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Human Subjects Protection and Federal Regulations of Clinical Trials

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ABSTRACT

Objectives: To explore the federal regulations governing clinical trials and human subject protection, the importance of research participant's informed consent, and the role the oncology clinical research nurse has within the clinical trial setting.
Data Sources: Peer-reviewed journal articles, internet, book chapters, white papers.
Conclusion: Federal regulations mandate the conduct of a clinical research trial, human research participant protection, and the informed consent process.
Implications for Nursing Practice: The oncology nurse supports the autonomy and safe conduct of the human research participant during a clinical research trial and provides education and support through the informed consent process.

Introduction

Twenty-first century human research is a vast and diverse field affecting all areas of clinical care and practice. Clinical research nursing is a sub-specialty of professional nursing and requires knowledge of research federal regulations related to clinical research. Clinical research nurses contribute not only to the clinical oversight but also facilitate outcomes related to the fidelity of the protocol, while safeguarding the human research participant's safety and autonomy.[1,2] The foundation of the nursing process and Code of Ethics for Nurses unites the core framework of human research participant protection while advocating for patient rights and dignity through the careful process of obtaining informed consent.[2]

This article aims to explore the federal regulations governing clinical trials and human subject protection, the importance of research participant's informed consent, and the role the oncology clinical research nurse has during the process of informed consent.

Regulatory History

A regulatory framework for human subject protection and informed consent can be traced back to the 1960s. The Declaration of Helsinki was developed by the World Medical Association to establish a set of ethical principles related to human subject research.[3] History identifies that the United States was a signatory of the Declaration of Helsinki in 1964; however, a formal law was not enacted in the United States until 1978 under the statutory authority of the National Research Act.[3] The National Research Act was the result of the research misconduct in the early 20th century, resulting in the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1974.[3] The National Commission for Protection of Human Subject developed the "Ethical Principles and Guidelines for the Protection of Human Subjects of Research," more commonly known as the Belmont Report.[4,5] The Belmont Report was published and formally recognized 40 years ago as a federal regulation in 1979.[4] The Belmont Report provides directives in human experimentation, including guidelines to evaluate the informed consent process, protection from harm, risks versus benefits, and the avoidance of unnecessary physical and mental suffering within the clinical trial.[4]

Informed Consent Regulations

Obtaining informed consent for research is tightly controlled, regulated, and monitored by an Institution Review Board, US Food and Drug Administration (FDA), Office of Human Subject Protections, and the Department of Health and Human Services.[6–9] Existing literature identifies a range of issues in the process of obtaining informed consent, which includes informed consent not obtained, improper consent conduct, failure to disclose the risk and benefits of the clinical trial, and inadequate documentation of the informed consent process.[9,10] Therefore, the informed consent process is a critical requirement for all human research subjects who participate in a clinical research trial and must be upheld with the highest integrity and autonomy. Without proper informed consent, the research conduct is egregious. For example, during World War II the Nazis performed research experiments on prisoners of war in concentration camps that was brutal, unethical, and without consent, resulting in the

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Table 1
Sample documentation of informed consent form.

Date of Main ICF Signed Date of Genetics ICF Signed	Version of ICF Version of ICF Genetics	
The informed consent document for **(list protocol here**) was presented to **(insert study subject name here)** on **(insert date here)** at **(insert time here)** AM/PM. Information on the protocol, procedures and risk/benefit were reviewed with study subject. Alternative therapies and treatments were presented during the discussion. An opportunity for questions and answers were provided prior to signing the informed consent document by **(list individuals conducting consent here)**. **(List study subject name here)** verbalized an understanding of the informed consent and study related procedures and informed consent was signed on **(insert date here)** at **(insert time here)** AM/PM.		
Verify the subject read and signed an IRB approved informed consent form before any procedures were preformed and a copy of the ICF was provided to the study subject	Yes (Initial/date)	No (Do Not Enroll Study Subject) (Initial/Date) (Comment)
May blood samples be used for future unrelated research and was an IRB approved ICF used for decision making process?	Yes (Initial/date)	No (May not use blood for future research) (Initial/Date) (Comment)

Abbreviations: ICF, informed consent form; IRB, institutional review board.

Nuremberg trials of 1946–1947 and the development of the Nuremberg Code.[11] This was the first time at an international perspective that the principle of consent was discussed in the context of the necessity for human subject protection.

