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The ethics of informed consent in Alzheimer disease research

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Abstract

Clinical research on Alzheimer disease (AD) is much needed but requires the participation of patients with substantial cognitive impairment who have difficulty providing informed consent. Despite decades of debate, policies regulating such research are not well-defined. Although numerous studies have underscored the difficulties of obtaining informed consent for clinical research from patients compromised by AD, there is also increasing evidence that such individuals and their surrogates can make decisions about research participation that are consistent with the patients' values. Policy discussions and future research should consider how the ethical reservations about enrolling incapacitated patients in research could be mitigated by developing ways to promote the congruence between surrogates' decisions and patients' values.

Alzheimer disease (AD) is incurable, devastating and highly prevalent. Research is, therefore, crucial but involves patients with substantial cognitive impairment that may hinder their ability to provide informed consent.[1,2] The dilemma is magnified when the research is invasive and burdensome, with unpredictable risks.[3,4,5] Despite several decades of debate in the USA, no clear policy exists regarding the involvement of adults with decisional impairments in clinical research.[6] This policy uncertainty is not unique to the USA: the UK, for example, has three different regulations that may apply depending on the location and type of research involving individuals with dementia.[7] AD research centers[8,9] and research ethics review boards[10,11] vary considerably in their policies and practices in dealing with this ethical issue.

More than a decade ago, when the US National Bioethics Advisory Commission published its report on the ethics of research involving people with decisional impairment, few empirical studies were available to inform the discussion.[12] Since then, the body of research in this area has been steadily increasing. What have we learned from those studies and what are the policy implications of their findings? In this article, I aim to address these questions by focusing on two ethical concepts—the familiar notion of autonomy (especially the impact of dementia on decisional capacity) and the perhaps less familiar concept of authenticity[13,14] (research participation that is congruent with the patients' values).

Two key ethical concepts

Defining autonomy

An autonomous decision is commonly understood in the medical literature as an act of self-determination exercised by a competent person.[13] In the research context, an autonomous decision requires that research subjects have the capacity to provide informed consent to participate in research. Those who cannot make autonomous decisions either are excluded from the study or participate based on a surrogate's consent. Since most policy recommendations limit the types of research that may be conducted with a surrogate's

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consent,[15] it is crucial to know the empirical conditions under which such policies will be implemented. For instance, what is the likelihood that people with dementias such as Alzheimer disease will be competent to give informed consent? How reliable and valid are capacity assessments? What is the likelihood that autonomy can be extended by means of explicit research advance directives?

Defining authenticity

A familiar concept in surrogate decision-making is that of substituted judgment, in which the surrogate attempts to decide what the patient 'would choose' were he or she able.[13] Brudney has pointed out that the moral authority of a substituted judgment does not depend on extending the autonomy of the incapacitated individual in his or her current state.[13] This is because autonomy requires a competent person exercising his or her power of self-determination—something that is impossible when there is not a competent self. What actually provides the moral authority behind substituted judgments is instead the idea of authenticity. Authenticity refers to the congruence between a person's values (including beliefs, commitments and relationships) and a decision.[13,14] In the research context, the relevant question is whether a subject's participation is consistent with his or her values. For instance, does the individual hold strong beliefs about genetic privacy that would potentially preclude depositing their genetic material into a shared database? Or does the patient hold strong religious views against embryonic stem cell research? In contrast to an autonomous decision, which can only be made by the patient, a decision can be authentic even when made by a surrogate, because authenticity does not require intact capacity for self-determination, only that the decision conforms to the individual's values.[14]

Preserved abilities in AD

In the context of AD research, the relationship between autonomy and authenticity is complicated because patients with AD may be impaired to the extent that they lack the capacity for self-determination but retain ethically relevant abilities such as communicating a preference, maintaining relationships and exercising some level of decision-making.[16] Important empirical questions arise as a consequence. How willing are patients with AD to participate in research? How valid and reliable are those preferences? What are the ethical implications of the 'preserved' abilities described above? It is important to study the nature and extent of these preserved abilities because they distinguish the AD research context from other situations of surrogate decision-making such as decision-making in the intensive care unit where an unconscious patient cannot provide any contemporaneous input.. Although studies have shown that surrogates' choices do not appear to closely agree with their principal's choices in the clinic[17] or in some research settings,[18,19] it would be a mistake to generalize those findings to the AD research context. Such studies do not simulate the situation that is common in AD research, in which patients with decisional impairments—who may retain some significant abilities such as communicating their values and preferences—remain in conversation about their decision with their surrogates.[20]

