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Temporal Stability of Receptiveness to Clinical Research on Alzheimer's disease

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Abstract

Research advance directives are a proposed mechanism for ensuring that decisions regarding research participation adhere to preferences voiced by persons with Alzheimer's disease (AD) prior to losing decisional capacity. While this approach rests on the assumption that preferences regarding research participation are consistent over time, little is known about the stability of such preferences. The purpose of this study was to evaluate the temporal stability of older adults' receptiveness to participation in clinical trials, neuroimaging studies, and psychosocial investigations on AD. One hundred and four participants in the University of Pittsburgh Alzheimer Disease Research Center (ADRC) were annually surveyed regarding their willingness to be contacted regarding clinical drug trials, neuroimaging studies, and psychosocial research for which they might be eligible. Receptiveness to contact regarding AD research was compared at two time points, one year apart. At baseline, most respondents were willing to be contacted regarding their eligibility for drug trials, imaging studies, and psychosocial research. Thirty-seven percent of respondents voiced a different set of preferences at Year 2 as compared to Year 1. Differences included both increased and decreased willingness to be contacted. Neither stability of preferences nor direction of change (more vs. less willing) varied by diagnostic group. Bivariate analyses revealed that participation in at least one ancillary research study was associated with an overall increase in willingness to be contacted. We conclude that a significant proportion of research-friendly individuals voice different sets of preferences regarding the possibility of research participation when queried at different points in time. Amenability to participating in clinical research on AD is a relatively dynamic personal attribute that may be influenced by personal experience with research participation. This finding has relevance for the policy debate around research advance directives, an approach which assumes that preferences regarding research participation are consistent over time.

Keywords

Alzheimer's disease; research ethics; human subjects protection; research advance directives

INTRODUCTION

The burgeoning demand for and soaring costs associated with dementia care make Alzheimer's disease (AD) a top priority for the federal research agenda¹ and a major focus of industry-sponsored neuropharmacological development.² While there is a clear need to involve large and representative pools of individuals into clinical research on AD, the recruitment of such persons is complicated by numerous factors including concerns about multiple medical comorbidities, questions of decisional capacity³⁻⁵ and the issue of involving participants' family members in enrollment decisions.^{6,7} Indeed, very few individuals with AD ever become involved in clinical research and those who do volunteer for research rarely remain involved for the duration of their illness.⁸

Interactions between study recruiters and potential participants are especially challenging given that specific neuropsychological deficits in the domains of memory and language can make it difficult for an AD-affected individual to understand, recall, or discuss with others information that may be conveyed during a research recruitment exchange. Because such deficits can undermine the authenticity of informed consent, many studies have sought to a) identify reliable methods of determining whether or not an individual can autonomously consent to research⁹⁻¹², and b) determine how enrollment decisions should be made when one lacks the capacity to consent.¹³⁻¹⁶ Regarding the latter, research advance directives are a proposed mechanism for ensuring that decisions regarding AD research participation adhere to preferences voiced by patients prior to losing decisional capacity.¹⁷ While this approach rests on the assumption that preferences regarding research participation are consistent over time, little is known about the stability of such preferences. The purpose of the current investigation, therefore, was to evaluate the temporal stability of older adults' receptiveness to participation in various types of clinical research on Alzheimer's disease.

METHODS

Between January 1, 2006 and February 1, 2008, participants of the University of Pittsburgh Alzheimer Disease Research Center (ADRC) were queried regarding their willingness to be contacted regarding ancillary research projects for which they might be eligible. This longitudinal analysis aims to characterize the nature and stability of such preferences over time. The University of Pittsburgh Institutional Review Board approved this secondary analysis of research preferences and waived the requirement for written informed consent.

Overview of ADRC Procedures

All ADRC subjects provide written informed consent or assent (with proxy authorization) upon initial presentation to the Center. A description of the baseline multidisciplinary ADRC clinical research evaluation has been published previously.¹⁷ Once enrolled, Center participants undergo annual neurological, psychiatric, and neuropsychological evaluations. Depending on interest and eligibility, ADRC participants may, over the course of their involvement with the Center, also choose to participate in clinical drug trials, neuroimaging studies, psychosocial research, and other studies, above and beyond their involvement with the ADRC. Annual checks of receptiveness to being contacted for these types of ancillary studies are one of several mechanisms for procuring ongoing consent to involvement in the Center.

