

Published in final edited form as:

*AIDS Behav*. 2010 December ; 14(6): 1313–1319. doi:10.1007/s10461-010-9785-x.

# How Researchers Define Vulnerable Populations in HIV/AIDS Clinical Trials

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## Abstract

In this study, we interviewed researchers, asking them to define vulnerable populations in HIV/AIDS clinical trials, and provide feedback on the federal regulations for three vulnerable populations. Interview data informed a conceptual framework, and were content analyzed to identify acceptability or disagreement with the regulations. Beginning with several characteristics of vulnerable enrollees identified by researchers, the conceptual framework illustrates possible scenarios of how enrollees could be considered vulnerable in clinical research. Content analysis identified barriers affecting HIV/AIDS researchers' ability to conduct clinical trials with pregnant women, prisoners, and children, for which the regulations specify additional protections. This study challenges current thinking about federal regulations' group-based approach to defining vulnerable populations.

### Keywords

HIV; AIDS; Vulnerable populations; Ethics; Clinical trials

## Introduction

Vulnerability is a central concept in protecting human subjects in research, and the term, *vulnerable populations*, was introduced as part of the guidelines for medical ethics in the 1949 Nuremburg Code, World Medical Association Declaration of Helsinki (most recent update:



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2008), and the 1979 Belmont Report to protect human subjects involved in research [1,2]. The US federal regulations for protection of human subjects, in 45 Code of Federal Regulations Part 46 (45 CFR 46) require special protections for three categories of vulnerable populations —pregnant women, fetuses, and neonates (Subpart B), prisoners (Subpart C), and children (Subpart D) [1]. In addition, 45 CFR 46, in Subpart A (also known as the Common Rule), requires Institutional Review Boards (IRBs) to consider additional protections for those who are "economically," "educationally," or "decisionally" impaired, without specifying these terms [1].

Using a group-based approach—in which individuals are considered vulnerable if they belong to specified groups—has been criticized to be both too narrow and too broad in scope; too narrow because it does not take into account other factors that lead to vulnerability, or persons or populations with multiple vulnerabilities [3,4], and too broad because some individuals who belong to these categories are not vulnerable in certain types of research [3,5]. Another criticism with the group-based approach to identifying vulnerable populations is that the federal regulations do not provide adequate guidance about what additional safeguards should be taken with each of the groups identified [3]. For example, protecting vulnerable populations by barring them from participation in certain clinical trials may be doing more harm than good. Indeed, the current conceptualization of vulnerable populations has made access to clinical trials more difficult for underrepresented groups [1].

While the debate concerning defining vulnerable populations continues among bioethics scholars, only a few empirical studies examine how researchers think about and address vulnerability in clinical trials [6-8]. To date, however, no studies have examined issues of vulnerable populations in the context of HIV/AIDS clinical trials, particularly from the perspectives of frontline researchers. HIV/AIDS, unlike other diseases/conditions, includes individuals and populations with a wide range of vulnerability characteristics—including racial/ethnic minorities, women, and/or injecting drug users—not necessarily specified in the current definition and categories [9,10]. HIV-positive subjects with one or more of these characteristics may not fit in 45 CFR 46's Subparts B,C, and D. Moreover, the terms, "educational, economic, and decisional impairment" in the Common Rule are not specific enough to assist HIV/AIDS clinical trial researchers to identify and protect subjects who they consider vulnerable.

The purpose of this study is twofold: The first part is to take a grounded-theory approach in developing a conceptual framework for understanding which enrollees are considered vulnerable from the perspectives of researchers working in HIV/AIDS clinical trials. The second part of the study explores HIV/AIDS researchers' perspectives on the subparts of 45 CFR 46 to gain a better understanding of the perceived utility and limits of these regulations for protecting pregnant women/fetuses, prisoners, and children from potential risks.

