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The ethics and regulatory landscape of including vulnerable populations in pragmatic clinical trials

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Abstract

Policies have been developed to protect vulnerable populations in clinical research, particularly the US federal research regulations (45 CFR 46 subparts B, C, and D). These policies generally recognize vulnerable populations to include pregnant women, fetuses, neonates, children, prisoners, persons with physical handicaps or mental disabilities, and disadvantaged persons. The aim has been to protect these populations from harm, often by creating regulatory and ethical checks that may limit their participation in many clinical trials. The recent increase in pragmatic clinical trials (PCTs) raises at least two questions about this approach. First, is exclusion itself a harm to vulnerable populations, as these groups may be denied access to understanding how health interventions work for them in clinical settings? Second, are groups considered vulnerable in traditional clinical trials also vulnerable in PCTs? We argue first, that excluding vulnerable subjects from participation in PCTs can be harmful by preventing acquisition of data to meaningfully inform clinical decision-making in the future. Second, we argue that protections for vulnerable subjects in traditional clinical trial settings may not be translatable, feasible, or even

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ethical to apply in PCTs. We conclude by offering specific recommendations for appropriately protecting vulnerable research subjects in PCTs, focusing on pregnant women, fetuses, neonates, children, prisoners, persons with physical handicaps or mental disabilities, and disadvantaged persons.

Keywords

Vulnerable subjects; pragmatic clinical trials; cluster randomized trials; research ethics; regulation; research with pregnant women; research with children; research with prisoners; research with diminished capacity; research with disadvantaged populations

Introduction

Vulnerable persons are those "who are relatively (or absolutely) incapable of protecting their own interests."[1] Research scandals have underscored the need for additional safeguards for those considered vulnerable,2, [a] resulting in policies created to safeguard and protect specific groups from harm. However, pragmatic clinical trials (PCTs) offer a reason to revisit the concept of harm in research for vulnerable populations.

This article discusses ethical and regulatory considerations for vulnerable populations in PCTs. PCTs have been defined as trials that "1) select clinically relevant alternative interventions to compare, 2) include a diverse population of study participants, 3) recruit participants from heterogeneous practice settings, and 4) collect data on a broad range of health outcomes."[3] PCTs streamline and simplify trial design to answer "questions that inform decision-makers about health and healthcare."[4] Features frequently found in PCTs, such as randomization at the group level, reliance on electronic health record (EHR) data, the availability of safety data, and comparisons of approved forms of medical care, may contribute to some PCTs meeting the criteria for minimal risk to human research subjects. Furthermore, for minimal risk PCTs, the additional protections afforded vulnerable subjects, primarily in the informed consent process, may be unnecessary or overly complicated.[5] A reevaluation of current regulations and institutional practices is prudent, as not all safeguards for vulnerable subjects may be appropriate, feasible, or ethical in PCTs.[6]

Traditionally, protecting research participants from harm was closely aligned with excluding them from research, but is exclusion itself harmful? We argue that the principle of justice, commonly interpreted as preventing an inequitable burden of research, should also prevent inequitable *access* to research and its potential benefits for vulnerable populations.[7] A turning point for this reconceptualization of harm started with AIDS research in the 1980s by patients advocating for access to life-saving experimental interventions.[8] This shift continued in research for cancer[9] and is evident in demands for expanded drug access on the grounds of compassionate use[10] and a desire to understand not only whether drugs and interventions are safe and effective, but also whether they are superior to other options.

[a]This paper will use the term *subjects* when referencing the research regulations, but will otherwise use the term *participants* when discussing individuals enrolled in research.

More recently, PCTs have the potential to provide access to useful knowledge beyond traditional clinical research, including vulnerable populations.[11]

General considerations for vulnerable populations in PCTs

Research regulations

From a regulatory perspective, human subjects research in the United States is conducted principally under the federal regulations overseen by the Office for Human Research Protections (OHRP),[12] and of the Food and Drug Administration (FDA),[13] in accordance with state and local laws, and is grounded by the ethical principles described in the Belmont Report.[14] The following populations are identified by specific regulations as needing additional protection: pregnant women, fetuses, neonates, children, and prisoners. Persons with physical handicaps or mental disabilities, and disadvantaged persons, are cited in the regulations. The Belmont Report adds three additional populations: racial minorities, the very sick, and the institutionalized.[15] The protections afforded by these policies have been criticized on the grounds they may be too broad or too narrow, too restrictive or not restrictive enough.[16]

These policies were developed for traditional clinical trials that test novel interventions. PCTs are also designed to answer important questions; however, they may compare two routine medical treatments or collect data from medical records of routine care, thus meeting the federal definition of minimal risk. Approaches need to be identified that would support the design and approval of PCTs that include vulnerable subjects, while still safeguarding their interests.

