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Risk disclosure and preclinical Alzheimer's disease clinical trial enrollment

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Abstract

To identify facilitators and barriers to recruitment to clinical trials in preclinical Alzheimer's disease (AD), fifty cognitively normal participants were interviewed after being randomized to one of two hypothetical AD risk scenarios: 1) the general age-related risk for AD, or 2) being at 50% increased risk for AD. Participants provided uncued barriers and facilitators to the hypothetical decision of whether they would enroll. Thirteen themes of facilitators and five themes of barriers were identified. The most common barrier was fear related to taking study drug. Those randomized to being at increased risk for AD more frequently cited lowering personal risk as a facilitator (p=0.01) and less frequently cited time as a barrier to enrollment (p=0.02). These results suggest potential challenges to recruitment to preclinical AD clinical trials and that disclosing risk information may enhance enrollment.

Introduction

Research criteria for preclinical Alzheimer's disease (AD) [1] and mild cognitive impairment (MCI) due to AD [2] will be used in clinical trials of investigational therapies in AD populations that are not demented. The goal of trials that enroll persons who demonstrate AD biomarkers but are not demented is to test interventions before neurodegeneration reaches a point at which therapy is not likely to succeed. The onset of dementia could serve as one potential outcome measure for these trials. Therefore, cognitively normal or only mildly impaired study populations may be recruited to participate in AD "secondary prevention trials."

Unfortunately, little is known about potential participants' attitudes toward enrolling in these trials. Investigation of patient preferences could inform trial design and optimize recruitment. Therefore, we sought to identify potential facilitators and barriers to preclinical

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AD trial enrollment and to assess if knowledge of certain factors might guide successful recruitment strategies. We hypothesized that the disclosure of different levels of quantitative risk of AD would alter attitudes toward the decision whether to enroll and increase willingness to participate.

Methods

Fifty cognitively normal, English-speaking participants age 46 years or older were recruited in person from the UCLA Alzheimer's Disease Research Center longitudinal study (normal control participants with no subjective memory complaint or study partners to persons enrolled with cognitive impairment) or through community outreach via public lecturing. To ensure that our methods did not contaminate or limit participant identification of important themes, we used open-ended interviews focused on positive and negative factors related to trial participation.

To measure facilitators and barriers to the decision whether to enroll in an AD prevention trial, we developed (1) a brief primer that described the incidence and prevalence of AD and the principles of prevention trials (e.g. randomization and blinding) (Appendix 1) and (2) two versions of a hypothetical scenario in which the potential clinical trial participant received a letter as follow-up to a physician visit (Appendix 2). Both versions stated that the individual was in overall good health and might be eligible for an ongoing AD prevention clinical trial. One version of the scenario described that "the risk for Alzheimer's dementia increases as people get older;" the other version stated that "clinical and laboratory tests suggest you are at 50% increased risk for Alzheimer's dementia, relative to other people your age." Uncued open-ended questions probed facilitators and barriers to a decision of whether to enroll in the hypothetical AD prevention trial. Specifically, participants were asked, "What types of things might lead you choose to participate?" and then "What types of things might lead you to choose not participate in the study?" After each response, participants were probed for further explanation and additional factors for both categories.

Fifty eligible adults provided signed informed consent for this UCLA IRB-approved interview study. Using a random number table, 25 were randomized to receive the scenario describing the age-associated risk for AD ("normal risk" group), and 25 to the scenario describing increased risk ("at-risk" group). One investigator (JDG) administered the interview in-person to all study participants. Interviews were recorded and transcribed. Participants were compensated with a $20 gift card.

Participant responses were separated into distinct text segments by one investigator (JDG) using an Excel spreadsheet, then printed onto cards having one text segment per card. We analyzed themes of participant-identified facilitators and barriers to enrollment using a cutting-and-sorting technique, blinded to randomization group and demographic data [3, 4]. One investigator (JDG) identified preliminary themes of facilitators and barriers, and consensus for the number of themes and included comments was reached by simultaneous review by three investigators. Frequencies of themes and subthemes were calculated. We explored associations of risk status with themes using Fisher exact tests.

Results

Mean age of study participants was 63.8 (±10.0 years; Range 46–89); 28 (56%) were female; and the mean level of education was 16.1 (±2.3; Range 12–20) years. Sixteen participants (32%) were African American, three (6%) were Asian American, three (6%) were Hispanic, and 28 (56%) were non-Hispanic White. Sixteen participants (32%) were AD caregivers, and 15 (30%) had a first-degree family history of AD.

