CLINICAL ETHICS

Clinical research with economically disadvantaged populations

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Concerns about exploiting the poor or economically disadvantaged in clinical research are widespread in the bioethics community. For some, any research that involves economically disadvantaged individuals is *de facto* ethically problematic. The economically disadvantaged are thought of as ''venerable'' to exploitation, impaired decision making, or both, thus requiring either special protections or complete exclusion from research. A closer examination of the worries about vulnerabilities among the economically disadvantaged reveals that some of these worries are empirically or logically untenable, while others can be better resolved by improved study designs than by blanket exclusion of poorer individuals from research participation. The scientific objective to generate generalisable results and the ethical objective to fairly distribute both the risks and benefits of research oblige researchers not to unnecessarily bar economically disadvantaged subjects from clinical research participation.

In recent years, controversy over ''vulnerable populations'' in clinical research has emerged as one of bioethics' hot button issues. The list of populations classified as vulnerable in the ethics literature encompasses a large and heterogeneous proportion of the human population, including, but not limited to, ill people, the elderly, those with cognitively impairments, children, women, ethnic and racial minorities, prisoners, and those with educational and the economical disadvantages.[1 2] On the basis of calls for increased protection for such an ill-defined assortment of groups, investigators and institutional review board (IRB) members may think it prudent to take a cautious approach regarding the inclusion of any possibly vulnerable population. Other researchers and advocate groups, however, have claimed that under-representation of vulnerable groups such as women and ethnic minorities in clinical research makes scientific findings needlessly less generalisable.

This argument is particularly salient with regard to the inclusion of economically disadvantaged (ED) individuals as clinical research subjects. On one hand, the lack of economic resources, health insurance and healthcare access that characterises the ED population may make them vulnerable to unethical practices in a research setting.[3 4] On the other hand, the inclusion of research subjects from all socioeconomic strata contributes to the generalisability of study results and to a fairer distribution of the benefits and burdens of research. Barring the ED population from research participation ''for their own good'' could be construed as paternalistic, and such exclusion may overgeneralise ''vulnerability'' to encompass a heterogeneous group of people.[5 6]

If researchers and IRB members believe that ED populations are particularly vulnerable in clinical research, domestic and international studies that enrol any ED individuals become ethically questionable. If these worries about the vulnerability of the ED are legitimate, the burden of proof ought to be on investigators to show why they should include ED subjects, rather than why they should not. Accordingly, research involving ED subjects would be limited unless scientifically necessary.[7] This thinking, however, begs the necessary question of whether the ED are categorically vulnerable and neglects to examine the strength of vulnerability claims.

VULNERABILITY TO IMPAIRED DECISION MAKING

Concern one: The ED may be vulnerable to impaired decision making if low education levels lead them to enrol in research without fully understanding study risks

Much has been written regarding research subjects' widespread difficulties in understanding the nature of research. Even with a clearly-written consent form and a relatively well-educated population, many research subjects inadequately comprehend basic aspects of the research studies they participate in, failing to grasp concepts of randomisation, risk likelihood, placebos or even the general non-therapeutic intent of a study.[8–11]

Limited comprehension of study information compromises autonomous decision making, as individuals' decisions to participate will rely on misunderstood information. This situation is ethically problematic for two reasons. First, if subjects were to fully understand study information, they might change their decisions regarding enrolment. Second, even if a given individual would not change her enrolment decision if she fully understood the nature of the research, the lack of understanding means that she does not give her informed consent, violating a basic requirement of ethical research.[12 13] This well-documented phenomenon among the research subject population as a whole remains an ongoing problem for investigators aiming to secure informed consent.

Abbreviations: ED, economically disadvantaged; IRB, institutional review board

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As ED individuals often have lower levels of education, the problems generally encountered with subjects' inability to understand research information are likely to be exacerbated in the ED population, resulting in a particular vulnerability to impaired decision making.[14 15] ED individuals are also more likely to have limited health literacy, which may significantly impair understanding of what certain medical procedures, such as a ''biopsy'' or ''sputum test'', entail.[16] Although economic disadvantage in itself does not necessarily imply increased difficulty understanding, educational and socioeconomic disadvantage often appear in the same populations, making it important to address this first concern.

