

Adults Unable to Consent

Goal: To develop an analysis of the ethics of research with adults who cannot consent, and empirically assess specific ethical issues that arise in the conduct of such research.

Section: Human Subjects Research- Unit on Vulnerable Populations

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Background: The U.S. Federal regulations do not include specific protections for adults who are unable to consent, beyond those in place for individuals who are able to consent, and the possibility of obtaining the permission of the individual's legally authorized representative (46.116). This regulatory gap has raised concerns over whether adult subjects who are unable to consent are being protected adequately in research. These concerns have been fueled by two incidents.

In 1991, three legal advocacy groups sued on behalf of six psychiatric patients hospitalized in New York who feared the state's existing regulations might permit investigators to enroll them in clinical research inappropriately. The resulting decision in the case of T.D. versus New York State Office of Mental Health threatened to shut down a good deal of research. Second, an OPRR investigation of the suicide of a schizophrenic patient who had participated in a research trial at UCLA raised questions about the extent to which individuals who are unable to consent, and those who are at risk of losing the ability to consent, are adequately protected. Whether or not these cases involved actual abuses, they have highlighted the need for additional protections for adults who are unable to consent.

There is widespread agreement that adults who are unable to consent should not be enrolled in research unless their participation is necessary to answer the scientific question posed. There is disagreement, however, over the scope of this requirement. Some argue that adults unable to consent should be excluded from all research unless their participation is necessary. Others argue that excluding

subjects from potentially beneficial research, simply because they are unable to consent, turns protection into a kind of discrimination.

It is also widely agreed that the research enrollment of adults unable to consent should be based on the permission of an appropriate surrogate. Most agree that adults unable to consent should be asked for their assent when capable, and that the dissent of adults unable to consent should be respected. Finally, it is agreed that the enrollment of adults unable to consent should be guided by their remaining preferences and interests.

There is disagreement over the extent to which the enrollment of individuals unable to consent should require an explicit research advance directive, executed by the individual while still competent. There is also debate over the use of independent monitors, and what methods should be used to assess subjects' informed consent. Many commentators argue that it is important to assess the capacity of groups that are at increased risk for lacking capacity. Finally, there is disagreement over the number of risk categories that should be included in any regulations for research with adults who are unable to consent. The NBAC proposed two categories: minimal risk and more than minimal risk. Others have argued that this approach leads to inappropriate protections for some research, and instead have endorsed the 3 risk categories included in the pediatric regulations: minimal risk, minor increase over minimal risk, and more than a minor increase over minimal risk.

Objectives:

- 1) To assess conceptually and empirically whether it is possible to conduct research with adults who are unable to consent without exploitation.
- 2) To evaluate critically proposals for additional safeguards for adults who are unable to consent, and distill core safeguards.
- 3) To assess empirically the potential of research advance directives as a method for providing evidence of impaired adults' competent preferences.
- 4) To assess empirically the extent to which the existing pediatric regulations offer appropriate protection for adults who are unable to consent.
- 5) To assess conceptually whether the 'necessity' requirement should be applied to research that offers a compensating potential for direct benefit.
- 6) To evaluate empirically potential methods for assessing subjects' informed consent.

Methodology: The primary ethical concern raised by enrolling adults unable to consent in research is the possibility of exploitation. Thus, determining whether such research is ethical depends largely on determining whether it is possible to enroll them without exploitation. Answering this question required an assessment of the nature of exploitation, and how it might be addressed in this context.

Based on this assessment of the ethics of enrolling adults who cannot consent, we undertook an assessment of specific proposed safeguards for such research in order to develop a consistent set of core safeguards.

Research advance directives, designed after clinical advance directives, allow individuals to document in advance their preferences concerning future research participation in the event they become unable to give consent. Many groups have endorsed research advance directives as an important safeguard for adults unable to consent. However, there is a wide preference/performance gap with respect to clinical advance directives for end of life care, with over 80% of individuals endorsing them, but only approximately 20% actually executing one. If a similar gap exists for research advance directives, requiring them could block important research even when patients want to participate. This result would be particularly problematic if they block the enrollment of individuals who are willing to participate, but never completed a research advance directive.

The appropriateness of several of the proposed safeguards for adults who are unable to consent depends upon individuals' attitudes. For instance, several groups argue that adults unable to consent should be enrolled in non-beneficial research only when it concerns a condition they have. This safeguard is based on the assumption that individuals are more willing to participate in research on conditions they have. Hence, limiting their participation to such research increases the chances that it is consistent with their competent preferences. Similarly, what effect research advance directives have depends on individuals' attitudes, and whether they are willing to fill them out. Finally, it is important to assess individuals' willingness to participate in research once impaired, and who they think should make research decisions for them.

To assess empirically individuals' attitudes toward participating in research once impaired, and their attitudes toward research advance directives, we conducted a telephone survey. We targeted individuals who were familiar with both clinical research and the difficulties presented by research with those who cannot consent. We surveyed individuals who were participating in longitudinal studies for individuals whose family history places them at increased risk for developing Alzheimer disease.

To assess individuals' willingness to complete a research advance directive as part of this process, we sent individuals a form and allowed them to complete it and send it to their research institution. To assess the completion rate of research advance directives in a more realistic setting, we assessed how many individuals who come to the NIH clinical center complete an NIH advance directive. The NIH clinical center offers an important opportunity to assess the completion rate of research advance directives because: 1) everyone who comes to the clinical center is part of or being considered for research participation; 2) the NIH advance directive, unlike state advance directives, covers research participation; and 3) everyone who is admitted to the clinical center is asked about their advance directive status and whether they are interested in completing an NIH advance directive.