## Methods

### Sample and Recruitment

A sampling frame of AIDS Clinical Trials was obtained from the AIDS Clinical Trial Information Service (ACTIS), which was a resource of federally and privately-funded AIDS Clinical Trial information through the Division of Acquired Immune Deficiency Syndrome (DAIDS), National Institute for Allergy and Infectious Diseases (NIAID) [11]. A list of Principal Investigators (PIs) was created in an Excel spreadsheet and categorized by Adult or Pediatric AIDS Clinical Trials Groups (ACTGs), and comprised 31 Adult AIDS Clinical Trials Group (AACTG) sites and 18 Pediatric AIDS Clinical Trials Group (PACTG) sites. In addition, 16 HIV Prevention Trials Network (HPTN) PIs were included in the spreadsheet. HPTN—established in 1999 by DAIDS—is an international clinical trials network that develops and

tests the safety and efficacy of primarily non-vaccine interventions designed to prevent the transmission of HIV [12].

All AACTG, PACTG, and HPTN PIs were sent an initial letter via regular mail requesting their participation in a telephone interview, and the names and contact information of their co-investigators or study coordinators so that they could be asked to participate. To PIs, co-investigators, and study coordinators who agreed to participate, a consent form was faxed to them; they were asked to sign the consent form and fax it back before the scheduled telephone interview. Several follow-up email or telephone contacts were made to both investigators and study coordinators to maximize the responses; both refusals and non-responses were documented. Once the interview was completed, investigator- and study coordinator-subjects were mailed a $50 incentive, or the $50 was donated to a charity of their choice. This study was approved by the UNC Biomedical Institutional Review Board.

## Data Collection

A semi-structured interview guide was developed and used to conduct the audiotaped, telephone interviews with the investigators/study coordinator subjects. The interview guide included two conceptual domains to explore (a) their definitions of what constitutes vulnerability in HIV/AIDS clinical trial populations, and how they see their study population (s) as vulnerable; and (b) what they think of the current categories of vulnerable populations for which there are special protections in the 45 CFR 46.

## Data Analysis

All audiotaped interviews from investigator/study coordinator subjects were electronically transcribed into Microsoft Word. Accuracy of the transcription was verified by a member of the research team, and any identifying information in the interviews was redacted to protect the confidentiality of subjects. The transcribed interviews were imported into the qualitative software program, Atlas.ti, v. 5.2. The first phase of qualitative data analysis involved identifying themes from the questions asked, and developing a codebook reflecting a thematic coding structure underlying the conceptual domains. Codes for each theme were assigned to text using Atlas.ti by a pair of coders per transcript, and inter-coder reliability was assessed by having the coders resolve any coding differences between them. Thus, the first phase of the analytical process yielded discrete and systematically coded textual data.

## Development of a Conceptual Framework

To develop the conceptual framework, we extracted coded textual data elicited from the questions (a) “What is your definition of a vulnerable population?”, and (b) “In general, how are AIDS clinical trial (or HPTN) study populations considered vulnerable?” These data were reviewed in a 2-step process. The first step identified indicators of vulnerability elicited from these two questions and organized them into three broad categories reflecting social, treatment-related, and research participation-related vulnerabilities. The next step involved examining co-occurrences between the themes from these broad vulnerability categories that informed a conceptual framework to explore how HIV/AIDS clinical trial populations could be vulnerable in *clinical* research.

## Investigator/Study Coordinator Views on 45 CFR 46 Subparts B, C, and D

To explore the perspectives of HIV/AIDS clinical trial researchers on the three categories of vulnerable populations for which there are special protections in the federal regulations, coded textual data were extracted from the following set of questions:

"IRBs identify three categories of vulnerable populations for which there are special protections. They are children, pregnant women/neonates/fetuses, and prisoners.

- Do you think each of these groups should be considered vulnerable populations with special protections, why or why not?
- Do these categories work well to help researchers understand vulnerable populations in HIV/AIDS clinical trials? Why or why not?"

Textual data were then collapsed into *why* or *why not* categories for each of the three vulnerable populations to create a matrix.