Apprehension about the ED's increased vulnerability to impaired decision making owing to low educational levels and/or limited health literacy is a legitimate worry. Yet, more progress can be made towards reducing such vulnerability by facilitating informed decision making and improving methods of communicating study information, rather than categorically excluding groups such as the ED from clinical research. Although a complete review of measures shown to reduce misunderstanding and impaired decision making is beyond the scope of this article, several tactics have emerged as particularly effective in both ED and non-ED populations. Assuring that study information is written in the appropriate language and reading level, having study staff on site to field questions and clarify information, and using a ''Teach Back'' method of informed consent have all been found to improve absolute subject comprehension, including in those with limited health literacy.[15 16] Additionally, special efforts to explain the basic nature of research may be indicated with certain populations, as some cultures may have particular difficulties understanding the purpose of certain research techniques or how research differs from clinical care.[17–19] These and other strategies to reduce ED vulnerability owing to low education levels are preferable to blanket exclusions that can weaken the scientific validity of study results and unfairly skew the distribution of the risks and benefits of research through the population.

Concern two: Clinical research may offer services or other goods so attractive that they impair decision making, causing the ED to irrationally disregard research risks

This second concern is often termed ''undue inducement''.[13] However, other concepts are sometimes included under the rubric of undue inducement as well, such as objectively large monetary compensations or any inducement that serves as the main motivation for enrolment.[20] To avoid confusion, we use the phrase ''decision-impairing inducement'' to emphasise how the offer of certain goods is thought to impair an individual's ability to make rational choices.

The fundamental concern with decision-impairing inducement is not that ED subjects cannot understand study information, but that what is offered as part of study participation (access to medical treatment, money, free healthcare and so on) is so enticing that the ED will sign up for the study no matter what, disregarding risks or giving risks insufficient weight in the decision-making process.[21] Decision-impairing inducements thus render subjects ''relatively or absolutely incapable of protecting their own interests'', the very definition of vulnerability.[2] If such impaired decision-making can occur as a result of certain offers, researchers and IRBs might well conclude that ED participation should be significantly restricted for research studies with compensation of a certain quality or magnitude.

This second concern should not be conflated with the widespread worry that poorer individuals will be more likely to sign up for trials that are unethical for reasons of their design. If we conclude that a proposed trial is exploitative, for example, or has an extremely unfavorable risk–benefit ratio, trial participation ought not to be offered to any individual, not only those from the ED population. Instead, this second concern examines whether an otherwise ethical trial could induce impaired decision-making particularly in ED subjects.

But do offers of healthcare, money or other goods impair decision making and actually cause ED individuals to disregard research risks? In two recent studies using hypothetical research scenarios, ED research subjects were not more likely to discount research risks when offered greater compensation.[22 23] One of the studies also found that subjects with incomes below the group average were actually less likely than wealthier subjects to change their willingness to participate in response to increased financial incentives.[22] These results should be interpreted cautiously, as both studies used small sample sizes and assessed hypothetical rather than actual enrolment. However, their findings indicate that offering sizeable monetary compensation for study participation does not necessarily lead subjects to disregard study risks, particularly among ED individuals.

Additional data suggest that the ED might be generally more experienced than the non-ED at making difficult decisions in the face of limited resources. After all, an ED individual may make daily decisions balancing limited means and life values: attending night school versus getting a second job, buying healthier groceries versus affording heating costs or accepting a physically demanding job versus receiving less pay elsewhere. Decisions regarding research participation (securing healthcare or money vs avoiding study risks) seem unlikely to create greater risk of impaired decision making than other dilemmas the ED face everyday. One recent study described the particular resilience and resourcefulness that ED individuals often show in response to stressful situations in their everyday lives.[24] This evidence, in conjunction with the previous findings of steady risk evaluation in the face of increasing compensation, suggests that ED individuals may be less vulnerable to decision-impairing inducement than their wealthier counterparts, or at least no more.

