

Protecting Vulnerable Subjects in Clinical Research: Children, Pregnant Women, Prisoners, and Employees

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Summary

The federal government has established guidelines and regulations for the protection of vulnerable research subjects, especially children, pregnant women, cognitively impaired persons, and prisoners. In addition, students, residents, and employees are recognized as special research populations. Clinical investigators need to be aware of and use these federal guidelines appropriately. This article provides practical guidance for respiratory therapists who conduct research with these patient populations and solutions to the barriers investigators commonly encounter when studying these patient populations. Key words: vulnerable subjects, children, women, pregnant, cognitively impaired, prisoners, students, residents, employees, special research populations, institutional review board, research. [Respir Care 2008;53(10):1342–1349. © 2008 Daedalus Enterprises]

Introduction

Respiratory therapists who conduct clinical research are in a unique situation. Because of their wide scope of

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practice, many of their patients are considered vulnerable research subjects by the Office for Human Research Protections, which is an office of the United States Department of Health and Human Services. The Office for Human Research Protections is charged with assuring that institutions that conduct clinical research fulfill the ethical and legal responsibilities mandated in federal law (Title 45, Part 46 of the Code of Federal Regulations, informally referred to as the Common Rule, <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>) and recognized by federal departments and agencies that conduct human-subjects research. Any institution engaged in human-subjects research conducted or supported by any federal department or agency must abide by the Common Rule, including the National Institutes of Health and the Food and Drug Administration (FDA).¹

Table 1. Vulnerable and Special Research Populations

Vulnerable
Children and minors
Pregnant women
Fetuses and human in vitro fertilization
Cognitively impaired persons
Prisoners
Special
Students
Residents
Employees
Terminally ill patients
Minorities

The purpose of the present paper is to provide guidance for respiratory therapists about the Common Rule, but not to duplicate the federal regulations. Many investigators become discouraged from conducting clinical research because they are uninformed about what an institutional review board (IRB) expects from them, especially when studying vulnerable research subjects.

Under the Common Rule children, pregnant women, fetuses, cognitively impaired or comatose patients, and prisoners are considered vulnerable research subjects. The Office for Human Research Protections also recognizes that students, residents, and employees require special consideration when recruited as research subjects. The Common Rule requires that IRBs and clinical investigators give special consideration to protecting the welfare of vulnerable research subjects and to ensure voluntariness and freedom from coercion (Table 1).²

History of Research Abuse

The list of human-subject research abuses in the United States is regrettably long. Most clinical investigators are familiar with the Tuskegee syphilis study of poor African-American sharecroppers.³ Less well known are the unethical experiments conducted at institutions for mentally retarded children, such as the New York Willowbrook hepatitis B studies in the 1960s.⁴ Cognitively impaired subjects were also victimized, such as in the studies conducted at the Jewish Chronic Disease Hospital, in which live cancer cells were injected into uninformed, elderly patients.⁵ Henry Knowles Beecher, in his landmark article in *The New England Journal of Medicine*, described a number of clinical studies at major research institutions that placed research subjects at substantial risk of harm and failed to obtain informed consent.⁶ Those reports outraged the public and led to a movement to reform human-subjects research in the United States.

On July 12, 1974, the National Research Act (Public Law 93-348) was signed into law, thereby creating the

Table 2. Types of Undue Influence

Coercion	A credible threat of harm or force to a research subject
Manipulation	Influencing a research subject's decision by altering the available options or information
Persuasion	Guiding a research subject to your way of thinking through the disclosure of truthful information, but in a manner that is meant to get person to think or act in a preferred manner

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report represented the culmination of that commission's work.⁷ In its emphasis on protecting human subjects from harm, coercion, or un-consented experimentation, the Belmont Report reflected the history of the preceding 30 years of research abuses.⁸ The findings emphasized that there is a basic moral difference between a research subject who willingly accepts the risks of clinical study and one who is manipulated and coerced.

What Is a Vulnerable Population?

Our society was called upon to no longer tolerate the exploitation of its vulnerable members for the sake of obtaining research results. Thus, for many decades, clinical investigators protected vulnerable research subjects by excluding them from research. That is no longer medically or morally acceptable. Though investigators are encouraged to design studies that broaden access to beneficial research trials for vulnerable people, the federal government has established guidelines and regulations to protect those people. To produce morally valid results, clinical investigators need to be aware of and use these federal guidelines and the requirements of their local IRB.