To assess whether the widely supported necessity requirement should apply to research that offers the potential for medical benefit, we considered first the fact that

certain groups are routinely excluded from research, for instance, individuals with reduced kidney function being considered for a chemotherapy protocol. We then developed an analysis of when such exclusions are appropriate, and applied that analysis to research with adults unable to consent.

Finally, many groups recommend that the evaluation of research subjects' informed consent should focus on groups that are at increased risk for lacking the capacity to give consent. We evaluated this approach, and considered whether there are any alternative approaches that might provide greater protections.

Results: We have developed a conceptual analysis of the possibility of enrolling individuals in research without exploitation or consent. This analysis suggests that the potential for exploitation traces to the possibility of investigators taking unfair advantage of individuals' inability to consent. Taking unfair advantage in this regard occurs when investigators enroll individuals unable to consent, even though their participation is not necessary, or there is insufficient reason to believe they would consent if there were capable of doing so. This analysis suggests that it is possible to conduct research without consent or exploitation provided the enrollment of adult unable to consent is necessary to answer the scientific question posed, and there is sufficient reason to think that enrollment is consistent with individuals' preferences and interests.

Based on this analysis, the Department developed a critical analysis of the existing proposals for safeguards for adults who are unable to consent. Using a side-by-side comparison, we distilled 6 core safeguards for research with adults unable to consent: 1) IRB risk-benefit assessment; 2) necessity requirement; 3) proxy decision maker; 4) sufficient evidence of subject's competent preferences; 5) respect for subject assent and dissent; 6) independent monitors and participation monitors in specified cases.

Our analysis of medical exclusions from research suggests that it is acceptable to exclude individuals from research when their participation poses clearly increased risk with no increased potential for benefit. Importantly, these exclusions are supported not on the grounds that they protect the individuals excluded, although they may do that, but on the grounds that they minimize the *aggregate* risks of the research. This is seen by the fact that such individuals often are excluded even though enrollment may be in their medical interests. This analysis suggests that individuals unable to consent should be excluded from research when their participation is unnecessary, and that these exclusions apply whether the research offers the potential for medical benefit or not. In both cases, the necessity requirement helps to minimize the aggregate risks of the research, in this case, its moral risks.

We found that many individuals are willing to participate in research, including non-beneficial research, when they lose the ability to consent. This suggests that such research should not be disallowed. Instead, individuals unable to consent may be

enrolled provided their participation is necessary to answer the scientific question posed, and there is sufficient evidence that enrollment is consistent with the preferences and interests of specific individuals.

We mailed a research advance directive to all individuals who had completed the interview, and gave them the opportunity to complete the form and return it to their research institution. Only 16% of subjects completed and returned a research advance directive. These data are striking given that these individuals were very supportive of research and willing to participate in research once impaired, and had completed our survey on the difficulties of conducting research with subjects who cannot consent and the ways in which research advance directives could address these concerns. To follow-up these data, we assessed how many individuals admitted to the Clinical Center complete an NIH research advance directive. Over a 6 month period, only 8% of approximately 4000 individuals completed a research advance directive despite the fact that all individuals who come to the Clinical Center are candidates for research participation. These data suggest that requiring individuals preferences be documented in a formal advance directive could block appropriate research.

Most commentators argue that it is important to identify groups that are at increased risk for lacking capacity to provide informed consent. The identified groups are given a formal capacity assessment prior to research enrollment. Against this capacity model, we have argued that it would be better to use a consent model, according to which all subjects' informed consent is evaluated informally, and those who raise questions are referred for more in-depth evaluation. This approach avoids endless debate over which groups are sufficiently at risk, avoids stigmatizing the identified groups, ensures that all subjects provide valid consent, and ensures that at risk groups are not held to a higher standard.

Finally, many groups and guidelines endorse the 'subject's condition' requirement: individuals unable to consent should be enrolled in non-beneficial research only when it is likely to yield generalizable knowledge about their medical disorder or condition. The subject's condition requirement appears to provide important protection by ensuring that individuals unable to consent are enrolled in non-beneficial research only when their participation is scientifically necessary. Others suggest that the subject's condition requirement may increase the chances that individuals unable to consent are enrolled in research only when it is consistent with their competent preferences.

Combining ethical analysis with empirical data from a recent survey of IRB chairpersons, we argue that the subject's condition requirement does not effectively implement the necessity requirement. Moreover, the importance of ensuring that research enrollment is supported by individuals' competent preferences suggests the need for an explicit evidence requirement, not the subject's condition requirement.

Future Directions: The safeguards for research with adults who are unable to consent rely on the appeal to their competent preferences. This approach seems reasonable, and may work for adults who were once competent, but have since lost the ability to consent. However, this reliance on competent preferences raises a concern about the ethics of conducting clinical research with adults who were never able to consent, or who never developed competent preferences. In the future, we plan to assess the ethics of conducting research with adults who have never been able to provide informed consent.

The existing pediatric regulations have been widely described as an appropriate foundation for developing safeguards for research with adults who are unable to consent. Our work on the pediatric regulations puts us in a position to assess to what extent they offer appropriate guidance in this regard.

Publications:

1. Wendler D, Martinez R, Fairclough D, Sunderland T, Emanuel E. Proposed regulations for clinical research with adults unable to consent: what are the views of those most likely affected? American Journal of Psychiatry 2002; 159:585-591.
2. Wendler D, Prasad K. Core safeguards for clinical research with adults who are unable to consent. Annals of Internal Medicine 2001; 135:514-523.
3. Wendler D. Informed consent, exploitation, and whether it is possible to conduct human subjects research without either one. Bioethics 2000; 14:310-339.
4. Wendler D. The importance of autonomy not being all-important. BioLaw 1999; S:445-451.
5. Wendler D. When should 'riskier' subjects be excluded from research? Kennedy Institute of Ethics Journal 1998; 8:307-327.