Participants provided 239 responses that were categorized into thirteen themes of facilitators and five themes of barriers to a decision to enroll in a prevention trial (Table 1). Altruism was the most common facilitator (56% of participants). The most frequent barrier was fear (62%), which was divided into two subthemes, fear of investigational drugs (48%) and fear of trial-associated medical procedures (22%). The theme of logistical barriers was subdivided into time (18%) and travel (8%) barriers.

As can be seen in Table 2, persons randomly assigned to the “at risk” group were significantly more likely to report the desire to lower risk for AD as a reason to enroll (76%, compared to 32% for the “normal risk” group; Fisher test p=0.01) and were less likely to cite time as a barrier (4%, compared to 32% for the “normal risk” group; Fisher test p=0.02).

Discussion

Cognitively asymptomatic participants in preclinical AD trials will need to be willing to undergo biomarker testing and to take investigational therapies that may have significant risk. Our results suggest that recruitment to these trials is likely to encounter significant barriers. Among a diverse sample of 50 cognitively normal adults, the majority of participants cited either (or both) unwillingness to take a study drug or fear, anxiety, or hesitation related to medical procedures as deterrents to a decision to enroll. These findings suggest that the decision to enroll in a preclinical trial will represent a balance between motivational factors and willingness to accept personal risk and hassle. In large part, the barriers and facilitators identified in this study were similar to those identified in previous studies of AD trial participation or clinical trial participation in general [5]. Understanding how barriers differ in AD prevention trials, relative to dementia trials, will require further study.

Even in this small study, we found that persons considering the decision whether to enroll in the hypothetical scenario of being told they were at increased risk for AD using a quantitative estimate were, compared to persons in a normal risk group, much more likely to cite a desire to reduce risk and less likely to cite time barriers. This supports our hypothesis that knowledge of AD risk information may influence the decision to enroll in a trial.

The Risk Evaluation and Education for Alzheimer’s (REVEAL) study of the impact of apolipoprotein E (ApoE) genotype disclosure has shown that, on average, individuals with a family history of disease randomized to learning their genetic risk for AD did not experience increased anxiety or depression, relative to counterparts randomized to nondisclosure [6]. Furthermore, among those who learned their genetic status, carriers of the ε4 allele (those at increased genetic risk for AD) more frequently reported taking steps to reduce that risk (taking vitamins or supplements) than did counterparts who learned they were noncarriers [7, 8]. Increased risk for AD has been described for family history of disease [9], carrying specific genetic variants [10–12], and more recently for demonstration of biomarkers for AD [13]. Our study suggests that people who learn they have increased risk for AD, independent of the modality by which risk is determined, may be more likely to enroll in preclinical trials.

This preliminary study has a number of limitations. We enrolled a small but diverse sample with a wide age range among participants. The diversity of our sample may not be representative of near future larger secondary prevention trials, as AD trials are currently predominated by non-Hispanic White participants [14]. Our statistical analyses did not correct for multiple comparisons. Because we assessed decision-making in a hypothetical scenario, it is unclear to what extent survey responses predict actual behaviors. We took no steps to address general barriers (or facilitators) to research participation versus those that

were specific to AD prevention trial participation. Finally, we provided a quantitative estimate of the risk for developing AD when, at present, other than ApoE predicted risk, such information is not available. It is unclear how different participants may have interpreted this risk information, or how any such differences may have been related to study results.

Overall, these findings support the need for further research on patient willingness to undergo different AD risk tests to guide design choices that increase recruitment efficiency to preclinical AD trials. Greater understanding of how to disclose risk information in the setting of a trial, and how participants will interpret this information, will also be crucial.

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Table 1

Frequencies of participant-identified facilitators and barriers to AD prevention trial enrollment, categorized by themes (out of N=50 study participants).