Sample

ADRC participants include individuals with diagnoses of Alzheimer's disease and related cognitive disorders as well as normal control subjects. Following a standardized dementia evaluation¹⁸, each case is discussed at a Consensus Conference meeting where diagnostic

criteria are applied to determine the presence or absence of Alzheimer's disease¹⁹ or another form of dementia. A diagnosis of mild cognitive impairment (MCI) may be applied to individuals who have subjective cognitive complaints and score in the mildly impaired range on neuropsychological testing, but whose deficits are not severe enough to qualify for a clinical diagnosis of dementia.²⁰ Control subjects are individuals who are recruited from the community to serve as healthy study volunteers. Control subjects have neither subjective nor objective evidence of cognitive impairment at the time of presentation to the ADRC. All subjects and controls must have a study partner (e.g., spouse, sibling, child or close friend) who has frequent interaction with them and can independently report on their functioning.

Research Preferences

Four to six weeks following the baseline cognitive evaluation, ADRC participants and their family members meet with a study team neurologist and a social worker to discuss the final diagnostic impression. At that time, participants are provided with treatment recommendations and given basic information about ongoing and anticipated clinical research studies involving ADRC investigators. It is explained to participants that the bulk of clinical research at the ADRC falls into 1 of 3 categories: randomized controlled trials (RCT), neuroimaging studies, and psychosocial investigations. Participants are then asked whether, during the next 12 months, they would like to be contacted about research studies falling into each category (RCT, imaging, psychosocial research), if a basic screening of their registry data indicates that they may be eligible. Responses are elicited in a yes/no fashion for each type of research, with the understanding that a willingness to be contacted implied receptiveness to such a study at a general level and will not be treated as a research advance directive. Formal assessments of participants' decisional capacity are viewed as decision specific and are not conducted as part of the general assessment of research preferences. The assessment of research preferences is repeated at 12-month intervals. As with baseline, these assessments follow the disclosure of updated diagnostic impressions and clinical treatment recommendations.

Analytic Approach

We used basic descriptive statistics to characterize participants' clinical and sociodemographic features and research preferences. Kappa values were calculated to test concordance of stated preferences at assessment years one and two. Characteristics of preference changers were compared to non-changers using ANOVA and Chi-square analyses as appropriate. Bivariate analyses were conducted to identify correlates of overall willingness to be contacted at Year 2.

RESULTS

Sample Characteristics

One hundred and four participants completed both baseline and one-year follow-up assessments of research preferences. Of these, 63 had a diagnosis of Alzheimer's disease or other dementia, 31 met diagnostic criteria for MCI, and 10 had no cognitive disorder. More than half (n = 60; 58%) were women and the vast majority (n = 102; 98%) were Caucasian. The average age of participants was 76 years (range 54–94 years old); the average age of primary family members/study partners was 70 years (range 45–92 years old). In 67% of these cases (n = 70), the participant's primary family member was a spouse and in 22% of cases (n = 23), participants were accompanied to the research center by an adult child. The remaining participants were accompanied by a sibling (n=2), other relative (n=1), friend or neighbor (n=1), or "other" individual (n=2). None was accompanied by a paid caregiver. In most cases (n=79; 76%), ADRC participants lived with the individual who accompanied them to the Center. On average, participants had 14 years (range 8–22 years) and family

members/study partners had 15 years (range 10–22) of formal education. Nearly half of the ADRC participants ($n=48$; 46%) reported having a family history of dementia. Of note, demographic data for family members were missing in 5 cases.

Overall Willingness to be Contacted

At baseline, most ADRC participants were willing to be contacted regarding potential opportunities to participate in clinical research on AD; and, willingness to be contacted increased as the general level of risk associated with a given research category decreased. Specifically, 77% of respondents were willing to be contacted regarding their eligibility for RCT studies, 78% for imaging studies, and 87% for psychosocial research studies. At Year 2, over one third of respondents voiced a different set of preferences as compared to Year 1. As shown in Table 1, changes in preference included both increased and decreased willingness to be contacted for research participation.

Sociodemographic and Clinical Factors

To identify potential correlates of change in participants' preferences over time, we examined whether various sociodemographic or clinical factors were associated with the presence of *any change* in a given respondent's set of preferences for being contacted. Research preference sets (e.g., yes-no-no to contact for RCT, imaging, and psychosocial research, respectively) that were identical from Year 1 to Year 2 were categorized as unchanged, while a discrepant response regarding any of the 3 types of research was categorized as a changed preference set. As shown in Table 2, ANOVA and Chi-square analyses showed no differences between preference changers and non-changers in terms of gender, or on such clinical factors as: cognitive diagnosis, family history of dementia, global cognitive functioning, or disease progression.

