Informed Consent, Participation in Research, and the Alzheimer's Patient

by Edmund Howe, MD, JD

Innov Clin Neurosci. 2012;9(5–6):47–51

ABSTRACT

Patients with Alzheimer's disease may want to participate in research on Alzheimer's disease, but their participation involves exceptional considerations. Plans should be made for determining these patients' cognitive capacity on a regular basis; for example, throughout a study, cognitive capacity may decline, making it necessary for a patient's pre-designated surrogate decision maker to become more involved. Patients with Alzheimer's disease may also choose to designate someone other than their primary caregiver to be their surrogate decision maker. This article discusses these and other core ethical issues.

KEY WORDS

Informed consent, Alzheimer's disease, research, surrogate decision maker, mental capacity, minimal cognitive impairment, MCI

INTRODUCTION

At a recent conference on new findings regarding Alzheimer's disease (AD), one expert stated that he thought *all* care providers should take the initiative to ask patients with AD whether or not they want to participate in AD studies. AD research is, of course, dearly needed since AD cannot now be prevented or cured.[1] There are two main factors that motivate patients to participate in AD studies: altruistic intent (i.e., the desire to help future patients with AD receive effective treatment) and immediate benefit (i.e., the desire to benefit medically from the new treatment being studied).[2] Patients with AD may be motivated by one or both of these factors, and psychiatrists should be mindful of these motivating factors in order to ensure the patients are adequately supported, their expectations are managed appropriately, and they have the emotional tools they need to successfully navigate throughout the research process. However, in addition to these motivating factors and perhaps more importantly, the psychiatrist should be ever mindful of the AD patient's capacity to give informed consent/assent, a requirement of any human clinical trial. This article will review key areas of concern surrounding informed consent unique to the patient with AD who wishes to participate in clinical trials.

CAPACITY TO CONSENT: GENERAL PRINCIPLES

Patients with AD may be especially impaired in their ability to give adequate informed consent to research. This may be the case even in the disease's earliest, mild stage.[3] Like most people, patients with AD want to make healthcare decisions for themselves for as long as they can.[4] I recall one patient with AD

who insisted on attending his appointments with me by himself until he was no longer able to do so. He wanted to be independent for as long as possible. Psychiatrists should support expressions of individual preferences, such as this, by patients with AD throughout their participation in studies in every way possible. Patients with AD should be enabled to participate to the degree to which they want, both when they can still legally consent and after they have lost the capacity to consent, and then can legally only give assent. In many other areas of research, consent requirements are sharply defined. This is not the case, however, when it comes to research participants with dementia.[1,5] State laws on patient consent can greatly differ; therefore, clinicians of patients with AD who wish to enroll in studies should carefully check these laws prior to enrollment.

Surrogate decision makers. Once patients with AD lose their capacity to consent, surrogate decision makers may be able to make decisions generally consistent with the patients' prior values.[5] Thus, even when patients with AD do lose competency during study participation, these surrogate decision makers may be able to follow through with what these patients would have wanted. Sometimes, surrogate decision makers want to maximize what they think is best for their patients, as opposed to pursuing what they believe their patients want.[6] This is not an uncommon occurrence in the clinical context. The best "remedy" for this may be to have patients with AD discuss their future desires as fully as possible with their chosen surrogate decision makers before they enter a study. Psychiatrists should encourage and help arrange these sessions. Some studies suggest that the "older, general public" supports surrogate decision makers making decisions on behalf of patients with AD regarding their participation in research.[7] For this reason, psychiatrists taking the initiative to pursue these discussions between patients and their surrogate decision makers seems to be something patients with AD would want.

Risks. A core concern a psychiatrist should have when a patient with AD is considering enrollment in a study is how great a risk the patient is willing to take. As a general rule, the greater the risk, the stronger a patient's capacity to consent should be. For example, a patient may experience pain, such as a headache, after a lumbar puncture; it might be optimal that a patient show a better degree of understanding risks such as this than the patient should show if he or she were only giving blood. Patients with AD may be willing to take on high risks, and they should be allowed to do so as long as they are legally competent and can thus give "advance consent."

