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Acceptable Approaches to Enrolling Adults Who Cannot Consent in More than Minimal Risk Research

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Research on diseases that cause cognitive impairment is of vital importance. It provides the opportunity to improve methods to prevent, treat, and possibly cure illnesses that cause significant morbidity to millions of people. When possible, investigators should conduct this research with individuals who are able to provide informed consent. And we should note that many individuals with mild cognitive impairment, when carefully evaluated, show evidence that they retain the ability to consent. To understand the nature of Alzheimer's disease (AD), autism, and diseases associated with cognitive impairment, however, investigators sometimes need to conduct non-beneficial procedures that pose greater than minimal risk with individuals who cannot provide informed consent.

When assessing the ethical appropriateness of this research, the first question should be whether the research is of sufficient value. Individuals, whether they can consent or not, should be enrolled in research only when it is socially valuable—especially when the research poses greater than minimal risk and enrolls adults who cannot consent.

Most guidelines and commentators permit minimal risk, non-beneficial research with adults who cannot consent (Secretary's Advisory Committee on Human Research Protections, Recommendations from the Subcommittee for the Inclusion of Individuals with Impaired Decision Making in Research). The present question is what level of additional risk is acceptable. Specifically, given the regulatory definition of minimal risk, the question is: Is it acceptable to enroll individuals who cannot consent in research that poses risks exceeding those considered appropriate as part of ordinary, daily life?

It seems appropriate to expose adults who cannot consent to risks greater than those permitted ordinarily if the research has the potential to gather important information that cannot be obtained with individuals who can consent and cannot be obtained in a way that poses lower risks. The key questions are under what circumstances would such research be permissible and what is the upper limit of such risk?

Consider first a situation in which an individual has designated someone, through assignment of durable power of attorney (DPA), to make research decisions for them and there is sufficient reason to believe that participation in the study is consistent with the individual's values. Suppose further that this person, although quite impaired, is able to understand some rudimentary information (e.g., that he is being enrolled in a study, even though he cannot explain the details) and to provide assent—as is the case with many people with dementia (Kim, Cox, and Caine 2002; Marson et al. 1995). It seems appropriate to permit such a person to enroll in research with greater than ordinary risk without prospect of benefit, if the person assigned DPA agrees.

The act of designating someone else to make decisions provides that designee with special moral authority to make decisions on the individual's behalf (Kim and Appelbaum 2006). There is good evidence that many people with cognitive impairments retain the ability to appoint a surrogate (over 90% of persons with early Alzheimer's will likely be able to appoint a DPA for research). Even some individuals who have lost the capacity to consent can appoint a surrogate (Kim, Karlawish, et al. 2011). These data highlight the importance of encouraging persons in early stages of diagnosis to designate a DPA for research, and the importance of evaluating whether or not individuals with moderate impairments who lack a designee with DPA are able to appoint one.

Moving on, we face the question of individuals who do not have and are unable to assign a DPA for research. Is it acceptable to rely on next of kin or the designee with the DPA for healthcare decisions to make research decisions in studies with greater than minimal risk and no prospect of benefit? As very few people fill out advance research directives or appoint a DPA for research, this is an important question from a policy perspective. The fact that an individual did not assign a surrogate for research decisions does not imply that next-of-kin decision makers are inappropriate. For instance, court-appointed guardians often are permitted make research decisions even though they were not appointed by the individual. It may be, for example, that most people would be willing to allow their family to make decisions for them in the event of their incapacity, much as family is expected to do for treatment decisions. What is the evidence for the public's view on this issue?

First, people generally are willing to participate in research that might be categorized as more than minimal risk research with no prospect of benefit based on family surrogate consent. Surveys of people at increased risk of Alzheimer's (Wendler et al. 2002; Kim et al. 2005), elderly people in clinics and senior centers (Karlawish et al. 2009), caregivers of patients with dementia (Kim et al. 2010), and the older general public (Kim et al. 2009) indicate that all these groups highly value AD research and many are willing to consider participation. In a survey of U.S. adults aged 51 and older, 71% were willing to consider participation, based on family surrogate, in studies involving lumbar punctures without prospect of benefit (Kim et al. 2009). Furthermore, most people are willing to give their future surrogates some or complete leeway regarding research participation decisions (Wendler et al. 2002; Karlawish et al. 2009; Kim et al. 2009; Kim et al. 2013).

Second, the public generally supports a societal policy of family surrogate consent for dementia research when necessary. For example, after a day-long democratic deliberation

session consisting of interactive expert education and peer deliberation, 92% of individuals drawn from the general public said they would probably (41%) or definitely (51%) support de facto family surrogate permission for studies involving lumbar punctures without prospect of benefit and 67% would support first-in-human gene transfer research (Kim, Kim et al. 2011).

Of course, when relying on a surrogate who is not chosen by the potential research subject for research decisions, it is important to follow certain safeguards. As in this case, this means that surrogates are evaluated to determine whether they a) have a good relationship with the potential research subject; b) understand the study involves research; and c) have sufficient reason to believe that enrollment in the study is consistent with the subject's preferences and values.

Finally, while we believe research that poses some level of risks greater than minimal can be acceptable, we think there should be an upper limit on the net risks to which individuals who cannot consent may be exposed. However, we do not think that this level of risk can be settled by philosophical analysis. Philosophical analysis can support the claim that it can be acceptable to expose individuals who cannot consent to some risks for the benefit of others. Such analysis, though, will not be able to identify the precise limit to risks. Hence, it will be important to gather data on what level of risks are regarded as appropriate by a majority of the public, and to couple this data with judicious safeguards.

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