

Willingness to Participate in Alzheimer Disease Research and Attitudes Towards Proxy-Informed Consent: Results From the Health and Retirement Study

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Objectives: *To evaluate public opinion about participation in Alzheimer disease (AD) research and willingness to have a proxy-informed consent.* **Design:** *Cross-sectional.* **Setting:** *A national survey of community-dwelling adults over the age of 50 and their spouse of any age.* **Participants:** *The 2006 wave of the Health and Retirement Study (N = 1,517).* **Measurements:** *Willingness to participate in one of four possible research scenarios and to have a proxy-informed consent for AD research.* **Results:** *Overall, 65.8% agreed to participate in AD research and 70.7% agreed to proxy-informed consent. Relative to a minimal benefit and moderate risk scenario, participants were more likely to favor participation in a moderate benefit and minimal risk scenario and less likely to endorse a minimal benefit and severe risk scenario. Those agreeing to participate in the study were more likely to agree to proxy consent and to give leeway to a research proxy to go against their will.* **Conclusions:** *Most participants view AD research favorably and are agreeable toward participating in such research as well as toward having a research proxy. Participants are able to distinguish between studies of different levels of benefit and risk. Nevertheless, over 50% agreed to a study of minimal benefit and severe risk. Researchers and clinicians should be aware that those less agreeable toward AD research are less interested in having a research proxy.* (Am J Geriatr Psychiatry 2009; 17:65–74)

Key Words: Dementia, ethics, caregiving, decision-making, informed-consent

Alzheimer disease (AD) is a lethal condition affecting a large segment of the population of older adults.¹ Because of the changing demographics, it is expected that by 2050, the prevalence of AD will increase three-fold.² At the public level, the costs

of caring for individuals with AD are high and are expected to account for 40% of the Medicare budget by the year 2050.³ Yet, the emotional costs of AD are even higher with a majority of caregivers of persons with AD reporting high levels of burnout and de-

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pression.⁴ Providing care to a person with AD also is a substantial risk for increased morbidity and mortality among caregivers.⁵ Given these considerable public health consequences, research on the treatments and etiology of AD has expanded in the past few decades and is expected to continue and increase in size and magnitude until a cure for the disease is found. Yet, to date, neither the etiology nor the treatments of AD are well understood⁶ and the scientific community is expected to face extensive research tasks in years ahead.

When enrolling individuals in research studies, the first stage usually involves the assessment of decisional capacity.⁷⁻⁹ Unlike cognitively intact individuals, who are able to provide voluntary informed consent before their participation in research, many individuals with AD are unable to provide such consent due to impaired decisional capacity,¹⁰⁻¹⁴ whereas those at the moderate to severe stages of the disease are most susceptible to impaired decisional capacity, even individuals with mild cognitive impairment have an impaired capacity to consent to research.⁷⁻⁹ For those individuals who lack decisional capacity, proxy decision regarding research participation is the norm¹⁰ in studies of minimal risk or in studies of direct benefit to the individual.^{11,12} In addition to proxy consent patient's assent (i.e., voluntary cooperation with the study procedure) also is required.¹²

Although these guidelines are informative, they are considered to be insufficient for several reasons¹³; there is no clear consensus on how to measure decisional capacity¹⁴ or on how to define and measure assent capabilities.¹⁴ In addition, researchers have shown that proxies usually make research decisions to maximize patients' well being as opposed to a substituted judgment.¹⁵ Furthermore, the effectiveness of research advance directives has been questioned.¹⁶

Given the ongoing and increasing need for AD research and current unclear regulations concerning the involvement of individuals with impaired decisional capacity in research studies,¹³ understanding public opinions about involvement of cognitively impaired individuals in AD research is imperative and has the potential for public policy implications. To date, very few studies have directly evaluated attitudes toward research involving proxy-informed consent. The few studies conducted found that a

majority expressed an interest in participating in AD research should they lose their ability to consent.^{10,17,18} However, among individuals with cognitive impairment, those who had more impaired decisional capacity were less willing to participate in research.¹⁹ In addition, a majority viewed proxy-informed consent favorably, especially under low risk research scenarios, but support for proxy consent declined for more burdened and risky scenarios, with a substantial number of participants arguing that individuals who lack decisional capacity should not be enrolled in high-risk studies.^{10,17,18} Although informative, these studies focused either on at-risk populations, such as individuals with cognitive impairment or family members of individuals with AD,^{10,17,18} or on those most involved with such research, such as researchers in the aging field and Institutional Review Board (IRB) members.¹⁰ Hence, the present study provides complementary information by reporting the public view on research involving individuals with AD.

