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The Basics of Human Subjects Protection

Linda H. Yoder

This is the last of several columns in a series that focused on basic aspects of clinical trials. In this article, fundamental concepts associated with protecting human subjects in clinical research will be addressed. Protection of human subjects is a complex topic, encompassing many regulations and guidelines. As discussed previously, a person diagnosed with cancer must make many decisions, ranging from selecting physicians to choosing treatment options (Yoder, 2006). In some cases, patients may be referred to a clinical trials program. It should be emphasized to patients that participation in a clinical trial does not make them "guinea pigs." The patients are research subjects who also are receiving state-of-the-art medical care. Therefore, there are many safeguards to ensure patients' rights are protected.

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Historical Background and Regulations

Several key events and documents shaped the current protection of human subjects. Most courses concerning the protection of human subjects require a basic understanding of this history and the resulting documents. During World War II, research atrocities were performed on prisoners of war. In 1946, during the Nuremberg trials, 23 physicians were tried for their ethical misconduct. As a result, in 1947 the Nuremberg Code was issued as the first internationally recognized code of research ethics. Many researchers, however, did not fully understand how this code applied to their research (The Nuremberg Code, 1949-1953).

In 1962, following the births of more than 300 babies with anomalies related to prenatal administration of thalidomide to mothers treated for nausea, the Kefauver-Harris Amendments were passed. These amendments were attached to the Food, Drug and Cosmetic Act, and they required companies to establish the efficacy of their products. Companies also had to adhere to new requirements regarding purity and safety before making the products available to the public (McCarthy, 1994).

In 1972 the accounts of the Tuskegee Syphilis Study sparked public outrage and an examination of the ethics of clinical trials. The purpose of the study, started in 1932 by the Public Health Service in Tuskegee, Alabama, was to determine the natural course of syphilis in adult black men. The study group included 400 men with untreated syphilis, and the control group consisted of 200 men without syphilis. Although penicillin was known to be an effective treatment for syphilis, the men were not treat-

ed. In fact, steps were taken to prevent the subjects from receiving treatment. Upon investigation, it became clear that information was withheld from study subjects. Many of the men did not understand the purpose of the study, and some did not realize they were participating in research. Reports from the study were published as early as 1936, but no action was taken to stop the study. As late as 1969, the Centers for Disease Control indicated the study should continue. After the public became enraged in 1972, the Department of Health, Education and Welfare halted the study (Bankert & Amdur, 2006; McCabe, 2004; Mulay, 2002).

Because of the Tuskegee Study and other ethically questionable situations, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established in 1974. This commission examined the ethical and human rights issues of experimentation with humans. The findings from the commission were published in 1978 in *The Belmont Report* (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research), which established stricter guidelines concerning information provided to research subjects. The principles outlined in the *Belmont Report* now govern all research supported by the U.S. government through its regulatory agency, the Food and Drug Administration (FDA). Basic tenets include respect for persons, beneficence, and justice (Bankert & Amdur, 2006; McCabe, 2004; Mulay, 2002).

Respect for persons acknowledges the dignity and freedom of every person, and requires that each potential research subject provide informed consent before participating in a clinical trial or any other research. *Beneficence* requires researchers to maximize benefits and minimize risks for research subjects to create a reasonable balance between risks and benefits. *Justice* requires that recruitment and selection of research subjects be equitable and that participants are treated fairly. The goal was to promote greater respect for individuals' autonomy, with greater attention to beneficence and justice for all humans involved in clinical trials. *The Belmont Report* required that the risks versus benefits of a clinical trial be documented in the consent form, and guidelines were established for special protection of children and the mentally ill (Bankert & Amdur, 2006; McCabe, 2004; Mulay, 2002). The Belmont report can be accessed online (http://www.hhs.gov/ohrp/).

In the early 1980s, the regulations for the conduct of research with humans were revised and published as Title 45 Code of Federal Regulations Part 46, Protection of Human Subjects (45CFR46). In addition to these regulations, all clinical trials must be conducted within *Good Clinical Practice* (GCP) guidelines, which is an international ethical and scientific quality standard for designing, conducting, recording, and reporting clinical trials that involve human subjects. The origin of the GCP guidelines was the Declaration of Helsinki in 1961. These guidelines provide public assurance that the rights, safety, and well-being of research participants are protected. The GCP guidelines provide a unified standard for the European Union, Japan, and the United States in order to facilitate the mutual acceptance of clinical data by the regulatory authorities in their jurisdictions (Mulay, 2002).

