed in 1964, served to extend the principles of Nuremberg to questions such as the validity of proxy consent and the need for institutional review board oversight and approval of research performed on human subjects.

Tuskegee. From 1932 to 1972 the U.S. Public Health Service (USPHS) conducted what is considered to be one of the most atrocious violations of human rights and medical ethics in U.S. history, the Tuskegee Syphilis Study. In Tuskegee, Alabama, the study examined the natural course of syphilis in black men aged 25 to 60. The participants were told that they would be joining a health program and were promised treatment of their "bad blood," a term used to describe any ailment, including venereal disease. Although it was clear by 1936 that these men had developed serious complications of syphilis such as cardiovascular, neurologic, and bone and joint conditions, the study continued, and they were kept uninformed of the nature of their illnesses and were not told that they were participating in a study. In the late 1940s, penicillin was available and found to be curative of syphilis, but it was deliberately withheld from the unwitting participants so that the long-term effects of syphilis could be studied. In 1969, even the Centers for Disease Control determined that the study should continue. The study, which was designed to take six months, lasted 40 years, and researchers actually
Jean Heller of the Associated Press, revealed the story using information from a whistleblower at the USPHS. The next day, the headline of the New York Times read “Syphilis Victims in the U.S. Study Went Untreated for 40 Years.”

After the details of the Tuskegee Syphilis Study were made public, the National Research Act of 1974 (P.L. 93-348) was passed and the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established to create a document that delineated the importance of protecting the patient in research trials and studies. The Belmont Report was the result of that effort and remains today a guide to the ethical treatment of patients who participate in clinical trials and research.

The Nazi experiments and the Tuskegee Syphilis Study have forever changed the standards of care and what health care professionals and the public believe to be the proper conduct of clinical trials and research. Although key research documents provide health professionals with codes and guidelines to help them better handle ethical research challenges, documents such as the Nuremberg Code and the Belmont Report cannot prevent an investigator from conducting research unethical, as codes and guidelines do not automatically protect patients. All health care personnel involved in providing care to research patients should understand the various resource documents, as well as the standards of fair clinical practice in research.

THREE ETHICAL DILEMMAS

Informed consent: Consider the following dilemma involving informed consent:
You are a nurse working on an oncology unit, and you overhear a physician talking to a patient about the investigational drug the patient will be taking during a clinical trial in which he has chosen to participate. You are unable to locate the patient's informed consent form, so you ask the physician for a copy. You are told that it is "somewhere in my office."

Ask yourself: What is my responsibility? Should I demand to see the consent form? Should I consult the nurse manager, my colleagues, or the hospital ethics committee about the matter? Should I ask the patient if he has a copy? Should I merely assume that the consent form is, indeed, somewhere in the physician's office and proceed with the treatment as ordered?

The nurse's responsibility lies with both the patient and the research team, and simply assuming protocol is being followed is not acceptable. If the patient's signed informed consent form is not in his chart, the nurse should request a copy of it from the principal investigator before treatment begins.

Violations of the ethical principles of informed consent are committed when there is no consent, or
when a consenting patient is either not fully informed of the details of a research study or trial or is not continually informed of study changes or results.

If the patient had not given informed consent, his participation in the clinical trial would have been morally wrong and legally prohibited, as written informed consent must be obtained from all patients participating in research. A copy of the consent form should be given to either the patient or the person signing for him. Informed consent is not simply a document, it entails a process that requires patients to have enough information to make an informed decision about the clinical trial or research in which they are being asked to participate. Nurses need to assess patients for both their willingness to participate and their understanding of the clinical implications of the study.

Open communication between the nursing staff and research personnel is also important in successful protocol management. All research must be conducted within the bounds of federal regulations, and this necessitates following the guidelines regarding all aspects of informed consent, the basic elements of which are included on all consent forms. Additional elements are added when clinically indicated by the type of study. Discussing the consent form with the patient affords him a better overall understanding and provides the nurse with the opportunity to clarify particular issues she thinks are especially pertinent to his case. (See Basic and Additional Elements of Informed Consent, page 30.)