Rethinking vulnerability

It is time to transition from viewing vulnerability as intrinsic to a specific population, to viewing vulnerability as situational, where the individual participant and study characteristics and circumstances intersect. In a characterization of pediatric vulnerability, Kipnis sets forth seven vulnerability characteristics[17] that can be extended to all vulnerable populations (Table 1). For example, those with a critical illness may have situational vulnerability “in which medical exigency prevents the education and deliberation needed to decide whether to participate in the study.” Another example is persons who are economically disadvantaged, where allocational vulnerability applies because individuals may find it next to impossible to decide not to participate in a trial in light of the proposed benefits offered. These examples show that individuals are not inherently vulnerable simply due to membership in a group; instead, characteristics of the individual in the context of the study are more relevant to determining vulnerability and thus the need for extra protection.

Ethical argument for inclusion

Central to the argument for inclusion of vulnerable participants in PCTs is allowing equitable access to the knowledge gained from research. Groups such as children and pregnant women have been described as “therapeutic orphans” due to the lack of data to support safety and efficacy of treatments in these populations.[18] For example, in a large study examining prescription drug use in pregnant women from 1996 to 2000, 38% used a

category C prescription medication for which safety during pregnancy had not been established.[19] Prescription and over-the-counter drug use in pregnant women have increased markedly over the past several decades,[20] and yet there remains a great disparity in available data despite efforts made to expand the inclusion of pregnant women in research.[21] Similar arguments have been made in the case of children.[22] PCTs, with minimal risk, can differentiate best practice from theoretical assumptions by using large datasets such as EHR and health insurance data; the research of maternal influenza vaccines and birth outcomes is one example.[23,24]

A primary reason people are considered vulnerable is the question of their ability to provide informed consent (ethical principle of respect for autonomy). PCT designs may make this question less relevant[11] when consent is modified. This in no way diminishes the obligation to inform participants. Instead, we advocate consulting with stakeholders, including participants, to modify consent language, design processes to minimize vulnerability, and ensure respect for participants. The integration of stakeholders during all aspects of PCTs will contribute to the integrity and legitimacy of PCTs and build trust in the research process. Specific considerations related to vulnerable populations are discussed in the following sections.

Pregnant women, fetuses, and non-viable neonates or neonates of uncertain viability

Sponsors and institutional review boards (IRBs) are often hesitant to include pregnant women in research for a variety of reasons, including “fear of harm to the fetus and threat of legal liability”[25]; consequently, the federal regulations that define pregnant women, fetuses, and neonates as a vulnerable population are generally conservatively interpreted. These regulations (45 CFR 46, Subpart B) focus on individual involvement of subjects in interventional trials where the “subject is simultaneously the unit of randomization, the unit of experimentation, and the unit of observation.”[26] Therefore, it can be difficult for IRBs to apply the regulations to research that does not fit into this “standard” design, for example cluster randomized trials (CRTs). In a CRT, “organizational, social, or geographically-defined units rather than individuals are randomized between or among comparator interventions.”[27]

An approach for certain CRTs would be to appropriately use the regulations and the definition of human subject research. OHRP defines a human subject as a living individual about whom an investigator obtains data through intervention or interaction with the individual or identifiable private information.[12] If CRTs study groups rather than individuals and the data are collected in aggregate, they may not meet the regulatory definition of human subjects research, and additional safeguards would not apply.[28]

Recent recommendations provide guidance on the ethical design, conduct, and regulatory issues of CRTs.[28,29] These recommendations address vulnerable subjects and help clarify considerations for IRBs. For example, if a CRT is minimal risk and the investigator or the IRB have no direct knowledge of the inclusion of vulnerable subjects, it is acceptable to assume the study does not include vulnerable groups.[28]