Institutional Review Boards

An institutional review board (IRB) is a committee whose primary responsibility is to protect the welfare and rights of human research subjects. Currently, no national directive or federal law requires all research to be reviewed in a *uniform* way. When research is subject to federal regulations, such as when federal funding is received, the definition of an IRB and the procedures for research review are described in detail in the Code of Federal Regulations. The two parts of the federal government that oversee functions of an IRB are the Office for Human Research Protections (OHRP) and the FDA (Bankert & Amdur, 2006).

The IRB is an institutionally based program of the protection system in place for research participants. In some multi-hospital systems, IRBs are centralized at the larger hospitals within the system. Federal regulations stipulate that the IRB must be composed of at least five people, who must come from diverse occupations and backgrounds. In addition, one member must be from outside the institution. Typically, IRBs comprise physicians, nurses, other health care specialists, chaplains, ethicists, and members of the community. Because more attention has been given to IRBs recently, national committees and commissions recommended that IRB membership be revised to better represent the community of potential research participants (McCabe, 2004).

The IRB is responsible for assessing the balance of risks and benefits in the clinical trials under review and evaluating the ethical components of the research. Once the study is approved, the IRB monitors the overall conduct of the research. In recent years, deaths of some clinical trial participants have prompted major changes

and improvements in the degree of independent oversight that must be present to monitor clinical trials and in the institutional support for IRBs (McCabe, 2004).

Informed Consent

The Nuremberg Code established the requirement that voluntary consent of the participant is absolutely essential. This measure, codified in the *Common Rule*, requires informed consent from the potential research participant or his/her legally authorized representative. There must be written documentation of the informed consent on a form approved by the responsible IRB. Specific requirements govern the content of the consent document, but it is actually the informed consent *process* that is of the greatest importance. Regulatory, legal, ethical, and medical groups have stated that the process needs to contain four essential elements: (a) understanding, (b) comprehension, (c) competence, and (d) voluntariness. Table 1 outlines the elements that must be included in the informed consent document to ensure that adequate information is presented to potential research participants (McCabe, 2004).

Table 1.
Essential Elements of Informed Consent

- Statement that the trial involves research
- Description and thorough explanation of the trial to include the purpose of the trial, duration of participation, procedures that must be followed, and which procedures are the experimental components versus standard of care
- Description of foreseeable risks and discomforts
- Benefits to the participants and others
- Alternative procedures or treatments
- Description of the confidentiality of records
- Explanation of procedures if the project involves more than minimal risk (for example, availability of medical treatment for complications/side effects, compensation)
- Contact person in case questions arise (this is usually the principal investigator or the project director of the study)
- Statement that participation is voluntary, that there will be no loss of benefits if the participant withdraws from the study, and that the participant may withdraw at any time
- Statement that if new findings are obtained, the patient will be informed. If a finding is significant the consent form may need to be revised and resigned by all participants.
- Statement that the participant's signature indicates a decision to participate, having *read and discussed* the information presented

Source: Adapted from McCabe, 2004

Clinical trials, and research studies in general, are often complex and include interventions or tests that possess risks. Therefore, the way in which information is presented is extremely important. After patients are evaluated to determine if they meet the criteria to be included in the clinical trial (*inclusion criteria*), they are provided with a thorough explanation of the clinical trial, verbally and in a consent form. The FDA requires that consent be obtained prior to any screening procedures. Therefore, if screening is completed on the same day that consent is obtained, the time of consent will indicate whether the FDA guideline has been met (Mulay, 2002).

The information in the consent form should be written and presented using clear and understandable wording, taking into consideration the educational level, language requirements, and cultural needs of the individual. Although improvements have been made, clinical trial consent forms often are lengthy and may be difficult for the patient to comprehend. It is imperative that patients receive explanations of therapy and possible risks/side effects in language they understand. Additionally, patients should be allowed to take consent forms home to review them or to share them with family members for consideration. Although the patient's signature is required on the consent, many institutions require the document to be countersigned by the investigator or the individual who explained the information in the consent form. The date and time must be included on the signature page. If the patient is a minor and has a guardian, or requires a translator, the guardian or translator must sign the consent, indicating the relationship or role of the person in the consenting process, as well as the date and time of the signature. If the investigator is attempting to recruit non-English-speaking individuals into the trial, the FDA requires that consent forms be translated into the native language of the patients being recruited (Mulay, 2002). These translations must be performed by a certified translation service and proof of certification must be demonstrated.