Autonomy and consent capacity

The impact of AD on capacity

Even mild cognitive impairment can have substantial effects on decisional capacity.[1,2,21] For example, in a study of 40 people with mild cognitive impairment (Mini-Mental State Examination [MMSE] mean score of 27.8, SD ± 1.8), 40% of the participants were judged by experienced evaluators to be incapable of providing informed consent to participate in a clinical trial.[21] In a study of patients with mild to moderate AD (mean MMSE score of 22.9, SD ± 3.8), 62% did not meet the threshold (validated by a clinician panel) on at least one standard of capacity for research consent.[1] Moreover, a UK study of participants (median

MMSE score of 22, IQR 18–25) in an AD drug trial found that only 42 of 176 participants (24%) were capable of informed consent, as determined by a procedure based on the recent Mental Capacity Act of England and Wales.[22]

Judgments of capacity

No clear-cut line exists between capacity and incapacity. Although some studies have found fairly good agreement among clinicians' judgments of patients' capacity,[1,23] others have found high rates of disagreement in the assessment of capacity.[24,25,26] In one study, five experienced clinicians (from geriatric psychiatry, neurology and geriatric medicine) who evaluated the capacity of patients with mild AD achieved only 56% agreement.[25] In an experimental video survey that asked 99 consultation psychiatrists to assess whether a subject portrayed on a video interview was capable of informed consent, 40% of respondents deemed the subject to be capable and the remainder deemed the subject to be incapable.[26]

In the most extensive study to date, 555 capacity interviews of 188 patients with AD were evaluated by five experienced psychiatrists. For any given pair of psychiatrist judges, there was wide variation in judgments of capacity, with pairwise kappa statistics ranging from slight agreement (0.17) to substantial agreement (0.64).[27] Although the majority opinion of a group of expert judges is considerably more reliable than single-clinician judgments,[26,28] a panel-based process is resource-intensive and may be impractical outside studies dedicated to studying decision-making capacity.

The capacity status of patients (as perceived by research personnel) who are enrolled in multi-site AD clinical trials can vary considerably between trial sites, with estimates of intact capacity status ranging from 0% to 100%.[9] Although this variation could be due to each site recruiting different subgroups of AD patients, this explanation probably does not fully account for the variation.

Why do capacity judgments vary so much? The inherently value-laden task of incorporating risk–benefit—considerations about which intuitions may differ—may create threshold levels that vary among evaluators.[27] However, extremely wide variations, as seen between trial recruitment sites, may be driven by more fundamental factors. One intriguing speculation is an inadvertent conflation of capacity with authenticity: even a considerably impaired patient with reduced capacity for informed consent may be able to convey a sense of his or her genuine (that is, authentic) willingness to participate in research. This expressed willingness can, understandably, be mistaken for a sign of intact capacity (Box 1).

Box 1

Distinguishing authenticity from capacity

In my lectures teaching aspiring researchers the concept of decision-making capacity, I use a videotaped interview portraying a man with Alzheimer disease (AD) undergoing an interview to determine his capacity to provide informed consent to participate in a clinical trial of an AD drug. The interview begins slowly, with the patient showing great difficulty remembering even recent events and statements. However, as the interview proceeds, although the cognitive deficits remain obvious, the man talks about what his life is like with AD and states his willingness to participate in research because of "two things … first of all I might benefit from it; and also it could make a real difference if [the drug] worked. I understand that it's totally unknown…"[26] When the trainees are asked whether they believe the person portrayed in the tape is "competent to give his own informed consent" a few tentative hands go up; however, when they are asked whether they believe that the person portrayed in the tape "genuinely wants to participate in

research," most raise their hands with confidence. In the context of a lecture focusing on the requirements of capacity, most of these students answer correctly that the patient does not seem have the capacity to provide informed consent. However, it is not difficult to imagine how research assistants relatively untrained in capacity assessments may confuse their impression that the person "genuinely wants to participate in research" with the view that person is able to make the decision to participate in research.

Some implications

The early impact of AD on decisional capacity and the broad gray area between capacity and incapacity have consequences for practice. Consider the following example. Suppose that, for a neurosurgical gene transfer trial for AD, it is decided that only patients who are competent to provide informed consent will be enrolled, owing to risk–benefit considerations. This is a theoretically reasonable approach but it relies on an empirically unproved assumption that it will be possible to enroll a sufficient number of patients with AD who are competent. For such a setting, the threshold for competence should be set high[12,29] and, thus, only patients with an unequivocally high level of decision-making abilities would be deemed competent and eligible. In a recent study of 188 patients with mild to moderate AD (80% of whom had MMSE scores of 18 or higher), less than 4% were judged to have the capacity to consent to a neurosurgical randomized controlled trial by all five clinicians who were shown the capacity interviews of the patients.[30] Even with the high prevalence of AD, recruiting unequivocally competent participants for such studies may prove challenging. Furthermore, given that these unequivocally competent patients comprise a small and unusual subset of patients with AD, such patients may represent an atypical subgroup of those who have AD, raising issues concerning external validity. They would also have the most to lose from an adverse event, given their higher level of functioning.