## Results

### Sociodemographics

Of the 65 sites (31 AACTG, 18 PACTG, 16 HPTN) contacted from the sampling frame, 27 (42%) sites' PIs agreed to participate: 14 (45%) representing AACTG, 5 (28%) from PACTG, and 8 (50%) from HPTN. Of the 38 sites that did not participate, 36 of the PIs from those sites never responded to our initial or follow-up requests, and two of the PIs declined to participate (no reasons were given). Furthermore, non-respondent PIs disproportionately represented the PACTG. Table 1 presents the sociodemographics of the 38 investigator- and study coordinator-subjects from the 27 participating sites. Investigators primarily were male (67%) and were physicians (72%), while the study coordinators primarily were female (65%) and were nurses (95%). The majority of the investigators and study coordinators were White (87%).

### Conceptual Framework Defining Vulnerable Populations in HIV/AIDS Clinical Trials

The two initial, open-ended questions asking about how study populations in HIV/AIDS clinical trials are vulnerable elicited an array of indicators that we first organized into three broad vulnerability categories: social (e.g., substance/ alcohol abuse, homeless), treatment-related (e.g., few options to treatment, newly diagnosed), and research participation-related (e.g., not understanding consent form, participating for inducement, physician-investigator influence). While organizing these vulnerable indicators into categories was useful, these indicators alone did not fully explain the possible circumstances in which HIV/AIDS clinical trial enrollees could be considered vulnerable in clinical research. To answer this question, we explored the thematic co-occurrences among these indicators, which were then used to develop a conceptual framework informing how researchers define vulnerable populations in HIV/AIDS clinical trials (Fig. 1).

The following quotation illustrates an example of the co-occurrences among some of the social, treatment-related, and research participation-related vulnerabilities depicted in Fig. 1; vulnerable population indicators are highlighted in italics. In this example, the study coordinator was sharing a story about a new enrollee who also just found out that he was HIV-positive:

> I'll take an extreme example where I was called into consent a patient…*They needed to be on meds years ago and just found out they're positive*. This individual was tearful through part of our consenting, *just overwhelmed with the new diagnosis, the pills, not understanding that they're not going to be dead in 2 years…And there's a lot of education there but they're only going to take home 10% of what you tell them*…So I mean that is a vulnerable person and I think they're informed as much as we can humanly inform them and they're making a legal consent, but they're vulnerable. *They have their faith in the physician that we're not going to lead them wrong. It's just my doctor said this would be a good study*. (HPTN study coordinator, male)

Relating back to Fig. 1, this quotation reflects the multiple vulnerabilities an enrollee can face in HIV/AIDS in clinical research. This particular enrollee had been sick for while, perhaps was motivated to participate because of the physician-investigator's influence, and believed that he was going to die given the HIV-positive diagnosis. The end result may be that this enrollee agreed to participate, despite understanding very little about the clinical trial during the consent process, because the trial in question may have been the only source of treatment/care available to him at that time.

Investigator and study coordinator subjects also described how their HIV/AIDS clinical trial sites have made efforts to provide special protections to enrollees who have one or more of the vulnerabilities presented in Fig. 1. One special protection that may not be required by IRBs, but was commonly cited by clinical trial researchers, was the implementation of various consent monitoring practices to improve informed consent comprehension at the time of enrollment. In this example, one AACTG female study coordinator stated:

> We do not enroll any study subject that we feel does not have a clear understanding. And we sort of give them like a little quiz…So, for example, we run studies for people that just got diagnosed and just found out they're HIV-positive…If we don't feel like they can handle not only the information of just being diagnosed with HIV and then on top of that a research study, we don't put them in the study.

Other special protections for HIV/AIDS clinical trial enrollees that were described included:

- Informed consent process could be re-visited periodically to make sure enrollees retain comprehension of key information in the clinical trial.
- Having trained staff to provide various services, such as translators to communicate with non-English speakers, social workers to help prevent crises in a patient's life arising from participating in a trial, or guardians present for the cognitively-impaired.
- Having a certificate of confidentiality approved by the IRB, especially for study populations involved in illicit activities.
- Working with high ranking officials and law enforcement officers to ensure research proceeds smoothly when there is illegal activity involved.