Highlighting the concern regarding inclusion of vulnerable populations in PCTs and/or CRTs, even when the trial involves randomization between interventions defined as "standard of care," is the recent controversy surrounding the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT).[30,31] The trial randomly assigned infants to a higher or lower target oxygen saturation range within levels used in clinical settings to determine the optimal saturation to reduce the incidence of retinopathy of prematurity and death. OHRP determined that randomization to specific oxygen levels, even though within standard of care, increased risk to the subjects;[32] however, it is important to note that neonatologists "generally...do not make individualized decisions about oxygen saturation targets for each patient" and that they "always treat babies by [that NICU's] protocol."[33] The trial results, along with those of companion trials outside the United States, helped change practice. However, OHRP determined that the informed consent did not adequately describe the potential risks of the study.[32] The controversies surrounding SUPPORT illustrate the need to reconsider issues of informed consent, outcomes, and risk in PCTs, while also considering the life-saving improvements in medical care that can result from inclusion of vulnerable populations in such research.[33-37]

Prisoners

The historical abuse of prisoners in research is well documented.[38-41] Nevertheless, the literature offers rationale for the broader inclusion of prisoners in medical research. Reasons include a rapidly increasing number of prisoners in the United States,[42,43] differences in the comparative effectiveness of medical treatments in prison settings, an aging prison population,[44] and the need to augment health resources for prisoners.[45]

It is the potential of coercion that results from loss of options in captivity[46] and the prevalence of mental illness[47] that distinguishes prisoners as a uniquely vulnerable group. Prisoners are protected by a separate Subpart in the regulations (45 CFR 46 Subpart C).[12] Research with prisoners must be minimal risk, study aspects of issues or conditions particularly affecting prisoners as a class, or study practices which have the intent and reasonable probability of improving the health or well-being of the subject.

Subpart C defines a prisoner as "an individual involuntarily confined or detained in a penal institution," covering multiple situations, including those detained "pending arraignment, trial, or sentencing."[12] Furthermore, it seeks to protect persons incarcerated before and after enrollment. Yet, the vulnerability of these groups is different. Those for whom the opportunity to enroll occurs before incarceration may not face coercion risks; however, they may face different risks due to the feasibility of continuing study activities after confinement.

Similarly, identifiable records of persons who are incarcerated are defined as prisoners and thus subject to Subpart C. However, prisoner records research would not involve coercion if it meets the same regulatory criteria for waiver of consent as non-prison research. Yet the regulations do not protect those on parole and probation, although they may be vulnerable to the same coercive risks as incarcerated persons because they may face the same loss of options.

For the non-prison population, the design and nature of PCTs may render informed consent unnecessary except to decline participation due to minor but meaningful effects on patients' interests.[48] Regulations permit the requirement for informed consent to be weighed against "practicability." Likewise, the additional protections afforded prisoners primarily through the consent process may not be "practicable" in settings where there is no choice because there is only one clinically relevant option.

The protections of Subpart C address the potential to induce or coerce consent to participate; therefore, if coercion in the consent process does not pertain, Subpart C may not be relevant. This is the case when consent was freely given prior to incarceration, or with medical records research if a waiver of consent was granted. Conversely, ethical considerations afforded prisoners should be extended to persons on parole or probation, as proposed by the Institute of Medicine.[47] There is now a waiver for epidemiological research involving prisoners that studies incidence and potential risks of specific diseases.[49] The desire to include prisoner data may be viewed as "an acknowledgment of overly restrictive requirements."[50]

Children

Children are a vulnerable population addressed in the federal regulations (45 CFR 46 Subpart D; 21 CFR 50 Subpart D).[12,13] As a group, "children" cover a wide range of ages, risk exposures, legal implications, and expectations for autonomy. From a regulatory perspective, research with children must fall into one of three risk categories: minimal risk, greater than minimal risk with a potential for direct benefit, or a minor increment over minimal risk with no benefit but likely to yield generalizable knowledge about the minor's disorder or condition. These categories dictate the types of protection required. Any research not in one of these categories must undergo additional regulatory review by the Department of Health and Human Services and is subject to public comment prior to approval. Research with non-vulnerable adults, in contrast, relies on only risk minimization and assessment of risk-to-benefit ratio. Many PCTs fall into the categories of minimal risk or greater than minimal risk with a potential for direct benefit, thereby aligning more closely with the required considerations of research with children, and reducing the need for special protections.

