Protecting Patients During Clinical Research

Jacqueline Fowler Byers, RN, PhD, CNAA

Clinical research, once performed primarily at academic medical centers, now occurs in virtually every practice setting. These studies are funded by more than $18 billion per year from the National Institutes of Health and $17 billion per year from pharmaceutical companies.

As a result, most critical care nurses are likely at some point to provide care for patients enrolled in a clinical research study of a device or drug. Many critical care nurses are also performing their own nursing research in order to promote research-based nursing practice. Critical care patients are exceedingly vulnerable from a research perspective. Such patients are very ill, may have cognitive impairment, and depend on the healthcare team for their survival. Patients’ family members may be too anxious to consent objectively to enrolling their loved one in a research study. Therefore, critical care nurses must understand and use ethical principles and follow federal guidelines regarding protection of human subjects during research. Examples of situations that a critical care nurse may encounter include the following:

- A patient undergoing cardiac catheterization has received midazolam intravenously. He has no family members at the hospital. The cardiologist determines that the patient is eligible for a cardiac stent study protocol and proceeds to discuss the study with the patient and ask for informed consent. The patient is cognitively impaired by the midazolam and may not have the mental capacity to consent.
- You are discussing a study with a patient and/or a patient’s family after enrollment and you realize that the patient or family is not aware that the patient could have been randomized to placebo (no treatment).

In this article, I discuss ethical and statutory obligations for protecting patients during the research process and explain how to meet those obligations in critical care research situations.

Historical Perspectives

Although research has been performed for centuries, protection of human subjects did not achieve prominence until after World War II, when 23 Nazis were charged with murders of concentration camp inmates who were used as research subjects, and 15 of the accused were convicted. The reported research cruelty was shocking and had no possible therapeutic benefit to the subjects. These events resulted in development of the Nuremberg Code and then in 1964 the Declaration of Helsinki. Nonetheless, these attempts to protect human subjects did not prevent some widely publicized human rights violations that occurred during that period (Table 1). The 1979 Belmont Report provided detailed regulations for clinical research performed in the United States. Federal regulations created in the 1970s and 1980s finally made compliance with ethical standards during research enforceable. Relevant legislation includes the National Research Act, 45 CFR §46 (1974), 45 CFR §46 revised (1981), and 21 CFR §50 (1981).
Ethical Foundations for Clinical Research

Protecting patients’ rights during clinical research is based on ethics. The 3 underlying principles for research (respect for persons, beneficence, and justice) are in total congruence with the American Association of Critical-Care Nurses Ethic of Care position statement. The Ethic of Care states the following:

An ethic of care is a moral orientation that acknowledges the interrelatedness and interdependence of individuals, systems and society. An ethic of care respects individual uniqueness, personal relationships, and the dynamic nature of life. Essential to an ethic of care are compassion, collaboration, accountability and trust. Within the context of interrelationships of individuals and circumstances, traditional ethical principles provide a basis for deliberation and decision making. These principles include Respect for Persons, Beneficence, and Justice.

Each of these ethical principles has equal moral force in consideration of the protection of research subjects. The Ethic of Care statement provides the foundation for both ethical care of patients and ethical research. All decisions regarding the protection of patients during research requires the understanding and application of the following ethical principles.

**Respect for persons** is the moral obligation to honor the intrinsic worth and uniqueness of each person and to respect self-determination, diversity, and privacy. For both clinical care and research, this principle means that patients or their legal surrogate have the right to true informed consent and privacy (confidentiality) of the patients’ health information and research data.

**Beneficence** is the moral obligation to promote good and prevent or remove harm, to promote the welfare, health, and safety of society and individuals in accordance with beliefs, values, preferences, and life goals. To this end, research studies are designed to maximize benefits and minimize risks to the subject. In addition, all research must be done by capable researchers in order to further minimize risks to the patient.

**Justice** is the moral obligation to be fair and promote equity, nondiscrimination, and the distribution of benefits and burdens based on needs and resources available and to advocate on another’s behalf when necessary. This principle in research requires selecting subjects in an equitable manner and avoiding exploitation of vulnerable populations, such as the critically ill or patients of low socioeconomic status.