The overall goal of this study was to obtain descriptive data on public willingness to participate in AD research and public attitudes regarding proxy-informed consent. I also evaluated demographic and clinical characteristics that explain variations in such attitudes. Based on past research which has shown that ethnic minorities are less likely to participate in research,²⁰ I expected ethnic minorities to report less favorable attitudes toward participating in AD research, but had no prior hypothesis about ethnic differences in attitudes toward proxy-informed consent. In addition, given past research,¹⁹ I expected cognitive functioning to be the best predictor of proxy-informed consent with those of lower cognitive performance being less willing to participate in research and reporting a greater preference toward proxy-informed consent. Last, I expected those more willing to participate in AD research to report more favorable attitudes toward proxy-informed consent and to be more agreeable toward proxy decisions that go against their preferences.

METHODS

The Health and Retirement Study (HRS) is a randomly selected national sample of 23,000 individu-

als, 50 years and older, and their spouse of any age (Health and Retirement Study, [2006 Core, Early, V2.0] public use dataset. Produced and distributed by the University of Michigan with funding from the National Institute on Aging [grant number NIA U01AG009740], Ann Arbor, MI, 2007). Blacks, Latinos, and residents of the state of Florida are oversampled. The HRS is sponsored by the National Institute of Aging (grant number NIA U01AG009740) and is conducted by the University of Michigan. The study is reviewed and approved by the University of Michigan's Health Sciences IRB. Participants take part in a biennial interview that covers a range of topics including income, wealth, work, retirement, health, healthcare utilization, etc. Most interviews are conducted over the phone. All participants read a confidentiality statement and gave oral or implied consent by agreeing to participate in the interviews. Participants receive \$40 for their participation.

The present study focused on cross-sectional results from the year 2006. Because the present study relies on publicly available data, analysis was not subject to IRB review. Of the 18,469 respondents who completed the core interview in the year 2006, 14,399 agreed to answer additional questions and were randomized to one of 10 experimental modules. One of these modules evaluated attitudes about proxy-informed consent for participation in AD research. Overall, 1,517 respondents were randomized for participation in this module. Of these, 48 respondents younger than 50 were excluded from further analyses because individuals under 50 are not sampled randomly in the HRS. Proxy interview respondents were not eligible to participate in this module.

Measures

Outcome Variable

Willingness to Participate. Participants were first given information about AD and AD research, "AD is a brain disorder that usually affects old people. People with AD slowly lose their ability to think, to remember, and to perform daily tasks. Overtime, they become totally dependent on others. 4.5 million Americans have AD and there is no known cure. To find effective treatments, researchers need to study people with AD. But many people with AD are unable to make informed decisions about whether to

take part in research and it is not clear if such persons should be enrolled in research. We want to find out your opinions about research with people with AD who cannot make their own decisions." Participants were then randomized to receive one of four possible research scenarios. Scenarios varied based on their degree of risk versus benefit. See Table 1.

After scenario presentation participants were asked, "Suppose you wanted to give a close family member instructions for the future, in case you ever became unable to make decisions for yourself. Would you say you would want to participate in the study?" Response options were yes (1) or no (0). Those responding as do not know or refusing to answer ($N = 73$) were classified as no, as this is usually the case in real life.

Attitudes About Proxy-Informed Consent for Participation in Alzheimer Research. Participants were asked whether our society should allow their families to make the decision in their place, if they could not make their own decisions about being in studies like this one. Response options were yes (1) or no (0). Those responding as do not know or refusing to answer ($N = 54$) were classified as no, as this is usually the case in real life.

Leeway to Proxy. Participants were asked, "How much freedom or leeway would you give the close family member to go against your preference and instead [not enroll/enroll] you in the study?" Response options were no leeway,¹ some leeway,³ and complete leeway.⁵ Those responding as do not know or refusing to answer ($N = 61$) were classified as no leeway.

Predictors

Sociodemographic Variables. Age (50–60, 61–70, and >70), gender, education (primary, secondary, and tertiary), marital status (married, not married), and ethnicity (White, Latino, Black, and other) were gathered based on self-report.