Regulations for Documenting the Informed Consent

The FDA appropriately acknowledges that the research process for the conduct of informed consent must ensure that the research participant understands the informed consent document.[4,12,13] The informed consent document should be reviewed in person with the potential research participant to assess the patient's individual level of understanding regarding the clinical trial (see Table 1) and to provide an opportunity to answer any questions. The informed consent process outlined by the FDA states the human research subject should have the ability to review and read the consent while having appropriate time to understand what the consent involves, opportunity to ask questions to seek clarification, submit voluntary agreement to participate without undue coercion, and be advised about the clinical trial process and clinical investigation progress.[12–14] The FDA further outlines that the informed consent document incorporates basic elements to support the engagement of human research subjects (see Table 2 for informed consent requirements).[14]

The clinical research nurse has a moral and regulatory obligation to verbally review and discuss the informed consent with the patient before the patient engages in a clinical research trial. The individual also has the right to take the informed consent home to review this document with their family/friends to make an informed decision. The clinical research nurse ensures that the patient is protected to make an autonomous informed decision during the informed consent process. Additionally, the clinical research nurse can offer educational opportunities and affords time for questions and answers during the informed consent process.[15]

Common Rule

The United States (US) Department of Health and Human Services issued an update in 2018 to the common rule policy 45CFR §46 that was published in 1991.[5] The 2018 common rule update outlined specific changes to the informed consent conduct and documentation process.[5] The new update indicates that clinical researchers must publicly post on ClinicalTrials.gov a final copy of the informed consent that has been approved to enroll human research subjects.[5] According to 45CFR §46.102, a human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens,[5] see Fig. 1.

The new update clarifies that whether an intervention (physical) or interaction (verbal) occurs the act of and intent of the investigator (whether professional or student) identifies and signifies the act of research conduct.[5] All interventions, whether physical or verbal interaction, are considered engagement in research and must be reviewed by an Internal Review Board.[8] Compliance with regulations

Table 2
Informed consent requirements by federal regulations.[14]

Combined Elements of Informed Consent Review 21 CFR 50.25 and 45 CFR 46.111	Yes	No
1. Statement that the study involves research		
2. Statement of the purpose for research		
3. Expected duration of the subject's participation		
4. Description of the procedures to be performed during the study		
5. Identification of any procedures which are experimental		
6. Description of any reasonably foreseeable risks or discomforts to the subject		
7. Description of any benefits to the subject or to others which may reasonably be expected from the research		
8. Disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject		
9. Statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the US Food and Drug Administration may inspect the records		
10. For research involving more than minimal risk, an explanation as to whether any compensation and explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained		
11. An explanation of whom to contact for answers to pertinent questions about the research and research subjects rights, and whom to contact in the event of a research-related injury to the subject		
12. A statement that participation is voluntary; that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled; and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled		
13. Statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable		

