

Ethical Issues in Research with Special Populations

Summary: This project attempts to identify groups whose participation in clinical research may require additional protections and to develop and recommend mechanisms to ensure that they are appropriately included and protected in research. .

Section: Ethics of Human Subjects Research

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Background: Regulations for clinical research call for additional safeguards for populations for whom the standard requirements may not offer sufficient protection. The most salient example of special populations involves vulnerable groups. Vulnerability in research is typically understood as an inability to provide informed or voluntary consent. For example, children are vulnerable due to an inability to give their own informed consent. The U.S. federal regulations include specific additional requirements for research with children, prisoners, and pregnant women, and call for additional safeguards to protect vulnerable adults. More recent work has recognized the potential vulnerability and need for additional protections for groups who are cognitively able to give informed consent, but may be susceptible to undue influence. For example, recent work has focused on the ethical concerns and possible safeguards for research with individuals who are economically disadvantaged or who lack access to health care. Members of the department have focused on understanding how certain groups might be “vulnerable”, to what extent the existing and proposed protections are sufficient, what additional requirements might be needed for the identified groups, and what other groups might need additional protections.

II. Research with special populations

A. Pediatric research

The federal regulations governing research with children have a number of controversial provisions that have been challenged by courts and commentators. A number of prominent commentators argue that it is unethical to expose children to research risks for the benefit of others. Recently, several courts have endorsed this view, raising concern that future rulings could limit, or even prohibit appropriate research that is vital to improving pediatric clinical care. To address this concern, a number of commentators have proposed ethical justifications for pediatric research without the prospect of clinical benefit. However, all have significant problems and none has gained widespread acceptance. Based on work conducted in the department on pediatric research over the past 10 years, a new justification was proposed and defended. This justification provides pediatric research with a more secure ethical basis (Wendler 2010).

Interpretation of the minimal risk standard provided in the federal regulations is also quite controversial, and is understood as providing a single risk threshold for research with children of all ages. However, empirical data find that teenagers are able to understand and make their own decisions regarding clinical research. These data support two different risk thresholds, one for younger children and a somewhat higher one for older children (Wendler 2009). This approach provides a way to protect younger children without blocking appropriate research in older children.

More generally, adolescents are a special group of minors that have received little attention in the literature regarding research with children. The Department conducted an empirical study of adolescents in research in order to better understand the assent/parental permission process (see BSC-Consent), as well as adolescents' views about research and willingness to take risks.

Another controversial provision of the federal regulations allows children to be enrolled in research that poses greater than minimal risk and offers no prospect for direct benefit when the research is likely to yield generalizable knowledge about the subject's disorder or condition. This 'subject's condition' requirement has led to a good deal of confusion about what research can be approved. To attempt to clarify this issue, we conducted the first systematic legal analysis of how this condition should be interpreted. This analysis suggests that the subject's condition requirement should be interpreted more broadly than most claim, but not so broadly as to allow investigators to enroll any children (Shah, Wendler 2010).

Children who do not have parents to make decisions for them and who are wards of the state are granted even more protection in the federal regulations, but media coverage has raised concerns about the ethical issues of involving this population of children in research. The department has undertaken an analysis of the present regulations for wards, and identified several modifications which should be adopted to ensure appropriate protection for this especially vulnerable population. In particular, the scope of the responsibility of advocates should be clarified and

expanded, and wards should be enrolled in research only when there is a compelling scientific reason for enrolling them (Varma, Wendler 2008).

B. Research with the economically disadvantaged

The federal regulations, international ethics guidelines, and commentators in the research ethics literature suggest that those who are economically disadvantaged should be considered a vulnerable population. If vulnerability depends on a compromised ability to give informed consent, then individuals who are economically disadvantaged may be vulnerable to the extent that they cannot understand information provided to them or make a voluntary choice or decision. Denny and Grady have argued that economically disadvantaged persons should not be categorically considered vulnerable and that additional protections should be based on clear and careful analyses of the ways in which individuals might be vulnerable in specific situations (Denny and Grady 2007; Grady 2009). Issues of vulnerability and exploitation in research involving individuals with limited access to health care were explored with a group of urban community representatives in Washington D.C. The participating community representatives were supportive of research and appreciated the opportunity to be heard. They noted the importance of respecting the circumstances, values, needs, and welfare of research participants; supported recruitment strategies that promoted diversity; and cited the positive benefits of providing care or treatment to participants as part of research. Monitoring participants' welfare, ensuring care at a study's end, full disclosure of information, and the involvement of advocates were emphasized as important aspects of research with urban residents (Grady et al. 2006).