Those who changed their preferences regarding RCT's differed from non-changers on the variable of age. Additional scrutiny of the data revealed that older individuals were more likely to voice a different preference (either increased or decreased willingness for contact) regarding RCT's at Year 2, than were younger individuals. Secondly, our comparison of preference changers to non-changers (Table 2) showed that, in the case of neuroimaging research, there were between group differences in average years of education. Having more years of formal education was associated with having stable, or unchanging, preferences for contact regarding neuroimaging research.

Additional analysis showed that 35% ($n = 16$) of participants with 12 or fewer years of education voiced a different preference for contact regarding neuroimaging research at Year 2, compared to only 12 % ($n = 7$) of those with 13 or more years of education ($X^2 = 7.7$; $df = 3$; $p = .05$). Of the 16 preference changers with 12 or fewer years of education, 10 were more willing and 6 were less willing to be contacted regarding neuroimaging studies at Year 2 as compared to Year 1.

Personal Experience with Clinical Research

Scrutiny of ancillary study tracking data indicate that individuals in the current sample participated in an average of one clinical research study ($M = 1.16$; $SD = 1.43$). While participation in an ancillary study was not associated with change in willingness to be contacted [$X^2 = .501$, $df = 1$, $p = .479$], there was a positive association between enrollment in at least one clinical research study and overall willingness to be contacted regarding other studies at Year 2 ($F = 4.88$, $p = .029$).

DISCUSSION

This study evaluated the temporal stability of research preferences in a sample of research-friendly individuals who have a reasonable likelihood of being recruited for clinical research on Alzheimer's disease or related disorders (ADRD) during the course of their dementia or normal cognitive aging trajectory. We found that while a majority of older adults with and without cognitive impairment hold stable preferences regarding willingness to be contacted for research participation, many do not. Over one-third of respondents voiced a different set of preferences for being contacted about opportunities for research participation at Year 2 as compared to Year 1. Differences included both increased and decreased willingness to be contacted.

It should be noted that the present study evaluated only the stability of individuals' willingness to being contacted about various types of research and did not evaluate the stability of preferences regarding current or future research enrollment. Receptiveness to clinical research is a broad construct that, in our view, serves as a conceptual antecedent to enrollment decision-making. That is, only those who are receptive to the idea of research participation will go on to engage, or have their proxies engage, in enrollment decisions. Enrollment decision-making may occur either in advance (as in the case of a research advance directive) or in real-time and is associated with strict requirements for capacity assessment.

Understanding Changes in Preference Sets

Commentators who acknowledge that research preferences may fluctuate or change over one's course of dementia, generally do so out of concern that later course expressions of preference by persons with dementia will be erratic and/or may conflict with statements made when cognitive functioning was less, or not all, impaired.²¹ Interestingly, our data fail to support a link between cognitive functioning and stability of research preferences. The mean Year 2 MMSE score of those voicing any change in their willingness for contact was 20; a value which, in other studies has been associated with a reasonable likelihood of being decisionally intact upon formal assessment.²² In the current study, individuals with and without cognitive disorders were equally likely to change their preference profiles at Year 2; and, changes in preference were not associated with a worsening of cognitive functioning. Our findings that being younger and more highly educated may influence the stability of one's research preferences did not hold across all three types of research, but nevertheless raise interesting questions that merit further exploration.

We found that participating in clinical research is positively associated with openness to doing so again in the future. There are many other mechanisms by which one's openness to participation in clinical research might change over time. In the context of dementia, the related notions of symptom progression and increased suffering or burden of illness, may lead a formerly research-averse patient, or her proxy, to consider research participation, especially when the study carries clear potential to directly benefit participants. At the same time, increasing perceptions of hopelessness, or an overwhelming degree of illness-associated or general medical burden, may lessen one's willingness to assume the burdens associated with research participation.²³ Finally, it is possible that the changes in research receptiveness reported herein merely reflect ambivalence toward research participation and do not stem from explicit deliberation about research participation (e.g., risk/benefit analysis) and/or reflection upon core personal values.