Cognitive Functioning. Four tests (e.g., immediate- and delayed-word recall, subtraction, and backward count) were used to represent overall cognitive functioning. The tests were modeled after the Mini-Mental Status Examination, a standard geriatric dementia screen.^{21,22} The immediate- and delayed- recall tasks involved hearing a 10-item list of words and recalling the words immediately thereafter and 5 minutes later. Each recall task yields a score between 0 and 10,

TABLE 1. Willingness to Participate in Alzheimer Research and Attitudes Toward Proxy-Informed Consent Across Research Scenarios

	Research Scenario					Chi-square	df	p ^b
	Across Scenario Type (1,469) ^a	Minimal Benefit and Moderate Risk Scenario* (363)	Moderate Benefit and Minimal Risk Scenario (382)	Minimal Benefit and Severe Risk (366)	Implicit Benefit and Moderate Risk Scenario (358)			
Willingness to participate								
Yes (%)	65.8	66.5	76.4	53.3	66.1	44.4	3	<0.001
Willingness to have proxy								
Yes (%)	70.7	70.6	80.6	66.3	65.0	27.5	3	<0.001
Amount of leeway to proxy								
Not at all (%)	41.8	42.6	35.4	48.6	41.1	17.2	6	0.06
Moderate (%)	37.9	38.4	39.2	35.6	38.2			
Complete (%)	20.2	18.9	25.3	15.9	20.5			

*Minimal benefit and moderate risk scenario: "Researchers want to study the fluid that surrounds the brain in patients with Alzheimer. The fluid is removed by a process called a lumbar puncture. In a lumbar puncture, a doctor inserts a long needle through the lower back into the spinal canal. The patients are given numbing medicine but they may experience a small amount of pain. About 5% of patients get headaches that go away with Tylenol. About 1% get a severe headache that requires a procedure which involves inserting a needle into the lower back again. The study will not directly benefit these patients. But it may lead to better understanding of Alzheimer disease that may help future patients."

Moderate benefit and minimal risk scenario: "Researchers want to test a new drug to see how well it treats AD. One half of the subjects will receive the new drug, and the other half of the subjects will get a sugar pill (that has no drug in it). The subjects will be randomly assigned (by chance, like flipping a coin) to get either the drug pill or the sugar pill. The new drug can cause upset stomach in some people, and in rare cases, bleeding in the stomach. The study may benefit some of these patients if the drug proves to be safe and effective. On the other hand, the drug may not work and it has the risks that I mentioned."

Minimal benefit and severe risk: "Researchers are developing a vaccine for Alzheimer disease. It involves getting one shot every 3 months (for a total of five shots) and two lumbar punctures (in which a long, thin needle is inserted into the lower back to obtain fluid from the spinal canal). In a previous study, 18 out of 300 persons (or 6%) who got the vaccine developed brain inflammation. This brain inflammation caused one or more of the following symptoms: confusion, headache, sleepiness, vomiting, seizures, and difficulty with balance and speech. Seven of the 18 persons had permanent problems. However, in 60 out of 300 persons (or 20%), the vaccine seemed to help their symptoms slightly. Researchers have now changed the vaccine to try to make it safer. The vaccine may directly benefit some patients who enter this study. On the other hand, the vaccine may not work and could cause brain inflammation."

Implicit benefit and moderate risk scenario: "Researchers want to begin testing a treatment for AD where doctors insert genetic material (DNA) into the brains of Alzheimer patients using brain surgery. This is to be the first study of this kind involving humans and the main purpose is to test its safety in just a few people, before moving on to larger studies. One risk of brain surgery is a 1%–4% chance of bleeding into the brain. This is usually minor, but rarely it can cause serious harm. It is possible that gene transfer could make Alzheimer symptoms worse, cause brain tumors or cause brain inflammation. No one knows how likely these risks are."

^aNumber of unweighted observations per cell.

^bChi-square analyses were conducted to identify variability across scenario type.

with 10 representing perfect performance. The subtraction task requires subtracting seven from 100 five times. Score on this task ranges from 0 to 5, with five representing perfect performance. The backward count required counting backward from 20 to 10. Perfect performance is scored 1 and a failure is scored 0. Because scores are highly correlated with each other, I used a composite score ranging from 0 to 26.

Participants were asked whether a doctor has ever told them they have a memory disease. Those who said yes were coded as having a memory diagnosis (0 = no; 1 = yes).