### Institutional Review Boards

The first level of protection of a patient’s rights during clinical research comes from institutional review boards (IRBs). IRB membership regulations require at least 5 members of both sexes with varied backgrounds, including at least 1 nonscientist, 1 scientist, and 1 nonaffiliated member. Typical members include researchers, physicians, social workers, chaplains, and community lay persons. This diversity is designed to ensure adequate ethical and scientific review of proposed research and to provide expertise on diverse and vulnerable populations.

### Table 1 Historical violations of the rights of human subjects

<table>
<thead>
<tr>
<th>Study</th>
<th>Violation</th>
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<tbody>
<tr>
<td>Tuskegee syphilis study (1932-1971)</td>
<td>A total of 399 black men with syphilis were followed up for decades without consent or treatment, even though an effective treatment was available starting in the 1940s. The subjects were misled that spinal taps were therapeutic in curing their disease.</td>
</tr>
<tr>
<td>Sanctioned by the US Public Health Service initially and by the Centers for Disease Control as late as 1969</td>
<td></td>
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<tr>
<td>Oakridge, Tenn (1944-1974)</td>
<td>Government employees were exposed to large doses of radiation without their knowledge or consent.</td>
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<tr>
<td>Willowbrook State School, NY (1950s)</td>
<td>Children’s parents were coerced to allow injection of live hepatitis strains into their impaired children. The parents were led to believe that the injection was a vaccine and that placement of their children in the state institution would be expedited if they approved.</td>
</tr>
</tbody>
</table>
All members of IRBs are required to be educated about the IRB purposes, functions, and membership responsibilities according to federal regulations (see resources in sidebar). If an organization does not have an IRB, IRB review may be performed by a local university or a contract IRB.

The federal criteria for IRB review (Table 2) address both scientific integrity and protection of human subjects. Through the review of these criteria, the IRB members ensure that the proposed study meets scientific and ethical standards.

An IRB review has several levels; each level is based on the level of risk to the subjects. All research involving human subjects must be reviewed by an IRB.

Another IRB function that is relevant to the critical care setting is approval for compassionate use in urgent or emergent situations of drugs and devices that have not been approved by the Food and Drug Administration (FDA). The FDA must approve the drug or device for compassionate use. Such approval is granted when the rarity of a disease precludes a randomized clinical trial or other compelling reasons prevent the drug or device from going through the traditional FDA approval process. The local IRB must then approve any compassionate use protocol, and the physician must report each instance of compassionate use to the IRB.

An example of compassionate use is the use of a device not approved by the FDA to occlude a patent ductus arteriosus in symptomatic patients. In that case, compassionate use provides a nonsurgical option for closure of the defect. Another example is when a patient is in a clinical trial elsewhere, and the study drug must be administered while the patient is visiting your community.

Researchers have several responsibilities to the IRB during a research study (Table 3). These requirements are intended to provide ongoing protections to human subjects during the research study. Researchers are also expected to terminate a study early if interim data analysis indicates that their results are much better or worse than expected. If the results are better than expected, the researchers can show significant differences with fewer subjects than projected. If the results are worse than expected or if serious adverse reactions occur, the only ethical course is to end the study. A recent example of early termination was the Alzheimer disease vaccine trial in which unexpected brain inflammation occurred in 12 of 360 study subjects worldwide. The sponsoring company stopped the clinical trial in early 2002.

In another example, in January 2003, gene therapy studies for the “bubble boy” immune

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### Table 2: Requirements for protocol reviews by institutional review boards

- Review done during convened meeting with quorum present (full review only)
- Protocol review to include:
  - Risk/benefit analysis
  - Informed consent/assent
  - Selection of subjects
  - Privacy and confidentiality
  - Research design/data analysis
  - Protection of vulnerable populations
  - Publicity/recruitment materials
  - Qualifications of researchers
  - Compliance with regulations

### Table 3: Responsibilities of researchers to the institutional review board during the study

- Ensure and document informed consent
- Obtain approval of any amendments to protocol
- Report adverse events/unanticipated problems
- Report violations of protocol
- Revise informed consent, obtain approval and obtain consent again from earlier subjects as needed, depending on new findings
- Submit annual report and obtain renewal approval
- Allow inspections of compliance with research protocol and of records

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Resources

- Applied Research Ethics National Association (ARENA)
  132 Boylston St., 4th Floor
  Boston, MA 02116
  619-423-4112
  [http://www.primr.org/arena.html](http://www.primr.org/arena.html)

  [http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm](http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm)

- Office for Human Subjects Research. The Warren G. Magnuson Clinical Center Room 1C-116
  Bethesda, MD 20892-1154
  301-402-3444
Informed Consent

