Review Article

# Vulnerability in Clinical Trials

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**ABSTRACT**

Vulnerability means that an individual or groups of individuals lack the ability to fully and independently protect their own interests and so are vulnerable to being harmed or wronged. The word vulnerability stems from the Latin vulner are, which means to wound. 19 October 2005 is an important day for bioethics. On this date the UN member states adopted the Universal Declaration on Bioethics and Human right. Article 8 of the declaration addresses the topics discussed here- "vulnerability" and "vulnerable groups". Different approaches to define vulnerable populations are Categorical approach and Contextual approach. Sources of vulnerability are Poverty and race, Social networks and lack of social support, Personal limitations, Physical location. In India there are multiple socio-economic disadvantages that members of particular groups experience which limits their access to health and health care. The task of identifying the vulnerable groups is not an easy one. Some of the prominent factors on the basis of which individuals or members of groups are discriminated in India, i.e., structure factor, age, disability, mobility, stigma and discrimination that act as barriers to health and health care. The vulnerable groups that face discrimination include Women, Scheduled Castes (SC), Scheduled Tribes (ST), Children, Aged, Disabled, Poor migrants, People living with HIV/AIDS and Sexual Minorities.

**Keywords:** Vulnerability, disabled, clinical trials.

## INTRODUCTION

Vulnerability means that an individual or groups of individuals lack the ability to fully and independently protect their own interests and so are vulnerable to being harmed or wronged.[1] The word vulnerability stems from the Latin vulnerare, which means to wound. In the context of human subjects' research individuals or groups are vulnerable if they are unable fully and independently protect their own interests, either due to intrinsic characteristics (e.g., age or immaturity), or circumstances (e.g., illness, incarceration, or poverty). It is a central tenet of the ethics of human subjects' research that additional steps be taken to protect vulnerable participants from harm. For example, the U.S. Code of Federal Regulations requires that institutional review boards (IRBs) approve research involving vulnerable participants only when "additional safeguards have been included in the study to protect the rights and welfare of these subjects."The World Medical Association's Declaration of Helsinki states that vulnerable groups and individuals "should receive specifically considered protection."[2]

19 October 2005 is an important day for bioethics. On this date, the UN member states adopted the Universal Declaration on Bioethics and Human Rights. Article 8 of the declaration addresses the topics discussed here – "vulnerability" and "vulnerable groups". The article has a dual focus:

- To proclaim "human vulnerability" as a basic principle of bioethics, and
- To ensure that individuals and groups of "special vulnerability" receive adequate protection in the development and application of medical, scientific and technological knowledge.

The declaration does not contain a definition of the terms "vulnerability" or "human vulnerability", but it is stated elsewhere in the declaration that also families, groups and communities can be vulnerable. It also points out a number of circumstances that can make individuals and groups vulnerable, like:

- Disease
- Disability
- Other personal conditions
- Environmental conditions
- Limited resources

The declaration is of an anthropocentric nature, in the sense that its frame of reference is human vulnerability, not the frailties of other life forms.

### Different approaches to define vulnerable populations

Determining which individuals or groups should be considered vulnerable and in need of additional protections as research participants is an ongoing challenge for researchers and IRBs. There are different Approaches to defining vulnerable populations that might be appropriate in different contexts. These include:

- Categorical approach
- Contextual approach

**Categorical vulnerability**

The categorical (or sub group) approach defines vulnerable populations as those groups in society whose members share features that might make them vulnerable. For example, the U.S. Code of Federal Regulations lists "children, prisoners, pregnant women, mentally disabled persons, and economically and educationally disadvantaged persons" as vulnerable groups.