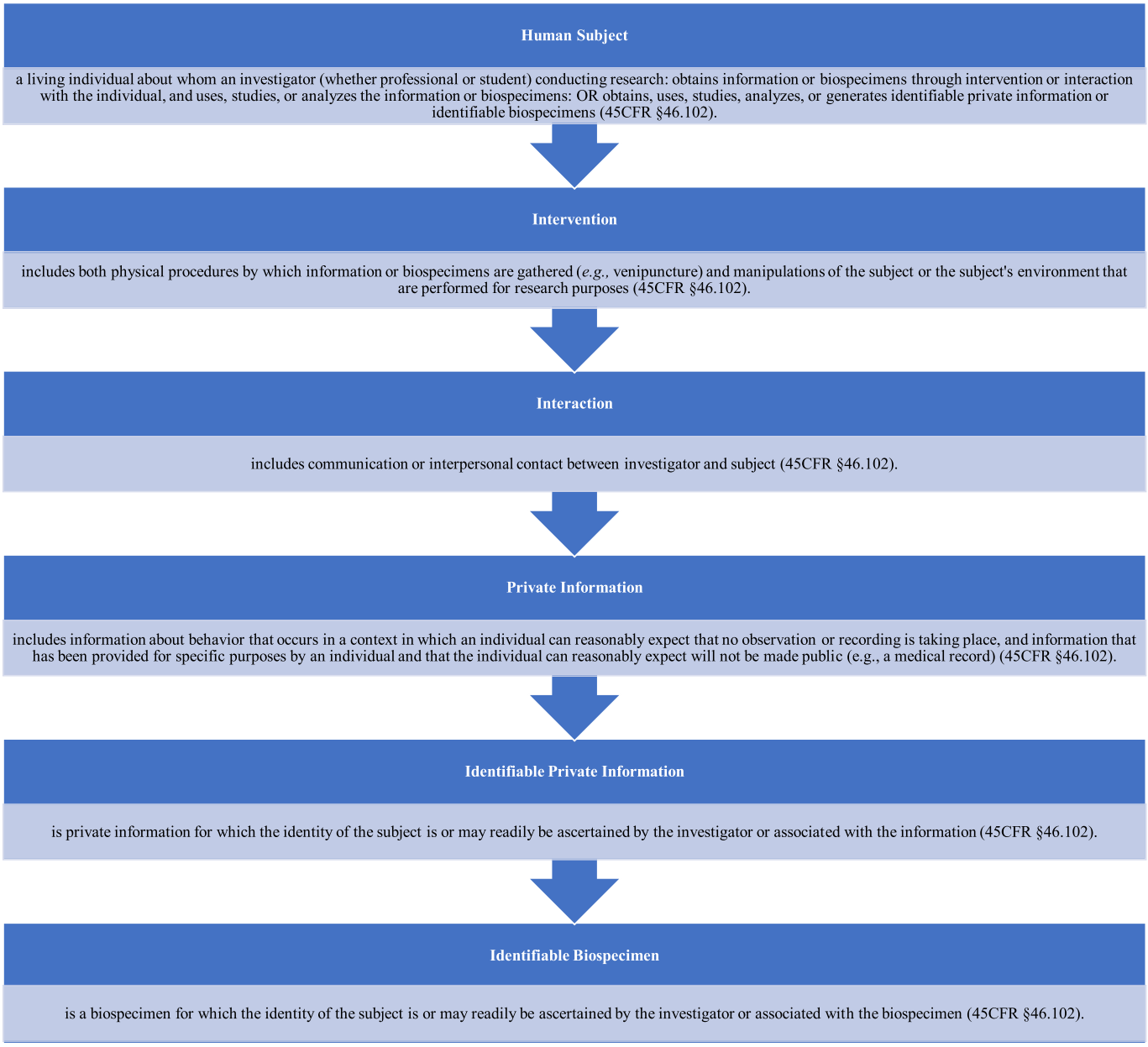

Fig. 1. Basic HHS policy for protection of human research subjects (45CFR §46.102).

as well as ethical conduct of research requires that the research participants are informed of new findings that may influence their continued participation in the research. Informed consent is an ongoing process that must be transparent, active, documented, and considered an ongoing process throughout the lifetime of the clinical trial.

The Common Rule update stipulates the careful consideration to the privacy of the research participant by separately defining the following terms: intervention, interaction, private information, identifiable private information, and identifiable biospecimen. Private information is defined as information or behavior that occurs in which the individual can reasonably expect no observation or recording is taking place.[5] Private information will not be made public under any circumstances.[5,16] A moral duty exists to properly inform and educate research subjects regarding the impact to the individuals and potential future generations when specifically researching specialist areas, such as genetics and biospecimens. As oncology clinical trials continue to advance and use genetics to match potential study subjects to clinical trials the oncology clinical research nurse's ethical and moral duty increases with respect to ethical regulations.[15,16] Oncology clinical research nurses must remain vigilant in educating themselves and the research participants to ensure all parties are educated and understand the genetic implications to their families today, and the possible implications to future members of their families.[17,18]

The Role and Impact of Nursing in Clinical Research

Nursing clinical research code of ethics

All nurses are bound to the Code of Ethics for Nurses[1] to respect the dignity, equal and inalienable rights of all humans regardless of the sex, race, and religion or belief system of the individual. Florence Nightingale was the first nurse to conduct clinical research by collecting statistical data during the Crimean War in 1854.[1] The Code of Ethics for Nurses outlines the clinical research nurse's duty and scope

Table 3
American Nurses Association code of nursing ethics for clinical research nurses.