Vulnerability occurs when a person's ability to protect himself is absent or diminished (Table 2). Vulnerable populations are more susceptible to both intentional and inadvertent harm. Vulnerable populations include people with psychiatric, cognitive, or developmental disorders, and are considered vulnerable if there are legitimate concerns about their capacity to understand information presented to them and to make informed choices. Children are considered vulnerable because they have undeveloped decision-making skills. Other vulnerable populations include people who are institutionalized and may not be free to choose without coercion or undue influence, such as prisoners. Women of child-bearing potential and pregnant women are considered vulnerable because of risks to their unborn children.

Coercion involves a credible threat of harm or force to another individual. Undue influence is when a person uses

his or her power to exploit the trust, dependence, or fear of others. Clinical investigators can use their power to deceptively gain control over the decision making of a research subject. Undue influence may include inducements, manipulation, and persuasion. Inducements include cash payments or other rewards, which may be acceptable in certain situations. For populations that are potentially vulnerable, such as prisoners, monetary inducements may be considered a form of undue influence because the population is not permitted free will in other situations.

Manipulation means influencing a research subject's decision by altering the available options or information. A classic example of manipulation was in the Tuskegee syphilis study, in which the subjects were not adequately informed that they were infected with syphilis nor provided information about alternatives to participating in the study, such as receiving beneficial treatment (eg, penicillin) when it became available.

Persuasion is defined as a process of guiding people to your way of thinking through the disclosure of truthful information, but in a manner that is meant to guide a person to think or act in a preferred manner. Persuading a research subject is not in and of itself a form of undue influence, but in some situations it may appear to be so to someone else. There are many ways a researcher can persuade a research subject. A research subject is more likely to consent to a study if he or she likes the investigator or if he or she sees the investigator as a representative authority figure. To decrease the appearance of undue influence, it is important for the investigator to present the study with as much impartiality as possible.

Research With Children

Children are one of several classes of subject to which the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research gave particular attention. By regulatory definition, children are persons who have not attained the legal age for consent to treatments or procedures involved in research. Generally in the United States the law considers any person under 18 years old a child. In 1983, based on recommendations from the National Commission, the Department of Health and Human Services developed specific regulations to protect the rights and welfare of children involved in clinical research.⁹

Involving children in research raises serious ethical concerns, largely because their autonomy and competence to give informed consent is less than that of adults. However, restricting children's participation in research is not appropriate, because their participation is necessary to develop new treatments and prevention methods that will benefit children, and to protect children from untested, potentially harmful practices.

Under what conditions is it acceptable to have children participate in clinical research? The usual approach to designing a study that involves children is to conduct preliminary studies in animals, adults, and older children, before young children are involved. There are some experimental interventions, however, in which data may not be entirely generalizable from older subjects, such as treatment of diseases of prematurity.

Does one or do both parents need to consent to research that involves children? It depends on 2 things. (1) Do the investigational procedures involve greater than minimal risk to the child? (2) Is there a prospect of direct benefit to the child? The permission of one parent is sufficient for a study that involves no more than minimal risk, or that involves greater than minimal risk but could benefit the child. For other categories of research, both parents need to give permission, unless one parent is deceased, incarcerated, or not reasonably available, or when only one parent has legal custody of the child.

The IRB must determine the risks and potential benefits to the child and society. The determination of risks is usually intuitive, but interpretation of the meaning of "minimal risk" and "prospect of direct benefit" may lead to confusion between the investigator and the IRB regarding how many parental signatures will be required. Minimal risk means the "probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological exams or tests."¹⁰ But questions remain. Is the definition of "minimal risk" different for a healthy child than a child with an illness? Do the federal regulations refer to the daily life of an otherwise healthy child, or is it relative to a specific child and his or her disease state? What is usual for a child in the midst of an aggressive treatment protocol for malignancy is far different than what is usual for an otherwise healthy child undergoing a tonsillectomy. Unfortunately, there is no consensus on what defines minimal risk for a child involved in clinical research. Therefore, a clinical investigator may find inconsistencies on how an IRB determines the required number of parental signatures.