Informed consent is a challenge in the critical care setting because of the time constraints and the potential cognitive impairments of patients. Informed consent is a critical element of protecting patients’ rights during the research process. Elements of informed consent include competence (legal definition) or mental capacity (clinical definition) to understand the study and voluntary participation. In practice, capacity is the criterion for informed consent. Capacity may be diminished because of pain, trauma, anesthesia, sedation, or narcotics. The healthcare team determines capacity subjectively by assessing the patient. If a patient’s mental capacity is questionable, consent must be obtained from his or her legal healthcare surrogate. State law determines the legal surrogate decision maker; your organization’s risk manager can assist in determining the appropriate person.

Informed consent requires providing patients or their legal surrogate the following information: purpose of the research, experimental procedures, alternative treatments, duration of participation, potential risks and benefits, how confidentiality will be maintained, cost to patient and/or compensation, contact information for questions or for a research-related injury, and assurance that the choice to participate or not will not affect their other treatment and that they are free to withdraw from the study at any time without penalty. Informed consent also entails clear, simple, unbiased, and noncoercive communication in a language and at a reading level that patients and/or their families can understand. Adequate time for patients or their family members to consider the study and to ask questions is necessary to ensure that the consent is truly informed. Because of the complexities of clinical research, the researcher enrolling subjects must assess whether a possible subject understands the study details. For patients 7 to 17 years old, consent of a parent is required in addition to consent from the child if the child is capable.

Nurses’ obligations during the research consent process include witnessing signatures on consent forms, communicating potential subjects’ lack of understanding to the investigator, and advocating for the patient’s rights as a research subject during informed consent and throughout the study. It is not the role of the bedside nurse to describe the study to a patient before consent is obtained. That step is the responsibility of the principal investigator and/or research coordinator, depending on state law. Table 4 describes potential informed consent situations and appropriate actions.

Recent Research Violations

Unfortunately, not all researchers in the United States follow research ethics and regulations. A few well-publicized incidents include a 19-year-old Asian American who consented to a bronchoscopy study to harvest alveolar macrophages in 1996 and died of lidocaine overdose. Research violations included that the subject was not monitored after bronchoscopy and that concentrations of lidocaine were increased without IRB approval. In 1999, a patient with a rare metabolic disorder died after a gene therapy trial. This patient’s disorder had been controlled with medication and diet before the trial. Violations included a conflict of interest of the investigators, lack of safety monitoring, and lack of informed consent. In 2001, a 24-year-old healthy female volunteer died during a research study. Violations included that conflicts of interest of IRB members were not documented, that the informed consent form did not state that the study drug was experimental and emphasized getting expensive tests for free, and that FDA approval of the study was not obtained.

Current Hot Issues in Clinical Research

Several issues in research are currently “hot,” primarily because of recent human subject violations. Such issues include the readability of consent forms (sixth-grade level in the person’s primary language), ethics of using placebos when treatment options are available, definition of standard of care in the comparison group, lack of blinding of investigators and data collectors, and conflict of interest of investigators because of financial or professional interests. Maintaining awareness of these issues and advocating for patients are ways of supporting patients’ rights during the research process.

Nurses as Patients’ Advocates During Clinical Research

Nurse executives have an obligation to ensure that their organizations have a well-functioning IRB in place or have access to an IRB. They
also need to make certain that sufficient resources are available to support nursing research on clinical practice issues. Nurse executives should ensure nursing representation on the institution’s IRB as well.¹⁴

When providing care for critical care patients in a clinical trial, nurses must understand the research study. Nurses must also monitor compliance with the study protocol to the greatest extent possible. They should review the consent form and the patient’s understanding of the study. Signed consent forms should be in the patient’s medical record and should also be given to patients or their family or legal surrogate. Acutely ill patients and anxious families may not accurately process or retain all of the information given by the researchers at the time of initial consent. Nurses make excellent translators of the research studies into laymen’s terms. Ideally, this translation would not be necessary, but you may need to clarify terms such as randomization, review protocol elements, or identify the experimental interventions in the study.

In a recent study¹⁵ of cancer patients in clinical trials, most patients thought that they were well informed about their clinical trial. However, 74% did not recognize nonstandard treatment, 63% did not identify increased risk from study participation, and 70% did not recognize the unproven nature of the treatment. Obtaining consent from patients again verbally and reviewing the protocol periodically through a long research protocol have been proposed as ways of ensuring ongoing voluntary informed participation in a study.