Can advance directives solve the problem of recruitment for such high-risk studies? Although advance directives are mentioned in most policy discussions, the rates of completion of research advance directives are likely to remain low.[31,32] One study found that even among a highly motivated group of people—people already engaged in a clinical research study for first-degree relatives of patients with AD and most of whom expressed a willingness to complete advance directives—only 16% completed a research advance directive during the year following the survey.[32]

Authenticity-relevant research

Most policy statements assume that once a person is deemed incapable of informed consent, the only ethically relevant input by the person is whether he or she assents or dissents to participation.[12,15] However, a lack of capacity to provide informed consent may not preclude the subject from making ethically meaningful contributions beyond assent because they retain preserved abilities relevant to the issue of authenticity.

Appointing concurrent proxies

One preserved ability is the capacity to designate a research proxy, or surrogate. By entrusting someone with the authority to make a decision in their place, patients rely on one of the most important values that makes them who they are—i.e., their relationships. A surrogate who is explicitly designated by the subject is ethically preferable to a *de facto* surrogate because such a designation expresses one of the most important values that the patient holds.[16]

In a recent study, we found that over 90% of patients with AD in the early stages of the disease (MMSE score of 24 or higher) are capable of appointing a research proxy, suggesting that, for early-stage disease, a presumption of capacity to appoint a research proxy may be appropriate. Notably, 38% (40 of 106) of those deemed incapable of consenting to a drug randomized controlled trial and 55% (86 of 157) of those deemed incapable of consenting to a neurosurgical randomized controlled trial were still found to be capable of appointing a research proxy.[30] Thus, a substantial proportion of patients with AD who are incapable of research consent may be able to appoint a proxy in a concurrent rather than an advance directive.[16]

Attitudes toward research

Another faculty that may be retained by a person with dementia is the ability to express preferences that are 'reasonable'—for example, preferences that are consistent with the choices of people without impairments. Using hypothetical clinical vignettes for two major medical decisions (treatment decisions regarding a neoplasm and a cardiac condition), one study found that the treatment choices made by patients with AD did not differ from those made by healthy controls. Of course, the patients with AD performed significantly less well on measures of decision-making capacity but, notably, the content of their choice was not significantly different from that of the choices of the controls.[33] In another study using four research scenarios (drawing blood, a drug clinical trial, a drug challenge with PET scan and a brain surgery study), patients with AD had similar participation preferences to controls for three (blood draw, PET study and brain surgery) of the four research vignettes, with their willingness to participate declining as the risk increases.[34] The study also found that the more impaired patients with AD are not more reckless than the less impaired patients but, rather, are less willing to participate in research.[34]

Another study has shown that patients with AD are able to discriminate between research scenarios with regard to whether they want proxy decision-making, and this desire varies according to the risk–benefit profile of the study; those who express reluctance to cede control furthermore cite desire of autonomy or study-specific features to explain their unwillingness, again indicating the presence of retained abilities.[35]

Without a controlled, longitudinal follow-up study comparing premorbid and post-diagnosis preferences and values regarding research participation, validating the authenticity of the preferences of patients with AD is difficult. However, cross-sectional data may provide estimates of premorbid willingness to consider research participation, as well as a measure of attitudes towards surrogate consent for dementia research. Surveys of people at increased risk of AD,[32,36] elderly people in clinics and senior centers,[37] carers of patients with dementia,[38] and the older general public[39] show that members in all these groups highly value AD research and many are willing to consider participation. In a nationally representative sample of US adults aged 51 years and older, 69% were willing to consider participation even in quite invasive experiments such as neurosurgical gene transfer for AD.[39]

Furthermore, people may be willing to give their future surrogates some or complete leeway regarding research participation decisions. The willingness to entrust wide decision-making authority to their future surrogates suggests that they value the role that their surrogates will play more than the specific preferences they currently hold.[32,37,39] Over one-quarter of the general population whose current wish is not to participate in future AD research also say that they would be willing to allow their future surrogates the leeway, if and when the times comes, to enroll them.[39] Among people who have first-degree relatives with AD, 80% state that their families could enroll them in potentially beneficial research even when their advance directive opposes enrollment in research.[32] This is not a paradox. Such people may

be aware that their current preferences are speculative and thus value them less than their trust in the judgments of their loved ones who may have a more complete set of facts in the future.