A subjective indicator of cognitive functioning was based on participants' rating of their memory (excellent or very good = 1; good or fair or poor = 0).

Emotional Functioning. The CES-D is a common measure of depressive symptomatology that has been used in a variety of population-based study.²³ The HRS uses eight items from the CES-D to measure depressive symptomatology. A cutoff of three and higher was used to represent depression (1 = present) (0 = absent).²⁴

Participants were asked whether a doctor has ever told them they have emotional, nervous, or psychiatric problems (1 = yes) (0 = absent).

Physical Functioning. Participants were asked whether they received a medical diagnosis of different cardiovascular risk factors, including: high blood pressure, diabetes, heart condition, and stroke. A composite score was calculated to represent no cardiovascular risk factors (0) versus at least one risk factor.¹

Impairment in activities of daily living was dichotomized to represent no impairment (0) versus at least one impairment.¹

Analysis

I first ran univariate and bivariate descriptive statistics of all variables. Next, I ran two separate logistic regression analyses with the following two outcomes: a) willingness to participate in the study and b) willingness to have a proxy consent. The third analysis was an ordinal regression analysis with amount of leeway one would give a proxy as the outcome. To test the hypotheses of the present study, ethnicity and cognitive functioning were entered into all three regression analyses as potential predictors. For the latter two analyses, willingness to participate in the study also was entered as a potential predictor. Age, gender, education, and scenario type were entered into all regression analyses as covariates. All other potential predictors (e.g., physical functioning, emotional functioning, marital status) were entered into the model only if bivariate relationship between them and the relevant outcome variable yielded a $p < 0.2$.²⁵ In interpreting multivariate results, because of the large sample size and the multiple comparisons, a more conservative estimation of $p < 0.01$ is used to indicate statistical significance. All analyses were clustered, stratified, and weighted to account for sampling design. All analyses were conducted using STATA intercooled 8.

RESULTS

Descriptive Statistics

See Table 1. Overall, 65.8% said they would agree to participate in the research scenario described to them and 70.7% agreed to have a proxy-informed consent. Twenty percent of respondents stated they

would give their family members complete leeway to go against their preferences and 37.9% stated they would give some leeway. Scenario type was associated with willingness to participate in research and to have a research proxy.

The largest age group was between 50 and 60 and women constituted 57.8% of the sample. A vast majority was White, followed by Black, Latino, and "other." The majority of the sample had secondary level of education or higher. See Table 2 for details.

Logistic Regression Results for Willingness to Participate in Alzheimer Research

In addition to those variables that were selected a priori (e.g., age, gender, education, ethnicity, cognitive functioning, and scenario type), I entered physical functioning into this model. There was no evidence of multicollinearity among covariates. Table 3 summarizes the results. Using a $p < 0.01$ criterion for statistical significance, the only significant predictor of willingness to participate in research was scenario type. Participants were more likely to endorse the moderate benefit and minimal risk scenario and less likely to endorse the minimal benefit and severe risk scenario relative to a minimal benefit and moderate risk scenario.

Logistic Regression Results for Willingness to Have a Proxy-Informed Consent

In addition to those variables that were selected a priori, depression, as evaluated by the CES-D also was entered into this model. Using a $p < 0.01$ criterion for statistical significance, the only significant variable was agreeing to participate in research. The odds of agreeing to a research proxy were 9.42 higher for those who had agreed to participate in research relative to those who had refused. See Table 3.

Ordinal Regression Results for Leeway to Proxy

In addition to those variables that were selected a priori, marital status, depression, and cardiovascular risk were entered into this model. As shown in Table 3, the only significant predictor was whether or not one had agreed to participate in research. Those agreeing to participate in the research study also

TABLE 2. Demographic and Clinical Characteristics of the Sample by Willingness to Participate and Have a Proxy^a