Importantly, higher enrolment of the ED in certain types of research, such as studies offering free healthcare for the uninsured,[6] is not necessarily evidence that the ED are subject to decision-impairing inducement and are disregarding the risks of the study. The mere fact that ED individuals might accept certain risks that wealthy people would not does not in itself show that such decisions are irrational. The ED's decisions to enrol in a study may be entirely logical: faced with undesirable economic circumstances, research participation may be one of their best opportunities to attain healthcare. Although some may argue that offering free healthcare in clinical research exploits the ED (a concern discussed below), accepting free healthcare or other desperately needed goods in exchange for research participation does not necessarily indicate an inappropriate consideration of risks or impaired decision making.

Further research is required on the effects of various offers on decision making among the ED, but those involved in research design should be duly skeptical of categorical claims of decision-impairing inducement for the ED population.

VULNERABILITY TO EXPLOITATION

Concern three: The ED are vulnerable to exploitation by studies that offer unfair levels of benefit in exchange for study participation

In lacking financial and medical resources, the ED may be vulnerable to exploitation by clinical research studies offering too little benefit for the risks and burdens of study participation. These studies, unlike the studies discussed in concern two,

are unfair at inception because of their design: they offer too little benefit for the associated burdens. For a hypothetical example, imagine that healthy volunteers in a phase I toxicity study are offered a single $50 payment with no recourse for any injuries caused by the drug, a benefit level that a neutral observer might consider unfair for the time, inconvenience and risk associated with the trial. Despite this unfairness, an ED woman might make a logical decision to enrol in such a trial—perhaps the $50 offered by the study presents a needed opportunity to meet her rent, one of her primary concerns.

Exploitation is defined as a transactional phenomenon in which A takes ''unfair advantage'' of B—that is, B receives an unfair level of benefits as a result of B's interaction with A.[25 26] The key question is not whether it is unfair in itself that the ED woman gets greater utility than a wealthier individual from the $50 because of her poor economic circumstances, nor is the fact that the ED subject benefits overall (by meeting her rent), enough to rule out exploitation. Rather, determining whether the research exploits this woman fundamentally depends on the fairness of her level of benefit from the interaction. In our hypothetical situation, the level of benefit, when compared with the nature of her research participation, is not considered fair or reasonable.[25] Thus, by offering an unfair benefit, researchers are taking unfair advantage of her desperate economic circumstances and so exploiting her.

Although the above example is hypothetical and perhaps overly simplistic, some contemporary research practices at least raise questions about the possible exploitative quality of certain research trials. The Surfaxin Trial, for example, has been decried as a modern example of exploitation. Some critics charged that the poor mothers enrolling their infants in this experimental drug study, especially those in the placebo arm, would not receive a fair benefit level for their participation, particularly because they would not receive the American standard of care and because the drug would not be available to the population after the study.[27] Wealthier individuals, whose circumstances offer better alternatives for meeting their general needs, are logically less likely to enrol in research with unfair benefit levels—they gain less overall utility from an unfair benefit level than do poorer individuals. This suggests that there may be a particular vulnerability to this kind of exploitation among the ED: because of limited resources and fewer options for meeting health and financial needs, they may be more likely to enrol in research with exploitative benefit levels. Accordingly, this third concern regarding ED vulnerability to exploitation merits careful evaluation.

The responsibility of avoiding exploitation and assuring that the benefits offered in research studies are fair and reasonable in light of subject contributions falls on those designing and regulating research: investigators and IRBs. Determining what constitutes ''fair'' or ''unfair'' benefits in terms of compensation for clinical research participation is an admittedly complex problem, but not insurmountable. Generally, the benefits offered in a given study should be considered fair from both the ED and the non-ED points of view. This does not necessarily mean that fair benefits will be equally enticing to ED and non-ED potential subjects—free healthcare, for example, might be more attractive to an uninsured individual than one with healthcare coverage, but could still be logically considered by an insured individual to constitute a fair benefit for research participation.

It is important to distinguish ED participation in studies with unfair benefit levels from studies with fair benefit levels. Although ED individuals may be attracted to both types of studies because of their limited financial options, the two situations are not equivalent in their ethical implications. This distinction is further discussed below.