The categorical approach is most applicable when all members of a particular group are vulnerable for the same reason. The categorical approach is more contentious, however, when a person's vulnerability results not from an intrinsic characteristic that makes the, unable to protect their own interests (e.g., immaturity in the case of children), but from circumstances (e.g., poverty, illness, or social marginalization) that affect individuals differently an might make some members of a group more vulnerable to exploitation.[3] .[4]Additionally, members of certain population subgroups might be vulnerable in some circumstances but not in others; for example, a pregnant women might be vulnerable during active labor, but not at other points of her pregnancy.[5]

**Contextual vulnerability**

In its 2001 report, Ethical and Policy Issues in Human Subjects Research, the National Bioethics Advisory Commission (NBAC) proposed an alternative to the categorical definition of vulnerability, highlighting the extent to which vulnerability in research subjects is sensitive to context. NBAC described six types of vulnerability that could apply to research participants in different circumstances:

- Cognitive and communicative vulnerability: the inability to understand information and make decisions, either due to capacity (e.g., young children), or circumstances (e.g., a stressful emergency or language barrier).
- Institutional vulnerability: being subject to an authority relationship in a formal hierarchal structure (e.g., prisoners or military personnel).
- Deferential vulnerability: being subject to the authority of others (e.g., children or military personnel).
- Medical vulnerability: having a serious health condition for which there is no satisfactory standard treatment.
- Economic vulnerability: being disadvantaged in the distribution of social goods and services such as income, housing, or health care.
- Social vulnerability: being a member of an undervalued or disenfranchised social group.

**Sources of vulnerability**

- Poverty and race: discussion of vulnerability inevitably involves poverty and race and related issues of stigma and discrimination. Low income and education from early life and often over the life course, more common among black than white Americans, is associated with a wide range of vulnerabilities. Poor socioeconomic status, for example, is linked to deficiencies in prenatal and early nutrition. Studies of parenting find that low family income and maternal hardship hamper children's cognitive and social competence.
- Social networks and lack of social support: Many people in impoverished communities and in much less deprived communities as well, are often vulnerable because of their precarious ties to social networks and lack of needed social supports.
- Personal limitations
- Physical location: A major part of the population is vulnerable because of location, such as in low-density and impoverished rural areas; urban ghettos; or other places associated with underdeveloped or deteriorating infrastructure; lack of employment opportunities; inadequate medical, social, and educational services; poor transportation and communication facilities; high crime and victimization; and exposure to environmentally adverse conditions.

**The role of informed consent and IRB**

Vulnerability has been defined in current ethical dogma largely based on the lack of ability to provide informed consent. Recent revision of the declaration of Helsinki states the following:

- Medical research is subject to ethical standard that promotes respect for all human beings and protect their health and rights.
- Some research populations are vulnerable and need special protection.
- Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research I combined with care.[6]

As the declaration of Helsinki suggests, informed consent relies on the concept of autonomy. According to Rhodes, there are two definitions of autonomy.

- First-person autonomy - "duty to be a good ruler over one's self".

- Second-person autonomy- "refers to respect for the autonomy of others"
- Such reliance on informed consent for the protection of the vulnerable has exposed flaws in the IRB review process. IRB review is often based on confirmation that informed consent will be obtained from all participants and that all vulnerable population will be protected, rather than considering the true ethical basis of a study.[7] By focusing on predetermined definition of vulnerable, IRBs might over estimates the true vulnerability of certain populations.

List of examples of individuals, groups, societies and populations classified as particularly vulnerable in research ethics guidelines and declarations:

**The Belmont report (1979)**

- Ethnic minorities.
- Economically disadvantaged.
- Terminally ill.
- Persons confined to institutions.

**The Declaration of Helsinki (2009)**

- Subjects unable to give informed consent.
- Subjects receptive to coercion or undue influence.
- Populations or societies that will not benefit directly from participation in research
- Patients who participate in medical research in combination with medical treatment and care.

**CIOMS (2002)**

- Persons unable to give informed consent.
- Children.
- Junior or subordinate members of a hierarchical group (e.g. medical students, nursing students, subordinate health and laboratory personnel at hospitals. e employees of pharmaceutical companies, military personnel and the police
- The elderly
- Residents of retirement and nursing homes.
- People receiving welfare benefits or social assistance.
- Poor persons.
- The unemployed.
- Patients in emergency rooms.
- Some ethnic minorities.
- The homeless
- Nomads
- Refugees and asylum- seekers
- Prisoners
- Patients with incurable disease
- Politically powerless individuals.
- Members of communities unfamiliar with modern medical concepts.