Research protocols. Consider the following dilemma involving research protocols documentation:

A physician writes an order for an investigational drug to be given as soon as possible to a cardiology patient admitted to the emergency room, but you are not familiar with the drug and information about it cannot be found on the unit. When you call the physician for more information, he says, "It's part of the research protocol. Just give it as ordered.

Ask yourself: What is a "research protocol"? Where can I find more information? Do I have the right to refuse a physician's order? Who else may serve as a resource in this situation?

A research protocol is a written document detailing how a clinical trial is to be conducted, elements of which are background information, study design, treatment plan, objectives, eligible patients, study requirements, and evaluation. Nurses need to know the outline of the protocol and how to find specific information related to it, such as drug dosages, side effects, and nursing implications. Such information could provide an additional mechanism to protect the patient and to make judgments about conflicts between the study and the changing needs of the patient.

The nurse may refuse a physician's order to administer an investigational drug if she is unsure whether it will interfere with her primary concern, which is to provide the best care possible. However, she does have the obligation to consult resources, and in regard to investigational drugs, this would entail a conference with the pharmacist, who fulfills the role of educator by providing information and support to nurses involved in clinical research care.

All research protocols should contain contact names and numbers of the sponsor, principal investigator (PI), all research personnel, and the chairperson of the IRB, any of whom can be used as resources if a nurse is confronted with the problem of having to refuse a physician's order. The protocol outline should be kept in a designated location on the nursing unit, as nurses need to know how and where to obtain it for the purpose of referring to any guidelines that pertain specifically to their roles.

Disclosure. Consider the following dilemma involving full disclosure and the patient's right to information:

You're working on a psychiatric unit and know that your patient is involved in a double-blind, randomized research study. As you dispense his medication, the patient says, "My doctor said I should participate in this study, and I was afraid that if I didn't, he'd get mad at me. Please, don't give me the placebo. I want the real stuff or I'm going off the study!"

Ask yourself: What can I do to support the patient? What information can I provide? What if the patient demands to know which drug he is taking? Should I inform the PI of the patient's concerns?

All research participants have the right to full disclosure of information. Nurses can help alleviate the patient's fear by answering questions related to the study, but the investigator or research nurse should obtain informed consent, which is contingent on full disclosure. The nurse should then support the patient's decision to participate in the study and encourage the research investigator to address the patient's concerns, as uncertainty can make the patient ambivalent about his involvement. It is hoped that patients who have chosen to leave the course of established medical practice for the research area have made an informed decision.

Randomization is a procedure used to arbitrarily assign research participants to either the standard treatment (control) or the experimental treatment (intervention), ensuring that each one has an equal chance of being placed into either one of the study groups. If a patient asks a nurse to make sure he is not assigned placebo treatment, she should explain the nature of randomized testing and also alert the PI, since this type of request from a patient may indicate that he does not fully understand the trial.

A patient may perceive subtle coercion to partic-
related topics. Nurses can use these resources for support during clinical research.

The Office for Human Research Protections (OHRP) is a U.S. Department of Health and Human Services subdivision designed to protect human subjects and to provide guidance on ethical issues regarding their participation in research. The OHRP oversees patient safety at more than 500 institutions as well as research that involves minors. In the October 2000 issue of AJN, the News reported on a nurse who blew the whistle on a research study in Oklahoma by contacting the OHRP. The nurse complained that the principal researcher violated safety and research protocols during the study, which was halted; an FDA investigation was begun.

An IRB is a committee in the institution or agency that sponsors or serves as a site for research and is required by the federal government in any organization receiving federal funds for research. It's responsible for reviewing and approving studies to ensure that clinical research is ethical, safe, and scientifically sound. All research and trial protocols are reviewed at least annually. A minimum of five members includes people of various backgrounds, races, cultures, occupations, and affiliations. If there isn't a nurse on the IRB, nurses should ask for one to be appointed. Nurses should learn how to contact their organization's IRB coordinator or chairperson and how to obtain a copy of the IRB manual.

Ethics committees often help nurses and other providers handle ethical dilemmas in clinical practice by offering consultation services and education; providers can serve as patient advocates by serving as committee members. The nurse should not only learn how her workplace handles ethical issues, but she should also discuss unethical practices and behavior with colleagues. Further, she should know where to find her institution's policies and procedures or ethics handbook.