In summary, there is considerable evidence that patients with AD, as well as other groups of people including the general public, have positive views about surrogate consent for AD research. But are these surveys valid? After all, the ethics of dementia research has remained an unsettled policy issue, with complex scientific, legal and historical dimensions. These concerns about the internal validity of opinion surveys in bioethics are now being addressed through the use of deliberative methods (Box 2), and the results of those studies support the view that laypeople generally support the policy of surrogate consent for dementia research.[41]

Box 2

Democratic deliberation

The traditional brief, vignette-based surveys are convenient ways of examining the opinions of lay people, but some researchers doubt whether they are internally valid.[40] To address such concerns, we assessed the views of carers of patients with Alzheimer disease (AD)[38] and of the older general public using democratic deliberation,[40] a method which involves an all-day, in-person education and deliberation session. In a study of over 500 people recruited by random digit dialing, we randomly assigned the participants to one of three groups: the deliberation group attended an all-day education and peer deliberation session; the education group received by mail written information only; and the control group received no intervention, simulating a traditional survey. The information materials—detailing AD clinical research and related ethical issues—were developed and vetted by an interdisciplinary panel that included lay people. Participants were surveyed about their attitudes towards a policy of allowing surrogate consent for research studies of varying risks and potential benefits (a lumbar puncture study, a drug randomized controlled trial, a vaccine randomized controlled trial, and an early-phase gene transfer trial). In the deliberation group, support for surrogate consent increased for all scenarios (range of support: 67–97%), with much of the increase sustained 1 month after the deliberation session. No sustained changes occurred in the other groups. Thus, when the issue of internal validity is carefully addressed using in depth education and deliberation, the support for a policy of surrogate consent for dementia research increases. When combined with the results of other studies with excellent external validity, such as a survey of a probablistic sample of older Americans,[39] these results provide solid evidence regarding the public's attitudes toward surrogate consent for dementia research.

Conclusions

Policies on the ethics of dementia research remain unsettled. The emerging empirical literature, however, shows two important trends that should inform future policy discussions. First, research on the decision-making capacity of patients with AD highlights the practical challenges for policies that rely on drawing a clear line between capacity and incapacity. This challenge is especially important for studies that attempt to enroll only competent individuals because of substantial research risks. Second, evidence is accumulating that incapacitated patients with dementia can be enrolled in research in ways that are consistent with their values, given that important, ethically relevant abilities may be preserved. Research also shows a consistent and broad support for surrogate consent for

dementia research (even for protocols with invasive procedures) among various lay stakeholder groups.

What are the policy implications of research in this area? Although decisional capacity is a necessary policy concept, it is still evolving in its real-world implications, especially for research consent.[29] Policymakers should be cautious about presuming how the concept operates in the real-world setting. Conversely, some of the difficulties of relying on a clear boundary between capacity and incapacity may be offset by placing greater emphasis on authenticity. Is enrolling presumably competent yet vulnerable individuals preferable to enrolling individuals who are not fully competent but can meaningfully contribute to their surrogate's decisions? The answer may require further analysis and debate, but in the meantime it seems reasonable to develop ways of increasing the likelihood that the participation of patients with AD in dementia research is congruent with their values.

Some specific steps can be taken now. First, the above discussion reinforces the importance of assent and lack of dissent as important ethical requirements when enrolling people with decisional impairments in dementia research. However, there is no consensus on how assent and dissent should be defined or on the procedures that should be used to incorporate these concepts into practice.[42] Further research and guidance regarding assent and dissent are therefore needed. Second, potential research participants should be given an opportunity to assign proxies when they are still capable of doing so; in early dementia, the capacity to assign a proxy may even be presumed. Even when a patient's dementia has progressed to the point of causing incapacity for informed consent to participate in specific research studies, the patient might retain the capacity to appoint a proxy, and this capacity could be assessed.

In addition to evaluating the effectiveness of these steps to enhance authenticity, other areas need further study. Clearly, the assessment of a patient's capacity to consent to research participation needs to become more standardized and reliable. More research is needed to evaluate the validity of the values and preferences of patients with dementia regarding research participation, including the relationship between the ability to convey a genuine desire to participate in research and the capacity to provide informed consent. Studying further surrogate-specific factors that may affect how a surrogate makes decisions with and for the incapacitated person with dementia will also be useful. The results of such studies will prove invaluable in developing ethically sound and empirically informed policies to protect vulnerable research participants while facilitating research that targets the causes of their vulnerability.

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