Thus, investigator and study coordinator subjects went beyond merely identifying different factors associated with vulnerability to suggesting specific measures to ameliorate the different types of vulnerability their participants faced.

## Perspectives on 45 CFR 46 Subparts B, C, and D

Investigator and study coordinator subjects were asked how they felt about the current categories of vulnerable populations for which there are special protections in the Subparts of 45 CFR 46. Table 2 dichotomizes their perspectives by why or why not categories for pregnant women/neonates/fetuses, prisoners, or children should be considered vulnerable.

In general, investigator- and study coordinator-subjects agreed with the need for special protections for the categories of vulnerable populations identified in Subparts B, C, and D of 45 CFR 46 for the following reasons: women/neonates/fetuses because of the potential or known harms to the fetus (25 [66%]); prisoners given their captivity (24 [63%]); and children because of their age (33 [87%]). Yet, the investigators and study coordinator subjects did not view these study populations as always being vulnerable. Their reasons for why they should not be considered vulnerable further demonstrate how they consider vulnerability situational, thus rejecting the regulations' categorizing of these groups as vulnerable in all types of research. The following are sample quotes that illustrate how IRBs sometimes have made it difficult for researchers to enroll potential subjects who are pregnant, prisoners, or children.

For pregnant women:

> Well, the kinds of behavioral research I do, the interventions are applicable or more applicable for pregnant women. There's nothing that we do that would in any way harm the fetus…But I have to explain to the IRB why I'm including them…I don't get it. (HPTN investigator, male)

In this example, the regulations would deem behavioral intervention trials, such as the types described, as having minimal risk to the fetus, but the IRB made it more difficult for this investigator's clinical trials site to include pregnant women.

For prisoners:

> We think it's a bad thing [considering prisoners a vulnerable population with special protections]. We would like to be able to continue their involvement in the clinical trial while they were in jail…but the logistics of actually being able to continue to provide research medications while somebody is in jail makes it very difficult. (AATCG investigator, male)

Investigators have to go though additional IRB procedures to be able to conduct clinical trials with prisoners. In this example, the investigator later explains when enrollees should be allowed to continue their participation in an HIV/AIDS clinical trial if they become incarcerated. Indeed, if enrollees are forced to withdraw from the trial, there is no guarantee that the antiretroviral medications they were taking before incarceration would be available to them during their jail time or imprisonment, which could have more harmful implications.

For children:

> In this country maybe if you're 15 and you want to go into a research study your parent or guardian would have to sign the consent as well. I don't think that's realistic in another country. I think that a 15-year-old who has been out working and might be married should be able to sign and consent to a study on their own. (HPTN study coordinator, female)

Similar to the quotation example for pregnant women, the regulations would permit minor assent without parental permission under certain conditions, but this researcher's experience with the IRB may not have allowed it.

## Discussion

This exploratory study provides an in-depth and multifaceted look at the ethical concept of vulnerable populations from the perspectives of researchers involved in HIV/AIDS clinical trials. A conceptual framework was developed that illustrates a combination of vulnerable population characteristics/categories identified from the broad definitions in the Common Rule (e.g., based on socioeconomics), and in prior reviews about HIV-infected and HIV-affected populations [9,10], but organizes them to show possible circumstances in which HIV/AIDS clinical trial enrollees could be considered vulnerable in clinical research, and for which special protections could be warranted (e.g., consent monitoring in cases where there is educational, cognitive, or treatment-related vulnerabilities). In addition, barriers posed by Subparts B, C, and D of 45 CFR 46 were explored in the context of HIV/AIDS clinical trials, further demonstrating that applying group-based vulnerability can result in unnecessary exclusion of individuals in the vulnerable population categories of pregnant women/fetuses, prisoners, and children. The study's findings are consistent with concerns from bioethicists that vulnerability in research has not been clearly or uniformly defined in the federal regulations on human subjects research, and special protections delineated for select vulnerable populations often

have made it difficult for these vulnerable populations to participate in HIV/AIDS clinical trials from which they could benefit [2,5].