In one study, a large majority of adults over 65 years of age indicated that they would be willing to give advanced consent for "blood draw studies," and *almost half* said that they would be willing to participate in blood draw studies that included lumbar punctures.[8] These findings suggest that *not* making opportunities to participate in such studies available to patients with AD would *disrespect* these patients. Having the capacity to appoint a surrogate decision maker when a patient with AD is competent may also mean that he or she should be able to both enroll in research studies *after* the onset of AD and in research that is *high* risk.[9]

ASSESSING CAPACITY TO CONSENT

How can the capacity for consent in a patient with AD be best determined? Measures such as the Mini Mental Status Exam (MMSI) may not be sufficient guides to whether or not patients with AD should be deemed to have adequate capacity to consent. This is because a patient's capacity to not only understand, but *appreciate* what he or she is consenting to in an affective or emotional sense may differ greatly, regardless of how the patient performs on the MMSI.[1] In one report,[10] for instance, some patients who scored 26 on the MSSE did *not* have sufficient capacity, as was determined on a separate clinical interview. Two patients, however, who only had a score of 19, *did*.[10]

Most importantly, in regard to capacity to understand and consent, even if a patient with AD lacks adequate capacity to give consent to be in research, he or she may retain wholly adequate capacity to determine who he or she would want to make decisions on his or her behalf. This is because the capacity needed for this (determination) is substantially less.[9]

The "gold standard" for measuring capacity to consent to be in clinical research is the MacArthur Competency Assessment Tool for Clinical Research (MacCAT-CR).[11,12] This standard should not suffice on its own, however. Rather, those assessing the capacity of consent of a patient with AD should ask the patient specific questions about his or her understanding of the particular study in which he or she wishes to be enrolled. This tool, even if used only as an initial screening measure, takes time to administer. Personnel who administer it must have specific training. Thus, there may be other measures that are preferable.[13,14]

Care providers assessing the capacity of consent in patients with AD should also seek to discuss the potential study with the patients more than once, since some patients with AD may only "get it" after discussing it for a second or third time. Steps for discussion are outlined elsewhere.[3] The person who is assessing the capacity of consent and level of understanding in a patient with AD must also try to ascertain whether or not the patient is simply repeating what those around him or her have just said. A patient with AD may make statements without understanding what he or she just said.[12,14]

Other problems involving consent. Kutschenko[15] has discussed whether or not participants should be enrolled in a study before they have AD. These types of pre-AD studies are, after all, critically important in order for us to better understand the disease. The patients whom Kutschenko discusses are those who have a condition or "pre-clinical state," such as minimal cognitive impairment (MCI), that increases the likelihood that they will develop AD later. Kutschenko raises the ethical question of whether early detection of AD would be, overall, more beneficial or harmful to the participants. In other words, some individuals may not otherwise know of their increased likelihood of developing AD if not for the recommendation that they participate in a pre-AD study. These pre-AD individuals may see themselves, as a result of participating in research, as "non-normal but not necessarily pathological."[15] Kutschenko adds, "Given that more and more people who are afraid of having early-stage AD are looking for medical assistance, this question mirrors a real concern leading to new demands of patients and physicians alike."[15] Kutschenko asks whether such patients should receive "a treatment plan" for a condition that does not "(yet) affect their daily life."[15]

Further additional questions involving consent arise when the research involves genetics. For example, how is confidentiality regarding genetic results handled? Is there an ethical obligation to either inform or not inform close relatives of a participant if researchers find a genetic link that suggests that the relatives are *also* likely to develop AD?[16] The views of different professional groups on ethical questions like this, not surprisingly, differ from one another. Thus, some authors have recommended that when questions like this arise during a study, it may be useful to convene an "interdisciplinary" group. It is suggested that this group include, at the very least, researchers, clinicians, and ethicists.[17]