C. Early phase research

Commentators are also concerned about the possible vulnerability of populations invited to participate in early phase research. These concerns extend both to phase 1 oncology research, in which the participants have advanced cancer that has not responded to standard treatments, as well as to first-in-human and other phase 1 drug development research which recruits healthy volunteers. In order to understand how these research subjects are vulnerable and thus apply the appropriate protections, members of the department have examined the claims made about each of these groups. Using data available from studies of phase 1 oncology patients, an analysis was done to show that phase 1 trial oncology participants are generally white, well-educated, middle class or above, who have health insurance and have previously been treated for their disease. (Seidenfeld et al 2008). Consequently, it seems strange to consider this group vulnerable in the sense that they cannot understand information about a proposed study or make an informed decision. Related concerns have been raised about healthy volunteers in phase 1 drug development studies based on the belief that they are motivated only by the payment offered for participation and may therefore be vulnerable to undue inducement. A systematic review of the literature (Stunkel and Grady, in press) showed that although money is certainly a principal motivating factor for most healthy volunteers, it is not their only motivation and they do appear to take account of risks involved before enrolling in a study. In a surprising finding from a consent study of healthy volunteers in a drug development study, those who had primary financial motives for participation actually had a better understanding of the study information than those motivated by other factors (Stunkel et al 2010).

III. Evaluation of the Research Experience for participants in longitudinal studies

Much of the existing empirical research focuses on the process of informed consent and whether subjects understand the research to which they consent. In contrast, there have been very few analyses of the views and experiences of individuals who participate in research. Over the past several years, the department has been working to address this gap in the literature. A primary project in this area has evaluated individuals from Argentina, Brazil and Thailand participating in a longitudinal randomized controlled trial of treatment for HIV. One of the primary concerns is that research may exploit individuals' desire to obtain treatment in order to get them to participate in research. We found that although individuals in both the treatment and the control groups were motivated by a desire to obtain treatment for their illness, this did not preclude their also wanting to contribute to the research effort and feeling that they were making an important contribution (Lazovski et al. 2009).

A number of commentators have argued that informed consent should be understood as an on-going process, rather than a one-time event. However, there has been limited empirical evaluation of whether there is need for this process. As part of the same survey, we evaluated whether individuals who had been participating retained information relevant to their on-going participation (Smith et al. 2010). This survey found that individuals were not sufficiently informed about crucial aspects of the study, such as their right to withdraw, and that many respondents felt that they did not have an opportunity to ask questions. These data provide empirical support for claims that clinical research should include a process of on-going consent.

A third analysis of responses from the study of the same cohort in the longitudinal HIV treatment trial examines self-reported adherence with study interventions and procedures and willingness to report lack of adherence to the study team. Overall, adherence was high, with less than 10% reporting missing study visits or not following researchers' instructions. Most reported willingness to report illnesses and side effects to the research team. About 2/3 of respondents in each group, however, reported concern about being removed from the study prematurely. More research is needed to follow up on this finding.

An analysis of children who were participating in research found that the children and their parents were willing to have the child face some risks for the benefit of others. This study also found that parents and children overall were equally willing to have the children face risks for others in the research and charitable contexts (Wendler, Jenkins 2008). These data suggest that perhaps clinical research does not pose unique concerns about exploitation, and that accepting risk to help others may also arise in other contexts. To evaluate how children experience clinical research and how they and their parents make decisions regarding research participation, we used the same study to evaluate the process of decision making (Varma 2008). To follow up on these results, we are currently completing analysis of the results of a study of teenagers participating in clinical research, and one of their parents.

Comment [s1]: And found what?

IV. Emergency Research: Research in emergency situations is vital to improving care in this context but raises significant ethical concerns regarding the timing and possibility of consent. Over the past 10 years, regulations have been promulgated regarding when such research can be conducted. However, there remained a need for an ethical justification for such research and an

account of when it is acceptable to perform emergency research. Groundbreaking work by the department has resulted in the first ethical justification of this research (Largent et al. 2010).

Impact of Research: The work of the department in this area has affected the way that investigators and review committees evaluate the appropriateness of research with vulnerable individuals. Our work has challenged much of the conventional wisdom about the meaning of and response to concerns about vulnerability. One important shift in the field has been an increasing recognition that vulnerability does not always require exclusion, but sometimes suggests a need for inclusion with additional protections specifically focused on the sources of vulnerability. Some of our work has also helped clarify ambiguities in the federal regulations that may make it difficult for IRBs to understand how to apply them. The new interpretation of the subjects' condition requirement has been endorsed by several committees. Similarly, the argument for two different thresholds for risk for pediatric research has been adopted by a number of IRBs.

Future Initiatives: Individuals who participate in phase 1 drug development research are often considered vulnerable to undue inducement and exploitation. In collaboration with Pfizer, we are studying the motivations for participation and perceived experiences of phase 1 participants at 3 Pfizer clinical research units- in New Haven, Brussels, and Singapore. In addition, we are conducting the first assessment in the U.S. of the risks of participation in phase 1 research with healthy volunteers.

U.S. federal regulations do not include specific safeguards for clinical research with adults who are unable to give informed consent in non-emergency situations. In response, the NIH Clinical Center was one of the first institutions in the country in 1987 to develop guidelines for how to enroll adults who cannot give their own consent to research. Based on recent revisions to the NIH policy, and in collaboration with the office of the Clinical Director of the National Institute of Mental Health we are working to develop, test, and publish procedures called for in the policy regarding assessment of capacity to consent, assessment of ability to assign a surrogate, assessment of the appropriateness of a surrogate, and assessment of assent and dissent in adults unable to give informed consent. This work will allow us to evaluate some of the most important practical questions that arise in this context, which have to date received little attention in the literature.

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