First, the study supports prior recommendations to look at vulnerability as situational, rather then group-based, as is typically used by IRBs in the United States and internationally [3,4]. At a practical level, we hope that AACTG, PACTG, and HPTN researchers could use the conceptual framework as a guide to identify areas of vulnerability within their respective clinical trial populations, and implement appropriate protections to their informed consent process and/or recruitment procedures. Furthermore, we believe that the factors comprising the conceptual framework are not necessarily distinct to HIV/AIDS and may broaden the conceptual framework's potential to understanding vulnerable populations for other diseases or conditions, or that are distinct to minority groups (e.g., being undocumented). At an institutional level, we hope that local IRBs could use this conceptual framework to expand their thinking about what makes subjects vulnerable in HIV/AIDS clinical trials, and to consider innovative and alternative ways in which researchers could implement additional protections for clinical trial participants with one or more vulnerabilities.

Second, understanding the concerns among HIV researchers on why pregnant women, prisoners, and children should not be considered vulnerable for all types of clinical research strengthens the argument to examine vulnerability as situational. At an institutional level, we hope that these findings could encourage local IRBs to think of these three vulnerable populations more on a case-by-case basis, particularly in situations where clinical trial participants who represent these vulnerable populations stand to benefit from the results of the research.

This study has two main limitations. For the investigator/study coordinator sample, the response rate of 42% at the site level was low even though all 65 sites (31 AACTG, 18 PACTG, 16 HPTN) were asked to participate. Given that we were unsuccessful in interviewing PIs, other investigators, or study coordinators from 38 of the sites, our conceptual framework may be missing other important factors that contribute to vulnerability in clinical research. This is particularly true for PACTG that may have other vulnerable population indicators more relevant when conducting clinical trials with children (and adolescents). Second, the conceptual framework for vulnerable populations in HIV/AIDS clinical trials is missing the perspectives coming from HIV/AIDS clinical trial enrollees with respect to how they consider themselves vulnerable. Future research may be useful to better explore vulnerability in clinical research from the enrollees' perspective.

In conclusion, the debate over vulnerable populations usually happens among bioethics scholars with little or no input from biomedical researchers about what they think, including if they agree with the current definitions, and their concerns with IRB regulations associated with vulnerable populations. The conceptual framework for understanding vulnerable populations in HIV/AIDS clinical trials was developed in this study from the perspectives of HIV/AIDS researchers to help us move beyond the broad categories of "economically," "educationally," or "decisionally" impaired, or the narrowly focused vulnerable categories of pregnant women, prisoners, and children for which there are special protections in 45 CFR 46. Indeed, the conceptual framework illustrates other plausible relationships of vulnerability, and this study's participants also identified interventions to address certain types of vulnerability, to which IRBs should pay greater attention. Future work on understanding vulnerable populations could expand the conceptual framework to include vulnerable population indicators for other diseases or conditions, and the conceptual framework could be used as a guide to develop interventions that address situational vulnerability in clinical research.

## Acknowledgments

Research was funded by a Career Developmental Award in Research Ethics through the National Institute of Allergy and Infectious Diseases (NIAID), Grant# K01AI055247-05. The research also was supported by the UNC-Chapel Hill Center for AIDS Research (CFAR), NIH Grant #P30 AI50410.