**What If You Are the Clinical Researcher?**

If you are the clinical researcher, you must know and follow all statutory and IRB requirements during your study. You are also responsible for training and monitoring your research team for regulatory compliance. You have an ethical and statutory obligation to develop clear, understandable consent forms and to provide plenty of time for reviewing the consent form, answering

<table>
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<th>Table 4 Informed consent situations and appropriate actions for nurses</th>
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<td><strong>Issue</strong></td>
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<td>A patient undergoing cardiac catheterization has received midazolam intravenously. He has no family members at the hospital. The cardiologist determines that the patient is eligible for a cardiac stent study protocol and proceeds to discuss the study with the patient and ask for informed consent. The patient is cognitively impaired by the midazolam and may not have the mental capacity to consent.</td>
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<td>You are discussing a study with a patient and/or the patient’s family after enrollment and you realize that they are not aware that they could have been randomized to receive a placebo (no treatment).</td>
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<td>You overhear a research coordinator provide biased information implying greater benefit than expected from a research study to a patient’s next of kin when requesting informed consent.</td>
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<td>A patient’s family member (legal surrogate) tells you, “I would agree to anything that Dr Garcia suggests” and verbalizes little understanding of the research study in which the patient is already enrolled.</td>
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<td>A patient shares that he was afraid that if he did not consent to the research study in the emergency department, he would not receive any other care.</td>
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questions, and enrolling patients in the study after full assimilation of the material.8,10 Meeting this obligation is a challenge in emergent situations. It is important to review the study protocol and obtain consent from your subjects again verbally at every data collection period to ensure they have consented to continued participation in the study. Interim data analysis will provide you needed information about potential early termination of the study. In addition, you must comply with all IRB responsibilities listed in Table 3.

Critical Care Research Dilemmas

If concerns arise at any time during a clinical research study, critical care nurses have several ethical and statutory obligations.8,10 These obligations include reporting adverse events and protocol deviations to the research coordinator immediately, communicating concerns to the research team and attending physician, reminding the patient that he or she can withdraw from a study at any time without penalty, and seeking out further resources as needed. Additional resources include bioethics committees, IRBs, advanced practice nurses, administration, research coordinators, principal investigators, risk management staff, and pharmacists familiar with the study drugs. These resources and the chain of command should be used until the nurse thinks that the concerns about the patient’s rights have been resolved acceptably. Examples of potential critical care research dilemmas and recommended actions are described in Table 5.

<table>
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<th>Table 5 Potential research dilemmas and appropriate actions</th>
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<td><strong>Scenario</strong></td>
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<td>You learn that an interventional cardiologist owns 30% of a cardiac device company. He is doing a clinical trial of one of the company's devices and doesn't state his financial interest on the consent form. Also, you are concerned that because of his financial interests, he may be biased toward reporting positive results.</td>
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<tr>
<td>A Haitian patient is admitted to your unit who meets inclusion criteria for a sepsis study. No one is available to translate the study and consent form for the patient. Can this patient be enrolled in the study ethically?</td>
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<tr>
<td>Karen, a nurse on your unit, states she will be collecting data from her patients and their medical records for a &quot;school project.&quot; When asked, she states she doesn’t think her protocol needs approval from the institutional review board and that she is under a deadline.</td>
</tr>
<tr>
<td>You are caring for a patient in a clinical trial. You are requested to administer &quot;the study drug.&quot; You are unfamiliar with the research protocol and the study drug.</td>
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<tr>
<td>You have administered a study drug and the patient appears to be having an anaphylactic reaction to the medication.</td>
</tr>
<tr>
<td>You observe a major violation in a study protocol. When you mention it to the study coordinator, you are told not to worry about it.</td>
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<tr>
<td>Your patient, who recently had cancer diagnosed, voices questions about whether he should enroll in an aggressive clinical trial, accept standard treatment, or decline all treatment except for management of signs and symptoms.</td>
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Clinical researchers have the wonderful opportunity to evaluate the effectiveness of an ever-growing number of medical and nursing treatment options. However, it is our ethical obligation to ensure that the rights of critically ill research subjects are protected and federal regulations are followed as new clinical treatment options are investigated. Awareness of the requirements and willingness to advocate for patients are the first steps in this process.

References
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