Provision 1: respect for the individual	• Establish relationships with participants • Assess participant's understand of research study • Assess informed decision to participate
Provision 2: commitment to the patient	• Balances advocacy for safety and efficacy of research protocol • Safety is primary consideration when conflict with protocol arises • First line of communication to participants and family
Provision 3: advocacy for and protection of the patient	• Protects participant's privacy • Properly document methods by limiting exposure and ensuring safety • Manage risk associated with stigmatizing of research subjects • Advocating and educating research participants and family members
Provision 4: authority, accountability and responsibility for practice	• Manage conventional clinical care (aimed at benefiting patient) and clinical research care (aimed at benefiting future patients and generalizable knowledge) • Responsibility and accountability for individual practice in highly autonomous role • Accountable for strict adherence to protocol and specialty practice
Provision 5: duties to self and others	• Preserve moral competence when faced with ethical dilemmas of competing priorities • Maintain educational opportunities and supportive resources • Seek guidance from senior leadership sources to support clinical research practice setting
Provision 6: ethical work setting and care environments	• Fair and respectful treatment of those participating in a clinical trial • Obligation to collect accurate data • Establish an environment that supports respect, beneficence, and justice
Provision 7: nursing profession advancement	• Foster intellectual inquiry that establishes evidence to inform practice • Contribute to science by translating research • Develop new knowledge, and disseminate through scholarly investigation • Sharing best practices and ethical principles
Provision 8:collaboration with the public and health professionals	• Collaborate with interprofessional research teams • Advocate for the quality of research • Educating the public on their rights and responsibilities when participating in clinical research
Provision 9: nursing profession's integrity and values and social justice	• Serve as experts in clinical research conduct • Engage in affiliations and committee memberships to advance clinical research • Influence health policy regarding clinical research

Adapted and reprinted with permission from American Nurses Association.[1]

of clinical practice while conducting informed consent during a clinical trial (see Table 3 for nursing ethical code overview).

Protecting rights of human subjects'

According to the American Nurses Association, the clinical research nurse has an integral role in delivering and conducting informed consent during a clinical trial.[2] The clinical research nurse continually reviews continued informed consent throughout the clinical trial by utilizing three essential elements. Firstly, by the provision of complete and accurate information; secondly, through assessment of the individual's comprehension; and thirdly, by safeguarding voluntary participation.[2] The clinical research nurse may have delegated authority from the investigator to discuss and review the components of the informed consent with the individual but has a duty to the nursing code of ethics (see Table 2). The initial informed consent discussion offers the research subject an opportunity to ask questions and verbalize their understanding of the consent, the procedures involved with the clinical trial, and to explore the risks versus benefits during the life of the trial.

Autonomy is given to the research participant to ensure informed decision-making regarding participation, protocol duration, study procedures and visits, risk or discomforts, and therapeutic intent.[2,5] Research nurses engage in educational communication during the informed consent utilizing the teach-back method.[15] The teach-back method allows the clinical research nurse to assess the research subject's understanding of the risks and benefits of the trial.[15]

Informed consent process

The primary focus of the nurse is ensuring safety to their patient.[2] With appropriate knowledge and education in clinical trials, nurses can confidently screen, recruit, consent, engage with patients, and give them autonomy in the decision-making process during a clinical trial. The patient must determine whether to participate or not to participate in a clinical research trial, with the support of the clinical research nurse.

Nursing Implications

The Code of Ethics for Nurses identifies the degree to which a nurse should uphold patients' rights regarding the nature of health care. Section 1.3 of the Code of Ethics for Nurses states "that the worth, dignity and rights of all human beings irrespective of the nature of the health problem that the worth of the person shall not be affected by disease, disability, functioning status, or proximity to death."[1] The education and training of a clinical research nurse provides the foundation to assist with and guide ethical conduct during a clinical research trial. The clinical research nurse is the advocate for the patient based upon the patients' dignity and rights as a human being while maintaining fidelity to the research protocol.

Nurses offer a conduit to bridge knowledge between the public and clinical research trials by ensuring protocol validity, providing education, advocacy for research, and trust. Establishing trust provides a platform to promote protection with a focus on the patient experience and should provide a positive community ensuring longevity participation of individuals in clinical trials.[19]

Conclusion

Without the willingness of individuals to participate in clinical research, medical advancement would not exist today in contemporary health care. The research community has afforded the promise of hope for future medical breakthroughs, with the research team forming a powerful collaboration for improved outcomes in medical advancements. The Code of Ethics for Nurses provides guidelines for nurses to work within the scope of clinical research and provides a framework for ethical judgment and ensures patients are the central focus. Nurses promote, advocate, and strive to protect the safety,

rights, and health of patients. Nurses and members of the research team can assist in improving the public perceptions of clinical research trials for future generations.

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