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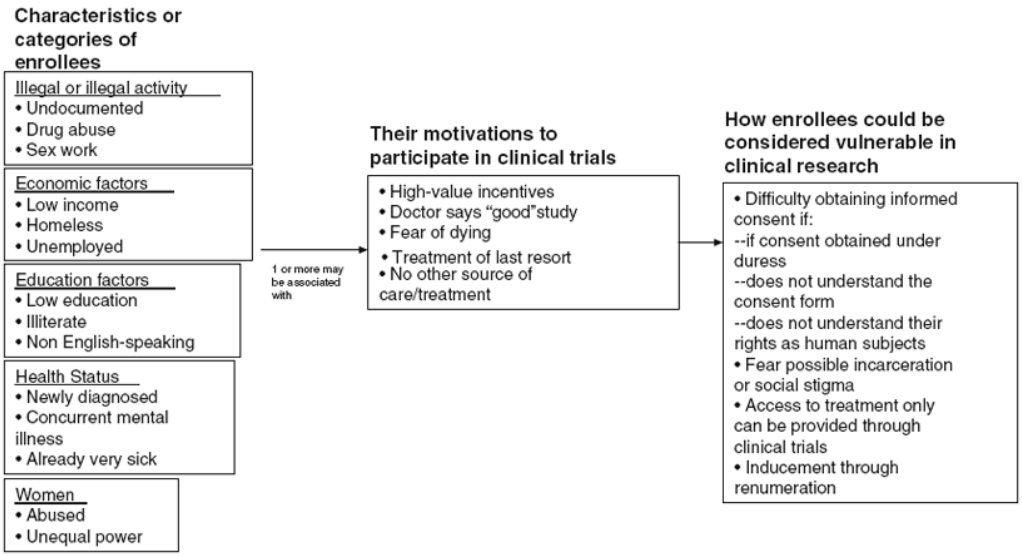


**Fig. 1.**
Conceptual framework for understanding vulnerability in HIV/AIDS clinical trials

## Table 1

Sociodemographics of investigator- and study coordinator-subjects

| Variables | Investigators (*N* = 18) *n* (%) | Study coordinators (*N* = 20) *n* (%) |
|---|---|---|
| Gender | | |
| Male | 12 (67) | 7 (35) |
| Female | 6 (33) | 13 (65) |
| Race/Ethnicity | | |
| White, not Hispanic | 16 (89) | 17 (85) |
| Black, not Hispanic | – | 2 (10) |
| Asian | 2 (11) | 1 (5) |
| Trial type | | |
| AACTG | 8 (44) | 17 (85) |
| PACTG | 3 (17) | 2 (10) |
| HPTN | 7 (39) | 1 (5) |
| Degree(s) | | |
| MD | 13 (72) | – |
| PhD or equivalent | 4 (22) | – |
| Nursing degree (RN, NP) | 1 (6) | 19 (95) |
| Master's degree (MA, MS) | – | 1 (5) |
| Location of trials | | |
| US | 7 (39) | 16 (80) |
| International | 4 (22) | – |
| Both | 7 (39) | 4 (20) |

## Table 2

Investigator and study coordinator subjects' perspectives on 45 CFR 46 subparts B, C, and D

| 45 CFR 46 subparts | Do you think each of these groups should be considered vulnerable populations with special protections? | | | |
|---|---|---|---|---|
| | **Why?** | ***n*** | **Why not?** | ***n*** |
| Subpart B: pregnant women/ neonates/fetuses | • Experimental drugs could: | 30 | • Just because a woman is pregnant does not make her vulnerable | 1 |
| | 1. Cause spontaneous abortion | 5 | • Becoming pregnant after starting a trial should not be the only reason to rule out a woman's ability to continue in the trial | 3 |
| | 2. Interfere with fetus development | 25 | | |
| | • Pregnant women only vulnerable if they are socioeconomically disadvantaged or affected by domestic violence | 5 | • Pregnant women should not be considered vulnerable in monitoring/ observational trials, many prevention trials, and in clinical trials with medications that are proven non-teratogenic | 13 |
| | • Hormonal changes affect pregnant women's decision-making | 7 | | |
| Subpart C: Prisoners | • Prisoners are a captive population. They do not have the ability to make their own choices | 24 | • Prisoners can make decisions for themselves since they are adults | 3 |
| | | | • Prisoners have better resources in prison than some populations on the outside | 2 |
| | • Co-morbid factors may be present, such as high rates of HIV infection or drug use that make them more vulnerable | 4 | • Entering prison post enrollment, prisoners not vulnerable—they already consented | 13 |
| Subpart D: Children | • Children cannot consent for themselves due to their age or lack of maturity | 33 | • Current age criterion is flawed given that it doesn't take into account cultural and maturity factors when qualifying someone as a child versus an adult | 22 |
| | • Parents can consent under duress or desperation and make bad choices for their children | 3 | | |