**Rights of vulnerable groups in India**

In India there are multiple socio-economic disadvantages that members of particular groups experience which limits their access to health and health care. The task of identifying the vulnerable groups is not an easy one. Some of the prominent factors on the basis of which individuals or members of groups are discriminated in India, i.e., structure factor, age, disability, mobility, stigma and discrimination that act as barriers to health and health care. The vulnerable groups that face discrimination include Women, Scheduled Castes (SC), Scheduled Tribes (ST), Children, Aged, Disabled, Poor migrants, People living with HIV/AIDS and Sexual Minorities. Sometimes each group faces multiple identities. For example, in a patriarchal society, disabled women face double discrimination of being a NBAC and being disabled.

**Important characteristics of vulnerable groups**

1. It suffers from discrimination and subordination.
2. They have physical and/or cultural traits that set them apart, and which are disapproved of, by a dominant group.
3. They share a sense of collective identity and common burdens.
4. They have shared social rules about who belongs, and who does not.

**Various vulnerable groups in clinical trials**

Until the early 1990s of the twentieth century, the inclusion of women of reproductive age in clinical trials Phases I and II is very limited. One of the reasons behind this is FDA's 1977 guideline, which recommended excluding women with child bearing potential from participating in early phases of drug trials. The recommended exclusion was broadly applied to any 'premenopausal female capable of becoming pregnant', but explicitly did not apply to women with life threatening diseases[9]. The results of such a major limitation were:

- The rights of sick women were limited, as they cannot get timely treatment with more effective drugs;
- The efficacy of many medical products on the women was unknown, although they were prescribed both men and women.

In 1998, experts from the World Health Organization (WHO) and United Nations (UN) issue a report 'Women and Health Mainstreaming the Gender Perspective into the Health participation must be accompanied by informed consent.

Studies on pregnant women should only be conducted in cases when the required data cannot be obtained from another patient's categories and when the purpose of the study corresponds to the mothers and foetus's health needs with minimal risk.

**Clinical trials on Children**

Children are a vulnerable population because of their inability ethically and legally to consent to participate in research; and because of a perceived need to defer to adult authority; a lack of independent resources for autonomous decision making; and potential influence by "longstanding institutionalized relationship of adult authority and power".[10]Additional protections are required to ensure that children participating in research are not placed at unnecessary risk for the benefits of others. These additional safeguards are articulated in existing regulations and include seeking and obtaining parental permission, seeking and obtaining meaningful child assent or dissent when developmentally appropriate, and limiting the degree of allowable research-related risk.

**Clinical trials on decisionally impaired individuals**

Decisionally or cognitively impaired individuals are potentially vulnerable because of limited capacity to give informed concern to participate in research. Informed consent is the process informing and obtaining permission from man individual before conducting medical or research procedures or test. In the research setting, this is involves research's educating prospective research participants about the risks and potential benefits of a proposed study and prospectively seeking the concern to participants.

Seeking and obtaining informed concern is part of ethical treatment of individuals in both clinical and research settings. Individual with impaired decision making capacity might be unable to fully understand the informed concerned process or the implications of participating in research's, as a result, their agreement to participate might considered ethically legally valid.