Children are legally unable to give valid consent, but they may possess the ability to assent to or dissent from participation. Out of respect for children as developing persons, children should be asked whether they wish to participate in the research, particularly if the research is unlikely to be of benefit and the child can comprehend and appreciate what it means to be a volunteer for the benefit of others. If the research could directly benefit the child, assent is not required. The federal regulations do not describe the assent process as they do the parental consent process, so it is up to the investigators to design a process consistent with the child's decision-making skills. The in-

formation given to the child should be age-appropriate, understandable, and tailored to the child's emotional and cognitive maturity. Dissent should be honored, and children should be allowed to withdraw at any time. The ability to give assent requires cognitive ability and the ability to engage in abstract thinking, which depend not on chronological age but on developmental achievement. Tait et al studied the use of pediatric assents in 102 children participating in anesthesia and surgical studies.¹¹ They noted that the children had a very limited understanding of many elements of the study that they had assented to. They concluded that children age ≥ 11 y had significantly greater understanding than did younger children.

The issue of financial or other forms of payment to children, or their parents, warrants discussion. The payment must be of an amount that minimizes the possibility of unduly influencing parents, whose permission is being sought for the child to participate in the research. Appropriate reimbursement for parental expenditures such as travel, meals, parking, babysitting, or time off from work, should be considered. Though there is the theoretical potential for parents to exploit their children for monetary gain, there has been no published study of that practice. Providing age-appropriate financial reimbursement to children will also be scrutinized by the IRB. For example, a large cash payment to a young child is inappropriate, though a small gift, such as a stuffed animal, at the time of a study-related procedure (eg, venipuncture) is appropriate. Mature children certainly understand the meaning of money, and the IRB will usually permit gift cards or monetary payments. Regardless of the subject's age, the IRB will question excessive financial compensation for any patient population.

Research With Women of Child-Bearing Potential

Historically, there have been concerns about the participation of women of childbearing potential in research trials because of potential risks to the fetus if a woman becomes pregnant. Society has been interested in protecting women in part because of discoveries of birth defects caused by certain drugs, including thalidomide and diethylstilbestrol. Such apprehension resulted in federal guidelines and policies that provide special protection for female research subjects. In the 1970s the FDA published a guideline that essentially excluded women of childbearing potential from early phases of drug trials until reproductive toxicity studies were conducted.¹² What resulted was a near moratorium by sponsors on drug trials with women. In the United States there are 60 million women of childbearing potential. The exclusion of women from clinical research raises considerations of justice, because exclusion deprives women the possibility of directly benefiting from participation¹³ and deprives society of valuable informa-

tion. Clearly there are differences in body size, extent and distribution of body fat, hormonal environment, and enzyme production between men and women, but there may also be different pharmacokinetics, pharmacodynamics, rates of adverse events, and effects of hormone replacement. To eliminate this regulatory barrier to the participation of women of childbearing potential in research studies, the FDA began a number of initiatives. In 1993 the FDA issued a new guideline that eliminated the restriction on participation of women of childbearing potential from all phases of drug trials.¹⁴ The new guideline (which was finalized in 1998) emphasized the need for representation of both women and men in research studies, to allow the detection of clinically important gender differences. The National Institutes of Health also examined the issue of participation of women in research, and decided that it was imperative to determine if an experimental intervention affects men and women differently.¹⁵

This shift away from the protectionist ethical framework of our society was also occurring in other areas of medicine. Earlier in the 20th century, the primary focus was on protecting vulnerable persons. As the millennium approached, society emphasized autonomy for individuals, including the widespread acceptance of living wills, advance directives, and shared decision making. Excluding informed female research subjects diminishes their autonomy. Women should be permitted to determine for themselves whether to enter a study, based on their informed decision. Clearly, all research subjects should be protected against risk, but they should not be categorically prohibited from receiving potential benefits from research.