In an attempt to protect children from research risks, they are often excluded; however, this may leave researchers and clinicians with incomplete evidence, or evidence based on adult data, as to how to treat minors.[51] That being said, even parents who are supportive of pediatric research are sometimes concerned that research may interfere with their child's care.[52,53]

The involvement of young children in research is dictated by parental permission, while older children are increasingly involved in participation decisions through an assent process. It is important that the level of child involvement in research decisions is varied in accordance with the child's level of development.[54] In addition, the context and risk level of the research should be considered when involving children in research decisions, particularly in PCTs where the line between research and clinical care may be blurred.

Because PCTs randomize minors to approved treatments, which they could receive outside of the research and inherently have some prospect of benefit, the risks of research are reduced to those associated with randomization versus clinician judgment rather than the overall risks of a novel intervention. Furthermore, CRTs that are conducted in hospitals or clinics may include children as indirect research participants. This means they are affected by the intervention through their exposure to the environment in which the intervention is being deployed.[55] It is important for their data to be included in the research outcomes, yet the risk to the minor is not direct. Thus, if the principal investigator or the IRB is not aware that children are included in the study, the level of oversight for the CRT should be appropriate.

Persons with diminished capacity to consent

Capacity is a functional determination and is an important indicator of an individual's ability to exercise autonomous choice.[56] Capacity is different than competence. Competence is a legal determination of a person's ability to understand and react. It is determined by a judge.[57]

Research that involves participants who may have diminished capacity to consent is not addressed by specific regulations as are other identified vulnerable groups. However, “balancing the obligation to respect the rights of those with mental impairments to be treated as autonomous members of the moral community, with the need to ensure that ill-informed or incompetent decisions will not place their welfare in jeopardy” is necessary.[58]

In studies directed at individuals, it is essential to assess the capacity to consent of all potential participants.[59] In other words, a broad determination cannot be made based on diagnosis or membership in a particular population. The methods to determine capacity in PCTs should increase in rigor as the degree of risk to the participant increases.[60] In studies that are minimal risk, as many PCTs are, asking the participant to restate their understanding of the risks and what they are being asked to do may suffice. In studies involving greater than minimal risk, a formal assessment tool or a third-party clinical assessment may be required to assure the subject has the capacity to consent. The need for additional safeguards does not depend on why adults are unable to consent, only that they are unable to consent.[61]

For PCTs involving standard clinical treatments (e.g., a comparison of two commonly used, FDA-approved medications used for labeled indications), one possible approach is to follow medical practice by identifying a surrogate decision-maker based on relationship to the participant. In the case of lower-risk studies, independent community/patient representatives could provide guidance on the design and oversight of a study. This approach may be ideal in CRTs, where a group, and not the individual, is the subject of study. State laws regarding who may serve as a proxy for those who lack capacity to consent will be necessary to consider.

Disadvantaged populations

In real-world healthcare settings, patients can be medically and socially complex. As a result, unique considerations emerge for PCTs. Beyond the vulnerable populations discussed

above, PCTs often include other disadvantaged populations, such as patients with multiple medical and mental health comorbidities, those with critical and acute illnesses, the uninsured and underinsured, as well as those with unstable social situations and limited financial resources.

Since PCTs are regularly conducted during a patient's routine clinical care, the cost of participating, such as co-payments and deductibles, may be borne by the participant, either directly or through their insurance scheme. This can pose a participation barrier for the underinsured, uninsured, or those with limited financial resources. Patients with financial hardships may not wish to participate in studies that carry risks of randomization to a study arm with more numerous, costly, or burdensome hospital or clinic visits than another arm. Financial difficulty may also pose a challenge for patients to stay enrolled in a trial. For example, discontinuation of phone services has been described as a barrier to long-term follow-up in PCTs,[62] and could create difficulties for the patient to contact the doctor if needed. These enrollment and retention challenges can bias trial results.

Investigators, study sponsors, and IRBs should strongly consider the potential benefits of including the underinsured or uninsured, economically and otherwise disadvantaged subjects in trials and engage stakeholders to seek potential solutions to participation barriers during study development. These populations should not be routinely screened out from trials since, as previously stated, it is important to include their data for generalizability of study results. Researchers should investigate approaches to help support the inclusion of all subjects.