Decision making capacity is a complex skill set, and incorporates the capacities to settle on and express a decision, understand information relevant to a clinical choice, appreciate the significance of this information for the individual's own circumstance, and reason with the relevant information in weighing options. For participants in research, decision making capacity also includes the ability to appreciate the differences between clinical care and research interventions.[11]

Decisional or cognitive impairment can stem from a number of causes, including some forms of mental illness, dementia, addiction, or mental disability, although individuals should not be presumed to lack decision making capacity simply in virtue of a diagnosis of a medical condition. Decision making capacity varies along a continuum, and individuals with some impairment might retain the ability to make certain types of decisions but not others. However, when potential research participants are likely to have impaired decision making capacity, they are appropriately considered vulnerable and in need of additional protections beyond those applicable to all research participants.[11]

Decisionally impaired individuals comprise an important group to consider in terms of susceptibility, both because of numerous historical cases of exploitation of this group in research, and because of an ongoing debate over when appropriate additional safeguards and regulatory protections should be in place.[12]

Current U.S. regulations include "mentally disabled persons" as a vulnerable group for whom additional safeguards should be provided. The guidelines likewise express that examination with people who can't furnish educated assent can continue just with authorization from a legally authorized representative (LAR), despite the fact that the assurance of who can fill in as a LAR fluctuates by state. However, the regulations don't provided the definitions of what constitutes a mental disability, nor do they specify what additional safeguards, beyond consent from an LAR, should be required for this group. Additional to the regulations have met with resistance from scientist concerned that additional regulations would impede the valuable research, and from those concerned about the adequacy of regulations to protect the dignity and well- being of research participants.[13]

Scholars have suggested various ways for decisionally impaired research participants might be strengthened. Some recommend regulations similar to those for children in research; which safeguards such as assessments of decision making capacity by someone independent of the research team, or inclusion in IRBs of members who are familiar with conditions that cause decisional impairment and the issues of the population being studied.[11]

**Clinical trials on Prisoners**

Prisoners are vulnerable because physical isolation, lack of independence, and power differentials within command structures place them at greater risk of being manipulated or coerced into research.[14]The circumstances wherein prisoners live restrict their autonomy and ability to workout loose preference, and therefore undermine their capacity to offer voluntary informed consent to participate in research.

For example, prisoners would possibly sense that they've no preference however to take part in research, fearing punishment or denial of basic services. Additionally, their confined approach would possibly make them extra

willing to tackle threat in change for unique favours or remedy (e.g., extra unfastened time or simpler work assignments).

However, prisoners might pick freely to volunteer for studies for a number of reasons. For example, a few prisoners have expressed a desire to take part to compensate for their crimes, and others have said that participation accelerated their shallowness. Regulations for the inclusion of prisoners in studies therefore attempt to reconcile the want to protect prisoners from exploitation and the need to allow them to pick freely the makes use of to which their bodies could be positioned.

**Clinical trials on Military Personnel**

Military employees additionally wouldfeel pressure to participate in research because of the structured hierarchy wherein they stay and works. They might experience that participation ought to make contributions to promotions, less difficult assignments, or unique privileges; or that refusal to participate should bring about demotions or other punitive measures. Moreover, the success of navy operations depends in component on giving up some individual autonomy for the coolest of the whole; because of this, infantrymen might be coerced to participate in research if it's far taken into consideration to be for the greater right; for instance, accepting an experimental vaccine to make sure that the whole force would be protected.

**Special considerations for children**

Regulations that protect the children, so as to prevent their exploitation are:

- OHRP 45 CFR 46 Subpart D
- FDA 21 CFR 50 Subpart DSP

Special Considerations for Children are:

- If the parents of the children are died, or not known then the legal guardian must give the consent.
- Step parents, grandparents, adult siblings, adult aunts and uncles may not consent a child to research.
- In case of life threatening events only consent from parents would be adequate, as there is expectation of direct benefit. The trial details should be explained completely to the child.

**Special considerations for women**

Regulations that protect women, so as to prevent their exploitation are:

- OHRP 45 CFR 46 Subpart B

Research studies involving pregnant women and fetuses should satisfy the following requirements to obtain IRB approval:

- Preclinical studies should include pregnant animals and clinical studies should include non-pregnant women to provide data for assessing potential risks to pregnant women and fetuses
- Risk of fetus is mainly caused by interventions or procedures which hold direct benefit for the women or the fetus.

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