This shift toward autonomy also led to questioning of the federal research guidelines that barred pregnant women, and in effect their fetuses, from research studies. The conflict between whether study participation could benefit a woman versus harming the fetus played out to its fullest early in the acquired immune deficiency syndrome (AIDS) epidemic. In the 1990s the National Task Force on AIDS Drug Development and the Institute of Medicine stated that a woman with a life-threatening disease should not be excluded from any phase of clinical trials, despite the risks or potential risks to an existing or future fetus. These groups decried the very policies that were meant to protect women, as they now were seen as discriminating against women. Women should not be deprived of potential benefit from research for fear of harming a fetus (Table 3)

What does your IRB want to know when you want to recruit women of child bearing potential? Valuable and morally acceptable results can be obtained from studying women of childbearing potential if proper safeguards are utilized. In general, reproductive-toxicity studies must be completed before beginning a large-scale trial of an experimental drug with women of childbearing potential. Appropriate precautions should be taken in research stud-

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Table 3. Protecting Women Who Participate in Research Studies

In General
Ensure that women are appropriately represented in research studies.
Review animal studies of drug effects on reproduction and development, including dose-response relationship and mechanism of toxicity.
Expand access to experimental drugs used to treat serious and life-threatening illnesses to all women, regardless of reproductive situation.
Women of Child-Bearing Potential
Do not exclude women of child-bearing potential from participating in clinical studies.
Discuss the potential risks to reproduction and potential offspring in the informed consent process, including, where appropriate, an adequate discussion of birth control.
Monitor subjects for pregnancy during the trial.
Monitor subjects for reproductive and/or developmental toxicity if pregnancy occurs.

ies to guard against inadvertent exposure of fetuses to potentially dangerous drugs and to inform female research subjects of potential risks and the need for precautions against becoming pregnant or breast feeding. Pregnancy testing may be used to detect unsuspected pregnancy prior to initiating a study drug or intervention. Timing the start of the study to coincide with or immediately follow the onset of menses is another method to help reduce the risk that the research subject is pregnant. The investigator should ascertain that the woman will responsibly use reliable contraception or abstinence while taking the drug. If pregnancy does occur during a trial, the usual procedure is to discontinue treatment and remove the woman from the study. The informed-consent document should include all available information regarding the potential risks of fetal harm. If animal reproductive toxicity studies are complete, the results should be presented, with some explanation of their relevance in humans. If no relevant information is available, the informed consent should explicitly state that the potential for fetal harm is unknown.

Research With Pregnant Women and Fetuses

Pregnant women are considered vulnerable because of the potential for harm to the fetus. Though the restrictions on including women of child-bearing potential in clinical research have been liberalized over the past 3 decades, there remain strict, detailed federal guidelines for the protection of pregnant women and their fetuses involved in research studies. Other than research directed toward the health of a pregnant women and/or her fetus, it is recommended that pregnant women be actively excluded from clinical research that involves greater than minimal risk. The potential for harm from exposure to a drug with unknown risks exists for nursing infants as well as fetuses, so

Table 4. Protecting Lactating and Pregnant Women Who Participate in Research Studies

Lactating Women
Do not exclude lactating women from clinical studies.
During the informed consent process, ensure that nursing mothers receive adequate information about the potential risks to the child.
Pregnant Women
Pregnant women are presumed to be eligible for clinical studies.
Pregnant women are competent adults capable of making their own decisions about participating in clinical studies.
Exclude pregnant women if there is no potential for medical benefit to the women <i>and</i> there are potential risks to the fetus.
Ensure that pregnant women are given adequate information about the potential risks and benefits to themselves, their pregnancies, and their fetuses during the informed consent process.

these recommendations also apply to breast-feeding women (Table 4).

Is excluding pregnant or lactating women justified? Approximately 10% of women 15–44 years old (ie, 6 million women) become pregnant annually in the United States. New medical problems may develop or old ones may become more severe during pregnancy. Compound that problem with the fact that about half of all pregnancies in the United States are unintended, and many fetuses are unintentionally exposed to medicines. More information is needed on the safety of common drugs and practices during pregnancy. But how do we go about doing this? To conduct morally acceptable research with pregnant subjects, the investigator and the IRB must determine if appropriate studies have been conducted with animals and non-pregnant women. For research directed toward maternal health, the investigator must ensure that the risk to the fetus is minimized. This rule applies to all studies, including studies that affect the fetus only indirectly. Minimized risk does not equate to minimal risk, and the regulations state that investigators and IRBs have an ethical obligation to protect the health-related interests of both the mother and the fetus. To say that the fetus has health-related interests invokes the ethics concept of the fetus as a person, which is a discussion beyond the scope of this article.