	Willingness to Participate					Willing to Have a Proxy					Amount of Leeway						
	Overall Sample (1,469) ^b	Willing to Participate (928)	Refuse to Participate (541)	Chi-square/ F-statistics	df	p	Willing to Have a Proxy (1,031)	Refuse to Proxy (438)	Chi-square/ F-statistics	df	p	Not at all (628)	Moderate (532)	Complete (309)	Chi-square/ F-statistics	df	p
Sociodemographic variables ^c																	
Age				4.0	2	0.29			6.5	2	0.20				5.2	4	0.53
50–60 (%)	40.7	42.5	37.2				41.8	38.1				40.3	43.4	36.6			
61–70 (%)	30.7	30.2	31.6				28.7	35.5				32.3	28.6	31.2			
>70 (%)	28.4	27.2	30.9				29.4	26.2				27.2	27.9	32.0			
Gender				12.8	1	0.003			10.7	1	0.02				0.60	2	0.78
Female (%)	57.8	54.5	64.2				55.1	64.2				57.0	59.0	57.1			
Education				11.9	2	0.008			7.2	2	0.12				8.04	4	0.16
Primary (%)	2.4	2.0	3.2				2.2	2.9				3.6	1.2	2.0			
Secondary (%)	48.8	46.2	54.0				46.9	53.6				49.4	48.1	49.2			
Tertiary (%)	48.6	51.7	42.7				50.8	43.3				46.8	50.5	48.6			
Marital status				0.87	1	0.42			2.31	1	0.24				7.8	2	0.05
Married (%)	64.9	65.8	63.3				66.1	62.0				61.1	66.7	69.6			
Ethnicity				15.7	3	0.009			1.73	3	0.65				12.1	6	0.21
White (%)	81.7	84.2	76.9				82.1	80.5				78.8	83.2	84.9			
Latino (%)	6.3	5.4	7.9				5.9	7.1				8.3	4.4	5.6			
Black (%)	10.4	9.3	12.2				10.4	9.9				10.6	10.9	8.4			
Other (%)	1.6	0.9	2.8				1.4	2.1				2.1	1.4	0.9			
Cognitive functioning																	
Cognitive performance (range: 0–26)	14.1 (0.15)	14.3 (0.19)	13.6 (0.24)	5.3	1,56	0.02	14.1 (0.18)	14.1 (0.24)	0.0	1,56	0.95	13.7 (0.24)	14.4 (0.26)	14.2 (0.30)	2.65	1,56	0.10
Subjective memory				2.34	1	0.16			7.44	1	0.02				12.4	2	0.01
Excellent/very good (%)	29.3	30.6	26.8				31.4	24.3				26.9	27.6	37.5			
Memory diagnosis				0.93	1	0.46			0.68	1	0.56				6.82	2	0.08
Yes (%)	1.2	1.4	0.8				1.4	0.8				1.4	0.4	2.5			
Emotional functioning																	
CESD ≥3 (%)	22.3	21.8	23.3	0.42	1	0.54	23.6	19.0	3.84	1	0.06	25.1	19.3	22.2	5.81	2	0.17
Emotional diagnosis				0.14	1	0.74			0.16	1	0.75				1.56	2	0.56
Yes (%)	17.9	17.6	18.4				18.2	17.3				19.1	17.7	15.8			
Physical functioning																	
Cardiovascular risk				2.04	1	0.13			1.64	1	0.26				6.99	2	0.11
Yes (%)	63.4	62.2	65.9				62.4	65.9				66.8	59.5	63.9			
ADL impairment				3.52	1	0.14			0.62	1	0.55				0.39	2	0.87
Yes (%)	15.5	14.3	17.9				16.0	14.4				16.2	15.1	14.9			

^aThis table reports aggregated results across all four scenarios.
^bNumber of unweighted observations per cell.
^cResults are reported as percentage for categorical variables and as mean (SD) for continuous variables.

^aThis table reports aggregated results across all four scenarios.

^bNumber of unweighted observations per cell.

^cResults are reported as percentage for categorical variables and as mean (SD) for continuous variables.

TABLE 3. Multivariate Models of Willingness to Participate in AD Research, Willingness to Have a Research Proxy, and Amount of Leeway Given to Proxy (n = 1,469)