INFORMING PATIENTS

When obtaining patient consent or assent before and during participation in research, attempts should be made frequently to present information to patients with AD in as clear a form as possible. For example, the information may be given interpersonally (i.e., through discussions with the principle investigator or his or her assistants). Empirically, this approach is best because it puts patients with AD at ease and, probably because of this, increases their level of understanding.[18] Information may also be presented visually using diagrams and pictures. With present technology, information can be provided to the patient in an interactive way that requires touch. Either of these approaches should be used in conjunction with person-to-person interactions.[18]

Another consideration that is essential for obtaining patient consent is that the patient is able to give consent freely. A central concern when patients with AD are deciding whether or not to be in a study is if the patients are sufficiently independent from others when they make their decision. This question comes to the forefront when patients decide who they want to be their surrogate decision maker. *They may not want this person to be their caregiver.* Yet, their caregiver may be the person who brings them in to the appointments and may be the person who also comes in with them during their participation in the research. The caregiver's presence may impact a patient's ability to give consent. Psychiatrists should be aware of situations such as this so that they can effectively intervene. They may, for example, discuss the research opportunities alone with the patients and then help the patients "explain" the research opportunity to their caregivers.

There are many reasons why a patient with AD may not want his or her caregiver to be the surrogate decision maker. One reason is that the caregiver is so close to the patient that he or she may not be emotionally equipped to make difficult decisions. Psychiatrists might also explain to patients and their caregivers that, in anticipation of making difficult decisions down the road, caregivers may inadvertently change their relationship with their patients in an unwanted, negative way. For example, the caregiver might distance him or herself from the patient without really wanting to, in order to prepare him or herself for this change in role.

CONTINUING ASSESSMENT OF CAPACITY TO CONSENT

A patient's capacity for understanding and consent should be determined not only before participating in a study, but also periodically during the study. Researchers should plan, prior to the

study's beginning, who will make the subsequent capacity determinations and how often these determinations should be made. Ideally, those making the subsequent assessments should be independent of the study personnel in order to prevent bias. Researchers, possibly with the patients' psychiatrists, also may determine beforehand the method and the frequency of patient capacity evaluation. If researchers wish to use a scale, such as the MSSE, to track and screen study participants, they should keep in mind that due to the nature of AD, mild variations in these scores will likely occur.[2]

Working with the psychiatrists of study participants, researchers should also determine in advance what constitutes a refusal by a patient to continue participating in the study overall or perhaps for just one small aspect of the study. For example, a participant may at some point during the study refuse to have blood drawn, but this may not necessarily indicate that the patient wants to discontinue participation in the trial. A patient with AD may refuse this blood drawing procedure just this one time but later be *willing* to and *want to continue* to participate in the study. Furthering this example, researchers may want to determine, beforehand, how many "sticks" they should attempt before they take a patient's refusal as a definitive "no" to having blood drawn.

CONCLUSION

Patients with AD may want to participate in AD research for altruistic reasons or because they hope to medically benefit from a new treatment or both. Psychiatrists should, therefore, consider taking the initiative to discuss participation in research with patients with AD.

If and when a patient with AD wishes to pursue study participation, several considerations surrounding patient consent may warrant special concern. In addition to using screening measures to help determine a patient's cognitive capacity, person-to-person interviews should be carried out prior to study participation. Different standards of capacity apply to patients with AD compared to other patient cohorts. It is suggested that while an individual with AD still maintains his or her capacity to understand, he or she should designate a surrogate decision maker to step in when the patient is no longer able to make decisions on his or her own. The patient, the surrogate decision maker, and the psychiatrist should have discussions together regarding study participation often. The patient may not want to designate his or her primary caregiver as the surrogate decision maker.

When devising the study protocol, researchers should plan who, during the study, will assess patient capacity, how capacity will be measured, and how often capacity will be measured. They should also consider such questions as what should count as a refusal to participate.

It may be ethically required that psychiatrists take the initiative to explore the desires of a patient with AD to participate in AD research. Not only will this maximize a patient's capacity to choose what he or she wants, but may also have significant meaning for the patient, both of which should be primary goals of the psychiatrist.