Ensuring Safeguards Are Met

There are several mechanisms in place to ensure that the

investigator, the medical institution, and the trial sponsor follow all appropriate regulations and guidelines. The sponsor is responsible for monitoring the conduct of the trial in several ways. Before the protocol is filed with the local IRB, the sponsor must agree that the proposed consent document is correct, properly representing the study. During the course of the trial, the sponsor monitors the activities at the research site by reviewing the data collected from the patients. These reviews ensure the protocol is being executed properly and the local IRB has been kept informed of all study activities. The sponsor's representative also visits the pharmacy to verify that investigational drugs are being dispensed properly and drug accountability logs are accurate (Mulay, 2002).

Within the institution, a committee of the IRB may conduct quality assurance audits. These committees often rotate their audits to monitor the activities of various researchers. A percentage of patient charts is reviewed to ensure that patients were consented properly and are being treated within the parameters of the protocol. The FDA also conducts audits to confirm the protocol is being executed correctly, that patients were consented properly, and that all data are true. If the FDA receives complaints about a particular investigator or medical facility, an audit may be called *for cause*, and the FDA visits the facility in response to the complaint(s). Typically, an FDA audit takes place to review the data when a drug is about to be reviewed for approval. If the FDA finds serious irregularities, the auditor has the authority to suspend all research at the facility. Any identified deficiencies must be corrected before the research can continue. If there is evidence of purposeful deception or fraud, the facility can lose the right to conduct any research (Mulay, 2002).

Clearly, the issues surrounding the conduct of clinical trials and research are complex. For more information about the protection of human subjects, visit the OHRP Web site (http://www.hhs.gov/ohrp/). Various training programs are available for investigators and data managers; some of these training programs are available on the Internet. IRBs typically require that investigators provide a certificate of completion from a training course for investigators. Additionally, project directors/coordinators/data collectors also are required to complete appropriate research training. There are excellent books concerning the complexities of human research protection; a recent publication by Bankert and Amdur (2006) is extremely comprehensive. ■

References

Bankert, E.A., & Amdur, R.J. (2006). *Institutional review board: Management and function.* Sudbury, MA: Jones & Bartlett.

McCabe, M.S. (2004). Principles of clinical research and development. In C.H. Yarbro, M.H. Frogge, & M. Goodman (Eds.), *Cancer nursing: Principles and practice* (6th ed.) (pp. 201-211). Boston, MA: Jones & Bartlett.

McCarthy, C.R. (1994). Historical background of clinical trials involving women and minorities. *Academic Medicine, 69*, 695-698.

Mulay, M. (2002). *Making the decision: A cancer patient's guide to clinical trials.* Boston: Jones & Bartlett.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1978). *The Belmont Report.* DHEW Publication No. (OS) 78-0013 and (OS) 78-0014. Washington, DC: U.S. Government Printing Office.

The Nuremberg Code, in Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Nuremberg, Oct 1946-April 1949. Washington, DC: US Government Printing Office, 1949-1953.

Yoder, L.H. (2006). Patient decision making concerning clinical trials. *MEDSURG Nursing, 15*(1), 38-40, 43.

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The Basics of Human Subjects Protection

This test may be copied for use by others.

COMPLETE THE FOLLOWING:

Name: _____

Address: _____

City: _____State: _____Zip:_____

Preferred telephone: (Home)_____ (Work)_____

AMSN Member Expiration Date: _____

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Answer Form:

1. If you applied what you have learned from this activity into your practice, what would be different?

_____

_____

_____

_____

Evaluation	Strongly disagree				Strongly agree
The offering met the stated objectives.					
2. By completing this activity, I was able to meet the following objectives:					
a. Discuss the historical background and regulation of protection of human subjects.	1	2	3	4	5
b. Describe the role and responsibilities of institutional review boards.	1	2	3	4	5
c. Define the requirements of informed consent.	1	2	3	4	5
d. List mechanisms to ensure patient safeguards are met.	1	2	3	4	5
3. The content was current and relevant.	1	2	3	4	5
4. The objectives could be achieved using the content provided.	1	2	3	4	5
5. This was an effective method to learn this content.	1	2	3	4	5
6. I am more confident in my abilities since completing this material.	1	2	3	4	5

7. The material was (check one) ___new ___review for me

8. Time required to complete the reading assignment: _____minutes

I verify that I have completed this activity: _____

Comments

_____

_____

Objectives

This educational activity is designed for nurses and other health care professionals who care for and educate patients and their families regarding human subjects protection in clinical trials. For those wishing to obtain CE credit, an evaluation follows. After studying the information presented in this article, the nurse will be able to:

1. Discuss the historical background and regulation of protection of human subjects.
2. Describe the role and responsibilities of institutional review boards.
3. Define the requirements of informed consent.
4. List mechanisms to ensure patient safeguards are met.

CE Instructions

1. To receive continuing education credit for individual study after reading the article, complete the answer/evaluation form to the left.

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