Conclusion

It is necessary to follow regulations and ethical principles to conduct responsible and compliant clinical research. The regulations codify protections for several vulnerable populations. For traditional, greater than minimal risk research, this approach is logical. However, these same regulatory requirements may create barriers for vulnerable subjects to participate in PCTs, resulting in an evidence gap for populations of patients. Thus, it is also logical to evaluate different approaches that will allow ethical, compliant research, yet avoid potential barriers to the important knowledge that PCTs can provide.[63]

As stated by Carol Levine, research ethics was “born in scandal and reared in protectionism.”[8] As a result, ethics and regulatory initiatives often aim more to protect vulnerable subjects from harm than to consider the importance of the inclusion of their data. This emphasis on preventing harm may make sense for traditional clinical trials, where the drugs, products, and interventions being studied are often new and unapproved by the FDA. PCTs generally study approved interventions already in clinical use. Therefore, the ethical focus may expand beyond only preventing harm to vulnerable populations to providing an understanding of how approved medical interventions work in their specific situations, settings, communities, and environments. In all cases, however, a risk/benefit evaluation is necessary.

All research, regardless of type, should begin by considering the risk posed by the study design before considering additional safeguards.[64] Considerations of who the targeted study

population will be, should also determine the need for additional safeguards. PCTs should be designed so that those in special populations are able to be included in the broad and representative study population. If a study is minimal risk, appropriate safeguards for potential vulnerable subjects should match that risk. Independent community/patient representatives, such as patient advisory boards to researchers or prisoner representatives on IRBs (45 CFR 46.304(a,b)), could help provide guidance during study development and throughout a study.[12] It is also important to ensure the information learned from the PCTs is publicly disseminated to contribute to generalizable knowledge and honor the participation of vulnerable subjects.

Our recommendations regarding vulnerable subjects in PCTs are summarized in Table 2. Evidence is critically needed to inform decisions made in clinical practice.[4,5] Although new treatments continue to be required, patients and the healthcare community also deserve answers to questions about the appropriateness of current therapies. Many more questions need to be answered from real-world situations using PCTs. The real world includes people who are in categories identified as vulnerable subjects. It is important that their information informs real-world results.

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Abbreviations

The following abbreviations are used in this manuscript:

CRT	cluster randomized trial
EHR	electronic health record
FDA	US Food and Drug Administration
IRB	institutional review board
OHRP	Office for Human Research Protections
PCT	pragmatic clinical trial
SUPPORT	Surfactant, Positive Pressure, and Oxygenation Randomized Trial

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Table 1

Individual characteristics of vulnerability to consider by population

Population	Incapacitational[a]	Juridic[b]	Deferential[c]	Social[d]	Situational[e]	Medical[f]	Allocational[g]
Children	X	X	X	X	X	X	X
Disadvantaged persons			X	X	X		X
Human fetuses	X				X		
Institutionalized	X	X	X	X	X		X
Neonates	X				X		
Persons with physical handicaps/mental disabilities	X	X	X	X	X		X
Pregnant women			X	Historically and non-US	X		
Prisoners		X	X	X	X		X
Racial minorities			X	X	X		
The very sick	X		X	X	X	X	

Note: Italicized populations are those covered by additional regulations.

Framework adapted from Kipnis[17]:

[a] Lacks "the capacity to deliberate about and decide whether to participate in the study."

[b] "Liable to the authority of others who may have an independent interest in that participation."

[c] "Given to patterns of deferential behavior that may mask an underlying unwillingness to participate."

[d] Belongs "to a group whose rights and interests have been socially disvalued."

[e] "In a situation in which medical exigency prevents the education and deliberation needed to decide whether to participate in the study."

[f] Has "been selected, in part, because of the presence of a serious health-related condition for which there are no satisfactory remedies."

[g] "Lacking in subjectively important social goods that will be provided as a consequence of participation in the research."

Table 2

Recommendations for vulnerable populations in PCTs

• When designing a PCT, inclusion of participants who may be members of a vulnerable category should be considered, and how the ethical and regulatory requirements will be assessed and managed should be addressed in the study.
• There should not be a differential burden of research nor differential access to research for one group relative to any other. Therefore, being part of a vulnerable population should not be an exclusion criterion.
• In general, PCTs not targeting vulnerable subjects should not seek to identify vulnerable subjects within the study for the sole purpose to exclude them. This could stigmatize the vulnerable group and risk violating confidentiality and loss of research data for that group.
• PCTs where a vulnerable population is the focus of the study rather than a member of a larger group, should address the protections for that group. PCTs where vulnerable subjects are included as part of a larger population should be evaluated based on the level of risk and the characteristics being studied.
• Revisit the regulations to consider the characteristics of the participants and the incremental risk of the research design to determine the need for added protection for vulnerable populations.

PCT, pragmatic clinical trial.