	Predictors of Willingness to Participate in AD Research ^a			Predictors of Willingness to Have a Proxy-Informed Consent ^b			Predictors of Amount of Leeway Given to Proxy Decision ^c		
	OR	95% CI	p ^d	OR	95% CI	p	Beta	Standard Error	p
Sociodemographic variables									
Age									
50–60									
61–70	0.94	0.62–1.43	0.80	0.83	0.53–1.31	0.43	0.11	0.18	0.54
>70	0.91	0.59–1.40	0.68	1.24	0.79–1.93	0.32	0.37	0.16	0.03
Gender									
Male (reference)									
Female	0.70	0.52–0.92	0.01	0.81	0.55–1.21	0.31	0.27	0.13	0.04
Ethnicity									
White (reference)									
Latino	0.63	0.39–1.03	0.06	1.13	0.61–2.07	0.68	–0.23	0.35	0.51
Black	0.75	0.52–1.09	0.14	1.41	0.87–2.29	0.15	0.20	0.19	0.30
Other	0.32	0.10–1.05	0.06	1.30	0.39–4.27	0.65	0.13	0.55	0.80
Education									
Primary (reference)									
Secondary	0.94	0.47–1.89	0.87	1.30	0.45–3.72	0.61	0.44	0.29	0.13
Tertiary	1.15	0.55–2.32	0.69	1.57	0.52–4.79	0.41	0.22	0.31	0.47
Marital status									
Not married (reference)									
Married	—	—	—	—	—	—	0.38	0.15	0.01
Cognitive functioning									
Cognitive performance (range: 0–26)	1.01	0.98–1.05	0.31	0.98	0.95–1.01	0.35	0.01	0.01	0.35
Subjective memory Good/fair/poor (reference)									
Excellent/very good	1.06	0.81–1.38	0.63	1.44	1.00–2.06	0.04	0.34	0.14	0.02
Memory diagnosis No (reference)									
Yes	2.10	0.47–9.32	0.31	1.13	0.34–3.74	0.83	0.40	0.78	0.60
Emotional functioning									
CES-D <3 (reference)									
CES-D ≥3	—	—	—	1.59	1.07–2.36	0.02	–0.04	0.18	0.82
Physical functioning									
Cardiovascular risk No (reference)									
Yes	0.91	0.71–1.18	0.50				–0.13	0.13	0.32
Activities of daily living Not impaired (reference)									
Impaired	0.84	0.57–1.24	0.38	—	—	—	—	—	—
Scenario									
Minimal benefit and moderate risk (reference)									
Moderate Benefit and Minimal Risk	1.64	1.22–2.29	0.002	1.48	0.91–2.42	0.11	0.19	0.17	0.27
Minimal benefit and severe risk	0.58	0.40–0.84	0.005	1.13	0.71–1.80	0.57	–0.01	0.20	0.95
Implicit benefit and moderate risk	1.01	0.71–1.44	0.91	0.74	0.47–1.18	0.20	0.10	0.20	0.59
Willingness to participate in Alzheimer research									
No (reference)									
Yes	—	—	—	9.42	7.31–12.14	<0.001	2.04	0.14	<0.001

^aLogistic regression. $F(16,41) = 4.19$, $p < 0.001$.
^bLogistic regression analysis. $F(16,41) = 21.81$, $p < 0.001$.
^cOrdinal logistic regression. $F(18,39) = 13.7$, $p < 0.001$.
^dBased on Wald Chi-square tests with 1 *df*.

were more likely to give leeway to proxy to go against their wish relative to those who refused.

DISCUSSION

The present study is the first national study to evaluate attitudes about participation in AD research and research proxy. A majority of respondents were willing to participate in AD research and even a larger number of participants were willing to accept a research proxy. Hence, current regulations that allow older adults with AD to participate in research and the practice of research proxy are endorsed by the general public. The results also demonstrate that participants are able to distinguish between studies of different risk and benefit. They have a preference toward studies that could potentially provide direct benefits and a dislike toward studies of severe risk.

Nevertheless, in the present study, more than 50% of respondents were willing to participate in a research scenario of severe risk and minimal benefit. This hypothetical research scenario was inspired by the A β 42 immunization trial that was prematurely terminated after reports of meningoencephalitis.²⁶ Despite the disturbing consequences of this particular study as well as others and the requirement to employ more stringent risk-benefit analysis in research involving individuals with impaired capacity,^{12,13} there are still ongoing efforts to develop a vaccine for AD²⁷ and other AD treatments.²⁸ Further, it is possible that at least some of these efforts will result in unfortunate consequences, such as the ones described above.²⁶ This ongoing tension between the ethical principle of nonmaleficence (i.e., do not inflict harm intentionally) versus the principle of beneficence (i.e., contribute to one's welfare)²⁹ are manifested by the dedication of the scientific community, individuals with AD, and their caregivers toward finding a cure for AD through continued clinical trials. It is, however, important to note that in contrast to the A β 42 immunization trial,²⁶ in which the exact risk-benefit analysis was not well established before the conduct of the study, in the present study, the risk-benefit analysis was explicitly presented to participants with over 50% of them still agreeing to this hypothetical trial of severe risk and minimal benefit. Hence, the present results re-emphasize the important role that IRBs and researchers alike should

play in protecting the safety not only of individuals with impaired decisional capacity but also of the general public.