Theme	Frequency, n (%)	Exemplary comment
Facilitators to study enrollment		
• Altruism	28 (56)	*It is a horrific disease and if there is anything I can do, if being in a study can help, I certainly would step forward just for that reason.*
• Desire to lower personal risk for dementia by enrolling in the study	27 (54)	*If I'm at increased risk, I would want to do whatever I could to increase my chances of not getting it. So I would want to participate.*
• Wanting to learn information that could be used to improve health or lower the risk for dementia	17 (34)	*…I really want to know if things such as lifestyle changes and dietary changes can do anything. I like that, I'm interested in that, I'd like to be on a regimented plan.*
• Having a family history	13 (26)	*My mother has it, everything she has, I have. So it seems it might be in my best interest.*
• Convenience	10 (20)	*…for me to participate, it would have to be something I could do over the phone or over the internet, or some other method instead of going somewhere physically. Unless it was something locally, something I could go and do at lunch.*
• To learn diagnostic risk for AD	8 (16)	*Just to see if I had risk, and to see where I stand in terms of Alzheimer's and dementia.*
• Because there was no reason not to enroll	7 (14)	*Because I'm not working…so I have all the time in the world.*
• To protect future generations	6 (12)	*If I was at risk for Alzheimer's then there would be the possibility that my child would be at risk and I would definitely like to participate in something that could create the ability for a drug to be developed to prevent her from getting it.*
• To receive free medical services	6 (12)	*I think it's a benefit to know that my cognitive abilities are being monitored and that's great.*
• Having access to a new or investigational drug	5 (10)	*If the study had drug therapy, I might want to try that.*
• Reputation of the investigator or institution	5 (10)	*That I would be dealing with researchers who are…some of the top people in the country … I would feel better for that.*
• Incentive/payments for study participation	4 (8)	*A lot of these things say that they'll pay you.*
• Potential to obtain social support	2 (4)	*Maybe meeting other people who have gotten this letter, so it would be like support.*
Barriers to study enrollment		
• Fear of participation	31 (62)	
○ Fear of drug side effects or a desire not to take new or investigational drugs (subtheme)	24 (48)	*Depends on if it would involve taking anything. It's one thing to take fish oil and another to take an investigational drug.*
○ Fear of medical procedures (subtheme)	11 (22)	*There could be things that are required in certain tests that I might not want to participate in. I know that some involve tapping spinal fluid and that kind of frightens me. It might not make me say no, but it might make me concerned.*
• Logistical barriers	12 (24)	
○ Lack of time (subtheme)	9 (18)	*The time factor. As part of a busy life it can be hard to get over here and you want to be committed so I'd want to know the time commitment and I'd want to make sure I don't jeopardize my*

Theme	Frequency, n (%)	Exemplary comment
		already busy schedule.
○ Travel (subtheme)	4 (8)	*It would depend on where the study was done. I don't want to have to drive 2 hours.*
• Lack of personal need	6 (12)	*If I didn't have anything wrong with me, why would I participate in a clinical trial?*
• Skepticism toward research	6 (12)	*You're a stranger and you are asking me to trust you with my life. So I have issues with that. I don't know you, I've heard bad stories about clinical research studies and people become disfigured and everything else. And in the African American community after Tuskegee experiment, oh no, I can't trust anything like that.*
• Hopelessness related to the disease or denial related to the diagnosis	4 (8)	*Denial. I'd throw it in the trash. If I throw it in the trashcan then it means that I did not get the letter.*

Table 2

Frequencies of participant comments for each theme in the randomized groups (FE, Fisher Exact Test)

Theme	Normal Risk Frequency, n (%)	At Risk Frequency, n (%)	p-value (FE)
Facilitators to study enrollment			
• Altruism	14 (56)	14 (56)	p=1.00
• Desire to lower personal risk for dementia by enrolling in the study	8 (32)	19 (76)	p=0.01
• Wanting to learn information that could be used to improve health or lower the risk for dementia	5 (20)	12 (48)	p=0.07
• Having a family history	8 (32)	5 (20)	p=0.52
• Convenience	6 (24)	4 (16)	p=0.72
• To learn diagnostic risk for AD	4 (16)	4 (16)	p=1.00
• Because there was no reason not to enroll	4 (16)	3 (12)	p=1.00
• To protect future generations	1 (4)	5 (20)	p=0.19
• To receive free medical services	3 (12)	3 (12)	p=1.00
• Having access to a new or investigational drug	2 (8)	3 (12)	p=1.00
• Reputation of the investigator or institution	3 (12)	2 (8)	p=1.00
• Incentive/payments for study participation	1 (4)	3 (12)	p=0.61
• Potential to obtain social support	0 (0)	2 (8)	p=0.49
Barriers to study enrollment			
• Fear of participation	16 (64)	15 (60)	p=1.00
○ Fear of drug side effects or a desire not to take new or investigational drugs (subtheme)	14 (56)	10 (40)	p=0.40
○ Fear of medical procedures (subtheme)	6 (24)	5 (20)	p=1.00
• Logistical barriers	9 (36)	3 (12)	p=0.05
○ Lack of time (subtheme)	8 (32)	1 (4)	p=0.02
○ Travel (subtheme)	2 (8)	2 (8)	p=1.00
• Lack of personal need	3 (12)	3 (12)	p=1.00
• Skepticism toward research	5 (20)	1 (4)	p=0.19
• Hopelessness related to the disease or denial related to the diagnosis	0 (0)	4 (16)	p=0.11