REFERENCES

1. Eth S, Leong GB. Toward revising the ethical boundaries of research with noncompetent subjects. *Am J Psychiatry.* 2009;166:131–133.
2. Knebl JA, Patki D. Recruitment of subjects into clinical trials for Alzheimer disease. *J Am Osteopath Assoc.* 2010;110:543–540.
3. Warner J, Normani E. Giving consent in dementia research. *Lancet.* 2008;372:19–25.
4. Hamann J, Bronner K, Marguill J, et al. Patient participation in medical and social decisions in Alzheimer's disease. *J Am Geriatr Soc.* 2011;59:2045–2052.
5. Kim SY. The ethics of informed consent in Alzheimer disease research. *Nat Rev Neurol.* 2011;7:410–404.
6. Karlawish J, Kim SY, Knopman D, et al. The views of Alzheimer disease patients and their study partners on proxy consent for clinical trial enrollment. *Am J Geriatr Psychiatry.* 2008;16:240–247.
7. Kim SY, Kim HM, Knopman DS, et al. Effect of public deliberation on attitudes toward surrogate consent for dementia research. *Neurology.* 2011;13:2097–2104.
8. Karlawish J, Rubright J, Casarett D, et al. Older adults' attitudes toward enrollment of non-competent subjects participating in Alzheimer's research. *Am J Psychiatry.* 2009;166:182–188.
9. Kim SY, Karlawish JH, Kim HM, et al. Preservation of the capacity to appoint a proxy decision maker: implications for dementia research. *Arch Gen Psychiatry.* 2011;68:214–220.
10. J Warner J, McCarney R, Griffin M, Hill K. Participation in dementia research: rates and correlates of capacity to give informed consent. *J Med Ethics.* 2008;34:167–170.
11. Appelbaum PS, Grisso T. MacCAT-CR, MacArthur Competence Assessment Tool for Clinical Research. Sarasota, FL: Professional Resource Press; 2001.
12. Dunn LB, Nowrangi MA, Palmer

BW, et al. Assessing decisional capacity for clinical research or treatment: a review of instruments. *Am J Psychiatry.* 2006;163:1323–1334.
13. Jeste DV, Palmer BW, Appelbaum PS, et al. A brief instrument for assessing decisional capacity for research. *Arch Gen Psychiatry.* 2007;64:966–974.
14. Palmer BW, Dunn LB, Appelbaum PS, et al., Assessment of capacity to consent to research among older persons with schizophrenia, Alzheimer disease, or diabetes mellitus/ Comparison of a 3-item questionnaire with a comprehensive standardized capacity instrument. *Arch Gen Psychiatry.* 2005;62:726–733.
15. Kutschenko LK. Diagnostic misconceptions? A closer look at clinical research on Alzheimer's disease. *J Med Ethics.* 2012;38:57–59.
16. Van der Vorm A, Vernooij-Dassen MJ, Kehoe PG., Olde Rikkert MG, et al., Ethical aspects of research into Alzheimer disease. A European Delphi Study focused on genetic and non-genetic research. *J Med Ethics.* 2009;35:140–144.
17. Van der Vorm A, Van der Laan AL, Borm G, Vernooij-Dassen M, et al. Experts' opinions on ethical issues of genetic research into Alzheimer's disease: results of a Delphi study in the Netherlands. *Clin Genet.* 2010;77:382–388.
18. Flory J, Emanuel E. Interventions to improve research participants' understanding in informed consent for research: a systematic review. *JAMA.* 2004;292:1593–1601.

FUNDING: There was no funding for the development and writing of this article.

FINANCIAL DISCLOSURES: The author has no conflicts of interest relevant to the content of this article.

AUTHOR AFFILIATION: Dr. Howe is Professor, Department of Psychiatry, Director, Programs in Medical Ethics, and Senior Scientist, Center for the Study of Traumatic Stress, Uniformed Services University of the Health Sciences, Bethesda, Maryland.

ADDRESS CORRESPONDENCE TO: Edmund Howe, MD, JD, A1040J, USUHS, 4301 Jones Bridge Rd., Bethesda, MD 20814-4799; E-mail: edmund.howe@usuhs.edu