Each of the above possibilities is problematic for programs and policies that would encourage the widespread adoption of research advance directives for enrollment decision-making among populations affected by fluctuating or deteriorating cognition. During real-

time research recruitment and informed consent processes, learning details about an individual study may prompt meaningful deliberation within an individual who has previously been ambivalent. Yet, in the context of research advance directives, preference statements are based on general descriptions of what participation in certain types of research may entail.²⁴ While these descriptions should be more detailed than the above-described overviews that were provided to ascertain receptiveness to research participation, there are significant limitations to the degree of detail that can be disclosed about studies which either have yet to be designed and/or may be implemented under a nearly unknowable array of clinical circumstances.²⁵ Our finding that receptiveness to clinical research may change over time suggests that decisionally intact individuals should periodically update statements concerning their preferences for future research participation.

Limitations

Our sample lacked racial and ethnic diversity. Another limitation of this retrospective analysis was our inability to examine the decision-making processes that led to the expressions of willingness for contact on which we report. Discussions of the current study with ADRC social workers revealed that in all instances participants and their family members *together* answered questions concerning research preferences in a manner consistent with the shared decision-making practice seen in clinical care. While mirroring “real world” practices may be viewed as a strength of this report, our inability to probe patients and their study partners regarding their decision-making practices raises important questions about the extent to which patients’, versus study partners’, preferences drove responses to our queries regarding willingness to be contacted.

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Table 1

Stability of Research Preferences by General Category Over Time

	Randomized Controlled Trials		Neuroimaging Studies		Psychosocial Research	
	No (Yr 1)	Yes (Yr 1)	No (Yr 1)	Yes (Yr 1)	No (Yr 1)	Yes (Yr 1)
No (Yr 2)	14	13	10	10	3	9
Yes (Yr 2)	10	67	13	71	10	82

Note: Yr = year; Bold text denotes total number of participants in disagreement from Year 1 to Year 2; Kappa for agreement in preferences regarding RCTs = .403; Neuroimaging studies = .327; Psychosocial Research = .136

Table 2
Demographic and Clinical Characteristics of Research Preference Changers and Comparison to Non-Changers*

Characteristic	Change in willingness to be contacted for RCT (n=23)	F or $\chi^2(df)$	Change in willingness to be contacted for neuroimaging research (n=23)	F or $\chi^2(df)$	Change in willingness to be contacted for psychosocial research (n=19)	F or $\chi^2(df)$	Any change in overall preference set (n=37)
Mean Age in Years (Range)							
Participant	79 (66–94)	4.93	76 (54–94)	1.00	76 (54–86)	0.65	77 (54–94) 1.90
Partner	69 (53–89)	0.40	70 (53–89)	0.02	70 (45–87)	0.02	69 (45–89) 0.19
Female Gender (#, %)							
Participant	12 (52)	0.37 (1)	14 (61)	0.12 (1)	10 (53)	0.24 (1)	20 (54) 0.31 (1)
Partner	14 (61)	0.58 (1)	13 (57)	0.15 (1)	12 (63)	0.15 (1)	23 (62) 0.56 (1)
Mean Years of Education (Range)							
Participant	14 (9–20)	0.30	13 (8–20)	6.16	14 (11–20)	0.03	14 (8–20) 0.25
Partner	14 (10–20)	2.95	14 (10–20)	3.67	14 (12–20)	2.89	14 (10–20) 2.00
Baseline Diagnosis (#, %)							
No cognitive disorder	3 (13)	0.48 (2)	3 (13)	0.65 (2)	3 (16)	1.23 (2)	4 (11) 0.47 (2)
Mild cognitive impairment	6 (26)		5 (22)		5 (26)		11 (30)
ADRD	13 (57)		14 (61)		10 (53)		21 (57)
Conversion to Dementia Diagnosis at Follow-Up (#, %)	5 (22)	0.41 (1)	5 (22)	0.41 (1)	6 (32)	3.31 (1)	8 (22) 0.75 (1)
Family History of Dementia (#, %)	14 (61)	2.46 (1)	9 (39)	0.83 (1)	9 (47)	0.02 (1)	17 (46) 0.06 (1)
Mean MMSE at Year 2 (range)	19 (3–29)	0.17	21 (4–29)	0.69	20 (3–29)	0.04 (1)	20 (3–29) 0.00
Mean CDR at Year 2 (range)	1 (0.5–3)	1.39	1 (0.5–3)	0.32	1 (0–3)	0.45	1 (0–3) 0.10
Mean Decline in MMSE (s.d.) (from Baseline to Year 2)	5 (5.93)	1.07	3 (4.67)	1.41	3 (5.77)	0.08	4 (5.63) 0.00

* Note that change in preference refers to both increased and decreased willingness to be contacted regarding study eligibility; **bolded** test statistics were significant at the level of $p < .05$