The most prominent predictor of willingness to have a proxy-informed consent and for the amount of leeway provided to proxy to go against respondent's preference was whether or not one had agreed to participate in AD research. Currently, there is no clear consensus as to who can serve as a research proxy and under what circumstances research with individuals with impaired decisional capacity should never be conducted.^{10,12} Given the present results, this study raises the question of whether those who had not assigned a research proxy in advance should even be enrolled in AD research.

The standard of substituted judgment that requires a proxy to make the same decision the individual with impaired decisional capacity would have made had he or she been competent²⁹ is most accepted in guiding proxy decision.¹² Yet, in the present study, over a quarter of the sample had agreed to a proxy decision that completely contradicted their research preferences. These results are somewhat consistent with Karlawish et al.¹⁵ who found that the standard of substitute judgment is in disagreement with the view of individuals who currently participate in AD clinical trials. Unfortunately, the present study failed to evaluate public opinion regarding other ethical standards that could guide proxy decision, such as the standard of best interest.²⁹

Unexpectedly, there were no ethnic differences in terms of willingness to participate in research or to have a research proxy. This is surprising given the well-documented lack of representation of ethnic minorities in research studies.²⁰ In the present study, respondents were presented with hypothetical research scenarios. Many factors, such as transportation, lack of financial resources, lack of trust in the medical system, perceived discrimination, or lack of knowledge may hamper the actual research participation of ethnic minorities in real life. These factors are not accounted for in hypothetical case scenarios such as these. Also, sampling bias could be present, such that minorities more willing to participate in research, in general, were more likely to participate in the HRS in the first place.

The present study does not go without limitations and, in many ways, raises more questions than an-

swers. As already stated, the study is based on a hypothetical case scenario and responses may not reflect real-life behaviors. In addition, the scenarios had failed to address the issue of life expectancy, even though one's willingness to engage in higher risk research may increase as life expectancy decreases. The study also neglected the issue of assent—a major factor in the involvement or lack of involvement of individuals with decisional impairment in research studies.¹² By neglecting this topic, the study fails to answer questions such as whether dissent sufficient? Should active assent be required? And what defines a meaningful assent? Further, the hypothetical research scenarios did not systematically vary in terms of degree of risk and benefit and the differentiation between these scenarios was not clear-cut. Nevertheless, it is important to note that this is often the case in real-life, where a clear classification of risks and benefits is equivocal even among IRB members.³⁰ Second, the present study was limited to those who were cognitively capable of participating in the interview and, thus, those individuals with severe impairments were excluded from the study. Hence, this study may fail to bring the opinions of those individuals with cognitive impairment who are the ones most affected by these

regulations. Finally, the study did not evaluate other factors that could potentially impact one's attitudes toward proxy consent, such as the quality of family relationship, or whether a respondent had a family member with AD.

Nevertheless, this study is the first national sample to evaluate public attitudes toward AD research. Results show that a vast majority views AD research favorably and is agreeable both toward participating in such research as well as toward having a research proxy. The study also demonstrates that the public is capable of distinguishing between studies of different levels of risk and benefit, yet, is agreeable even toward a study of minimal benefit and severe risk. Finally, clinicians should be aware that those who are less agreeable toward AD research also are less interested in having a proxy or in giving leeway to proxy to go against their will. Hence, the importance of obtaining the assent and cooperation of individuals with dementia cannot be overstated.

Health and Retirement Study, public use dataset (Core Early V2.0, September, 2007). Produced and distributed by the University of Michigan with funding from the National Institute on Aging (grant number NIA U01AG009740), Ann Arbor, MI.