Formal ethics education. The ethical responsibilities of researchers have gained increased attention with the advent of bioethics as an academic discipline, but unfortunately most health care training programs do not focus on the subject. Nurses can advocate ethics education at the basic and advanced levels at colleges and universities as well as hospitals. Instruction could include topics such as ethical decision making, legal issues, and the impact of ethical dilemmas in research on clinical practice.

Public perception. It's clear that scientific misconduct erodes public trust and that confidence must be regained. Nurses need to be aware of violations that have occurred. Also, the public needs to be made more aware of progress in medicine and public health that has resulted from clinical trials and research.

Without clinical research, new drugs, devices, and therapies might not become available. The importance, safety, and benefits of research need more favorable publicity. Only then will the public be able to appreciate the benefits.

REFERENCES


http://www.nursingcenter.com
### BASIC AND ADDITIONAL ELEMENTS OF INFORMED CONSENT

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<tr>
<th>Basic Elements</th>
<th>Additional Elements</th>
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<tr>
<td>• Nature, purpose, procedures, drugs, or devices involved</td>
<td>• Unforeseeable risks (such as harm to a fetus if a participant becomes pregnant)</td>
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<td>• Identification of any experimental procedures</td>
<td>• Circumstances under which investigator may stop participation</td>
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<td>• Potential benefits, risks, and discomforts to participant</td>
<td>• Costs to patient</td>
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<tr>
<td>• Alternative treatments</td>
<td>• Explanation of the effects on the participant if he withdraws from the study</td>
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<tr>
<td>• Confidentiality of research records</td>
<td>• Whether new findings developed during research will be divulged</td>
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<tr>
<td>• Compensation if injury occurs</td>
<td>• Approximate number of participants</td>
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<tr>
<td>• Persons to contact about rights, and what to do if research results in injury</td>
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<td>• A statement indicating that research is voluntary and that withdrawal does not incur penalty</td>
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ipate in a study if he believes his health care would otherwise be compromised, and according to federal regulations for research patient rights, patients must receive standard care and no one is to be "punished" with inadequate care for not participating in a study or trial. [7]

**CLINICAL IMPLICATIONS FOR NURSES**

The nurse is vital to the success of clinical research and also has the right and the responsibility to question suspected research misconduct. If a nurse is only slightly familiar with research protocol, she may not realize how her involvement can be crucial to the success of a trial.

Each situation must be evaluated and resolved individually, in accordance with the codes, laws, and regulations pertaining to clinical research. The nurse must also exercise good clinical judgment as best she can. The conduct of high-quality clinical research requires the honesty, integrity, and expertise of all members of the research team. Nurses can address their own concerns and those of the patient by bringing them to the attention of the PI, the research coordinator, or the research nurse, as well as the nurse manager, the clinical nurse specialist, or the case manager.

Strategies to help nurses handle research dilemmas are given below.

**Education.** In order for nurses to improve their knowledge of research, a research component must be included in nursing curricula, and health care facilities involved need to offer courses or inservices on the basic principles of clinical trials and research.

**Research documents and publications.** Nurses should familiarize themselves with documents such as the Nuremberg Code, the Declaration of Helsinki, the Code of Federal Regulations (CFR), and the Belmont Report, which help to identify the principles of good clinical practice and possible violations of ethical conduct. These references are available at most institutions and public libraries, and the CFR is published in the Federal Register and can be found on the Food and Drug Administration (FDA) Web site (www.fda.gov).

**Informed consent process.** Nurses can support research subjects, investigators, and other colleagues by helping to ensure that participants understand their rights as well as the implications of a study. Most consent forms are written either at or above college level; since most adults read at an eighth-grade level or lower, the standard form may be too difficult for some patients to read and understand.

The researcher and patient should have the opportunity to discuss the patient's concerns, and nurses can help to ensure that the participant is sufficiently informed to make decisions. Nurses must recognize that if a patient or family member repeatedly asks questions that indicate the need for further clarification, the research team must be contacted immediately. However, a discussion about the consent form can become difficult when a patient is incapable of understanding its content because of mental disability or when a patient is in a situation, such as emergency or trauma, that makes it difficult to decide whether to participate in research. [8][9]

**Regulatory offices and resources.** There are offices and governing bodies that oversee research.