Respiratory therapists rarely conduct research directed at the fetus alone, though with the increase in fetal surgery, this may change. There are extensive federal regulations regarding clinical research directed toward the fetus, which are beyond the scope of this paper.¹⁶ However, in general, for research in which the fetus is the sole subject of the research, the consent of the mother and the father on behalf of the fetus is required. Exceptions to that requirement are permitted if the father's identity or whereabouts cannot reasonably be ascertained, the father is not reasonably available, or the pregnancy resulted from rape. The requirement of 2 parental signatures is another layer of protection for the vulnerable fetus. Research directed solely at the health

of the fetus is rare. More commonly, respiratory therapists conduct research directed toward the health of the mother or the mother and the fetus. In such situations only the consent of the mother is required. This requirement recognizes the autonomy of the mother as a person.

Research With Prisoners

Historically, prisoners were a readily available and easy-to-manipulate population and they suffered deplorable physical and psychological abuses in research that held no potential for directly benefiting them. In the 1940s, 400 prisoners in Chicago were infected with malaria to study the effects of new experimental drugs. The MK-ULTRA project was a CIA-run clinical investigation in which prisoners were administered hallucinogenic drugs in an attempt to develop incapacitating substances and chemical mind-control agents.¹⁷ Until the early 1970s, about 90% of all pharmaceutical and cosmetic products were tested on prisoners. But such research diminished sharply in 1974, after exposure of abuse at prisons such as Holmesburg, where inmates were paid hundreds of dollars a month to test items from dandruff treatments to dioxin, and were exposed to radioactive, hallucinogenic, and carcinogenic chemicals.¹⁸

Today federal regulations make it much more difficult to use prisoners as subjects in medical research, and little research is conducted in United States prisons.¹⁹ "Prisoner" means any individual involuntarily confined in a penal institution, and includes individuals detained pending arraignment, trial, or sentencing, and the institutionalized mentally infirm. Prisoners can be recruited for research only under certain conditions, and usually not at all. When considering designing a study that would enroll prisoners, the investigator and IRB must determine if it is permissible even to study prisoners. Generally, only research that has the potential to benefit the prisoner is permitted. Recruitment practices are closely scrutinized by the IRB and must be fair to all prisoners. Prisoners must be informed that parole boards and other prison officials will not take into account any prisoner's participation in the research. It is recognized that prisoners may not feel free to refuse to participate because of undue influence by prison officials and clinical investigators. A financial inducement that would be considered minimal for a non-incarcerated person may be deemed unreasonable for a prisoner earning pennies a day working in a prison laundry or machine shop.

Though research with prisoners is severely restricted, when a study has the potential for direct benefit, a patient who happens to be a prisoner should not be excluded from receiving that benefit. The punishment for a crime is incarceration, not exclusion from potentially beneficial research. However, an investigator who wishes to enroll

prisoners in a clinical study must understand the complexity of the federal regulations that protect this vulnerable population and work with the IRB to get the study approved.

Research With Employees and Students

An underlying principle of the federal regulations on human-subjects research is that the subject's participation is voluntary. Students and residents in training are considered vulnerable when a decision to participate is perceived to be required to prevent discrimination, either in determination of course grades or performance evaluation in an academic department. The relationship of instructor and student is inherently of unequal power. No matter how well-intentioned the instructor is, students and residents may feel compelled to participate, believing that failure to do so will negatively affect their grades, evaluations, and the attitude of the instructor (and perhaps other students and residents) toward them. Employees are also considered vulnerable when a decision to participate is perceived to be required to prevent loss of benefits, privileges, opportunities, or job-advancement associated with employment.

When studying students, residents, or employees, an investigator must balance the competing interests of this vulnerable subject protection and the value of the research. The recruitment strategy must be free of pressure and must respect the subject's reasonable expectations of privacy. No pressure should be applied to encourage participation. Participation must be presented as a voluntary option.²⁰ When recruiting their own students, residents, and employees, clinical investigators should not directly ask them to be research subjects, as it may be hard to refuse such a request. Personal solicitation increases the likelihood that participation will be the result of undue influence and compromise the voluntariness of the participation. It is preferred that the investigator post flyers and allow volunteers to initiate contact about the study. The study must be introduced in a way that allows subjects ample time to consider, with no undue pressure because of the timing of the request.