References

1. Plassman BL, Langa KM, Fisher GG, et al: Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology* 2007; 29:125–132
2. Hebert LE, Scherr PA, Bienias JL, et al: Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Arch Neurol* 2003; 60:1119–1122
3. Saving lives, saving money: dividends for Americans investing in Alzheimer research. A report commissioned by the Alzheimer's Association, Washington DC, The Lewin Group, 2004
4. Clyburn LD, Stones MJ, Hadjistavropoulos T, et al: Predicting caregiver burden and depression in Alzheimer's disease. *J Gerontol B Psychol Sci Soc Sci* 2000; 55:S2–S13
5. Schulz R, Beach SR: Caregiving as a risk factor for mortality: the Caregiver Health Effects Study. *JAMA* 1999; 282:2215–2219
6. Hardy J, Selkoe DJ: The amyloid hypothesis of Alzheimer's disease: progress and problems on the road of therapeutics. *Science* 2002; 297:353–356
7. Warner J, McCarney R, Griffin M, et al: Participation in dementia research: rates and correlates of capacity to give informed consent. *J Med Ethics* 2008; 34:167–170
8. Okonkwo O, Griffith HR, Belue K, et al: Medical decision-making capacity in patients with mild cognitive impairment. *Neurology* 2007; 69:1528–1535
9. Marson DC, Ingram KK, Cody HA, et al: Assessing the competency of patients with Alzheimer's disease under different legal standards. A prototype instrument. *Arch Neurol* 1995; 52:949–954
10. Bravo G, Paquet M, Dubois M-F: Opinions regarding who should consent to research on behalf of an older adult suffering from dementia. *Dementia* 2003; 2:49–65
11. Report from NHRPAC on informed consent and the decisionally impaired, National Human Research Protections Advisory Committee, 2002
12. Kim SYH, Karlawish JHT, Caine ED: Current state of research on decision-making competence of cognitively impaired elderly persons. *Am J Geriatr Psychiatry* 2002; 10:151–165
13. Kim SY, Appelbaum PS, Jeste DV, et al: Proxy and surrogate consent in geriatric neuropsychiatric research: update and recommendations. *Am J Psychiatry* 2004; 161:797–806
14. 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
15. Karlawish J, Kim SYH, 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
16. Stocking CB, Hougham GW, Danner DD, et al: Empirical assessment of a research advance directive for persons with dementia and their proxies. *J Am Geriatr Soc* 2007; 55:1609–1612
17. Wendler D, Martinez RA, Fairclough D, et al: Views of potential subjects toward proposed regulations for clinical research with adults unable to consent. *Am J Psychiatry* 2002; 159:585–591
18. Kim SY, Kim HM, McCallum C, et al: What do people at risk for

- Alzheimer disease think about surrogate consent for research? *Neurology* 2005; 65:1395-1401
19. Kim SY, Cox C, Caine ED: Impaired decision-making ability in subjects with Alzheimer's disease and willingness to participate in research. *Am J Psychiatry* 2002; 159:797-802
 20. Moreno-John G, Gachie A, Fleming CM, et al: Ethnic minority older adults participating in clinical research: developing trust. *J Aging Health* 2004; 16:93S-123S
 21. Folstein MF, Folstein SE, McHugh PR: "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12:189-198
 22. Brandt JS, Miriam; Folstein, Marshal: The telephone interview for cognitive status. *Neuropsychiatry Neuropsychol Behav Neurol* 1988; 1:111-117
 23. Radloff LS: The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas* 1977; 1:385-401
 24. Steffick DE: Documentation of affective functioning measures in the health and retirement study, HRS documentation report DR-005, 2000
 25. Hosmer DW, Lemeshow, S: *Applied Logistic Regression*. 2nd ed. New York, NY, John Wiley, 2000
 26. Orgogozo JM, Gilman S, Dartigues JF, et al: Subacute meningo-encephalitis in a subset of patients with AD after Abeta42 immunization. *Neurology* 2003; 61:46-54
 27. Okura Y, Matsumoto Y: DNA vaccine therapy for Alzheimer's disease: present status and future direction. *Rejuvenation Res* 2008; 11:301-308
 28. Fleisher AS, Raman R, Siemers ER, et al: Phase 2 safety trial targeting amyloid beta production with a gamma-secretase inhibitor in Alzheimer disease. *Arch Neurol* 2008; 65:1031-1038
 29. Beauchamp TL, Childress, JF: *Principles of biomedical ethics* 5th ed. Oxford University Press, 2001
 30. Shah S, Whittle A, Wilfond B, et al: How do institutional review boards apply the federal risk and benefit standards for pediatric research? *JAMA* 2004; 291:476-482