Concern four: Even if a study offers a fair level of benefit in exchange for study participation, the fact that ED individuals only enrol because of their limited economic options makes the study exploitative

If ED individuals enrol in clinical studies because it is their only opportunity to attain healthcare or meet financial needs, some ethicists claim that this research is taking unfair advantage of the unjust socioeconomic status of the ED and thus exploiting them.[28] Whether or not ED subjects actually do sign up for research studies that wealthier individuals shun is debatable—studies to this effect have differed in their findings.[29 30] But even if empirical data conclusively showed that ED individuals enrol because of their poor economic circumstances in studies that they would otherwise avoid, we would still want to know whether we should consider this phenomenon as evidence of exploitation.

If a study takes unfair advantage of the ED's economic circumstances as discussed previously, by offering a benefit level less than what is fair and reasonable, an exploitation claim is warranted. But in studies where the benefits offered for participation are fair, is the fact that subjects enrol only because of unjust background circumstances enough to term the research exploitative?

Although some have argued for labelling the latter situation exploitation as well,[4] this seems to confuse concern about unjust socioeconomic circumstances with concern about the unjust nature of a trial itself. Researchers might well be taking advantage of the socioeconomic situation of the ED by offering them healthcare or other resources otherwise unavailable in exchange for their participation. But if the research transaction offers a genuinely fair level of benefit to study participants, researchers are not taking *unfair* advantage. After all, much clinical research relies on taking advantage of the disadvantageous situation of certain groups. Cancer trials, for example, necessarily take advantage of patients unlucky enough to have untreatable cancer. But we do not say that these trials are exploitative just because subjects enrol only because of their undesirable health circumstances—to be exploitative, the study must offer an unfair level of individual benefit in exchange for participation. Just as researchers do not cause and are not responsible for incurable cancer, they are not responsible for the unjust socioeconomic circumstances of the ED. Similarly, in the private sector, ED individuals are more likely to enlist in the military, for example, or to be employed in dangerous jobs such as coal mining. Given better socioeconomic circumstances, it is likely that some ED individuals would not accept positions as soldiers or miners. When the benefits offered in exchange for involvement by the military and mining industry are reasonable and fair, however, we do not consider these transactions exploitative. If the military or the mining industry were to alter the inherent risk–benefit ratio of these transactions, perhaps by failing to provide appropriate body armour or failing to ensure safe working conditions, our evaluation might appropriately change. However, when the level of benefits specified in the contract is appropriate to the risks and both parties live up to their agreements, an exploitation claim seems unwarranted.

Investigators and IRB members must take pains to distinguish between an exploitative trial—one that takes unfair advantage by offering an unfair benefit level to research subjects—from a non-exploitative trial that offers a fair level of benefit, but may take advantage of the ability to recruit individuals because of their unjust background conditions.

CONCLUSIONS

Our arguments are not meant to discount the fact that ED populations often lack social, political and economic power in society, but rather to examine how such power deficits actually

play out when the ED are invited to participate in clinical research. Investigators and IRBs tend to worry that every study that enrols ED individuals is ethically problematic, either because of its potential to impair decision-making or because of its exploitative in nature. However, these concerns are not always justified. Excluding the ED from research without valid reasons leads to a lose–lose situation for researchers, research subjects and society, and is unethical in itself, violating ethical principles governing fair subject selection.[12] Although attempts to limit ED access to research participation are well-intentioned, they may needlessly impair the quality and scope of research findings and eliminate a potentially beneficial and often desired option for poor individuals. The clinical research community should pay careful attention to information disclosure techniques, ensure fair benefits for study participants and reduce unnecessary barriers to participation for the ED.

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Correction

In the response by Ives (*J Med Ethics* 2007;**33**:119–22), there are several typographical errors. There are listed below.

Abstract: The second sentence should read ''In this response, I take up the challenge they issue and try to reconcile this conflict.''

Footnote i: Should read, ''See Brecher's, *Why the kantian ideal survives medical learning curves, and why it matters,* for a discussion of this issue.[1a]''.

Page 120, column 2: the second 'a' should read ''b''.

Page 121, column 1, line 28: remove reference ''6''.

Page 121, column 1, line 39: 'does' should read ''do''.