The second major concern when enrolling students, residents, or employees is to determine if there are adequate means for maintaining confidentiality. Research that collects data on sensitive topics (eg, work performance, mental health, sexual activity, or use of illicit drugs or alcohol) presents risks to subjects. The close environment in an academic department of the university amplifies this problem. Respiratory care investigators must take special precautions to ensure that enrollment data, screening results, research data, videotapes, and publications protect the privacy of the volunteers.

Research With Cognitively Impaired Persons

Cognitively impaired persons, such as people with psychiatric, cognitive, or developmental disorders, and patients who are unconscious or critically ill, have a diminished capacity for judgment and reasoning. Decision-making capacity should not be confused with the concept of “competence,” which is a legal determination made by a court of law. Someone who is judged legally incompetent to handle their own financial affairs might still retain sufficient decision-making capacity to make a meaningful choice about taking part in a particular study. Additionally, a person with normal cognitive functioning (ie, legally competent) might be in a circumstance in which his or her decision-making capacity is temporarily impaired by acute illness or trauma. Though research with cognitively impaired people might generate valuable biomedical data, it also raises substantial ethical challenges. How should investigators conducting research on cognitively impaired subjects balance the societal commitment to advance general knowledge with the ethical obligation to protect the rights and welfare of vulnerable research subjects? Research should involve cognitively impaired subjects only if they are the only appropriate subjects, the research question focuses on an issue unique to people in that population, and the research involves no more than minimal risk. Research that involves greater than minimal risk may be acceptable if there is the prospect of direct therapeutic benefit to the research subject.

No single set of standards for defining and assessing decision-making capacity has received universal acceptance. There are also various opinions as to who is most appropriate to administer such assessments, what instruments should be used, and how formal the assessment procedure should be. At a minimum, the investigator should describe who will conduct the assessment, the method of assessing decision-making capacity, and the criteria for identifying incapable subjects. In most situations it is a common-sense determination that a research subject is capable of proving informed consent. However, in situations such as in an intensive care unit, where decision-making capacity may be in question, it is unlikely that an IRB would permit an investigator to determine decision-making capacity.

Additional safeguards to protect cognitively impaired subjects include the use of surrogate consent, the use of assent, and the use of a simplified study summary (frequently asked questions sheet). A surrogate decision-maker or a legally authorized representative, can consent to research on behalf of a cognitively impaired subject. The definition of a legally authorized representative varies state to state, as does the type of research to which the surrogate may consent. In some states a surrogate cannot consent to

research that holds out no expected therapeutic benefit if the research has more than minimal risk.

Most critically ill patients usually cannot give fully informed consent. The controversy over study design and informed-consent issues in the studies by the Acute Respiratory Distress Syndrome Network in the United States led to a more conservative approach about surrogate consent by local IRBs and the Office for Human Research Protections. Even when clinical trials have been approved by local IRBs and investigators have followed existing guidelines for obtaining consent from subjects or their surrogates, post hoc investigations may criticize the consent process and the study design. This environment may inhibit the development of clinical trials in critical care, and clinical research will suffer unless investigators understand and implement the necessary protections in their study designs.²¹⁻²⁴

The use of assent can help protect cognitively impaired subjects. In the case of research that involves more than minimal risk, objection by an adult who is incapable of consenting should be binding, unless the research is expected to directly benefit the subject and the intervention is available only in the context of the research. The investigator should review the main elements of the study with the subject. A simplified study summary may be useful as an aid to emphasize and remind the subject of the major points. The individual's capacity to understand all of the concepts may not be necessary in order to assent to participate in a particular study, though surrogate consent is still required. Some cognitively impaired patients regain capacity as they recover from acute illness or trauma. Investigators should have in a place a process for informing and assenting recovered subjects post hoc.

Summary

To produce morally acceptable study results, investigators must design clinical studies that protect vulnerable research subjects. To ensure that subjects' rights and welfare are not violated, investigators should be aware of the federal regulations and the challenges they impose on clinical studies. Investigators should report on their use of special protections when publishing clinical studies that involve vulnerable research subjects.

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