Neurobiology of Aging 39 (2016) 147–153

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Disclosure of amyloid status is not a barrier to recruitment in preclinical Alzheimer's disease clinical trials

Joshua D. Grill [a,*], Yan Zhou [b,1], David Elashoff [b,c], Jason Karlawish [d,e]

[a] Department of Psychiatry and Human Behavior, Institute for Memory Impairments and Neurological Disorders, University of California, Irvine, Irvine, CA, USA
[b] Department of Neurology, Mary S. Easton Center for Alzheimer's Disease Research, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
[c] Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
[d] Penn Neurodegenerative Disease Ethics and Policy Program, Department of Medicine, Penn Memory Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
[e] Penn Neurodegenerative Disease Ethics and Policy Program, Department of Medical Ethics and Health Policy, Penn Memory Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

ARTICLE INFO

Article history:
Received 8 September 2015
Received in revised form 3 November 2015
Accepted 11 November 2015
Available online 22 November 2015

Keywords:
Preclinical Alzheimer's disease
Disclosure
Biomarker
Recruitment

ABSTRACT

Preclinical Alzheimer's disease (AD) clinical trials may require participants to learn if they meet biomarker enrollment criteria. To examine whether this requirement will impact trial recruitment, we presented 132 older community volunteers who self-reported normal cognition with 1 of 2 hypothetical informed consent forms (ICFs) describing an AD prevention clinical trial. Both ICFs described amyloid Positron Emission Tomography scans. One ICF stated that scan results would not be shared with the participants (blinded enrollment); the other stated that only persons with elevated amyloid would be eligible (transparent enrollment). Participants rated their likelihood of enrollment and completed an interview with a research assistant. We found no difference between the groups in willingness to participate. Study risks and the requirement of a study partner were reported as the most important factors in the decision whether to enroll. The requirement of biomarker disclosure may not slow recruitment to preclinical AD trials.

1. Introduction

Biomarkers of Alzheimer's disease (AD) are present years before a person has overt cognitive impairment (Bateman et al., 2011; Lim et al., 2014; Morris et al., 2009; Pietrzak et al., 2015; Price et al., 2009), supporting the hypothesis that interventions initiated at these early "preclinical" stages, when neurodegeneration is minimal, may have the greatest likelihood of altering the natural history of AD (Sperling et al., 2011b). To facilitate testing this hypothesis, a working group sponsored by the National Institute on Aging and the Alzheimer's Association proposed research diagnostic criteria for a preclinical stage of AD (Sperling et al., 2011a). In this stage, cognition remains normal or only subtly impaired, but biomarker evidence of AD is present.

Preclinical AD trials must implement 1 of 2 designs: blinded or transparent enrollment (Kim et al., 2015). Blinded designs do not disclose biomarker results to participants. They enroll a proportion of participants who do not demonstrate AD biomarkers so that enrollment is not a *de facto* disclosure of biomarker status. These participants are nonrandomly assigned to placebo, undergo all study procedures, and are followed for the duration of the study. With transparent enrollment, only those who demonstrate biomarker criteria are enrolled and randomized. Biomarker results are disclosed when an investigator informs a person whether he or she is eligible. Both designs have unique risks. For example, blinded enrollment trials may inadvertently disclose biomarker status to participants who do not wish to learn it (Hooper et al., 2013; Kim et al., 2015), whereas transparent enrollment trials bring unique challenges related to confidentiality and the social and psychological impact of learning biomarker results (Arias and Karlawish, 2014).

Which of these designs should researchers use? The answer to this question engages several considerations, including the use of limited resources, the need for timely progress, study feasibility, and the ethical implications of trial designs. The purpose of this

* Corresponding author at: University of California, Irvine, 3206 Biological Sciences III, Irvine, CA 92697-4550, USA. Tel.: +1 949 824 5905.
E-mail addresses: jgrill@uci.edu (J.D. Grill), yan.zhou@theABA.org (Y. Zhou).
[1] Present address: The American Board of Anesthesiology, Inc, 4208 Six Forks Road, Suite 1500, Raleigh, NC 27609-5765, USA. Tel.: (919) 745-2294; fax: (919) 745-2201.

0197-4580/$ – see front matter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2015.11.007

study was to empirically inform 1 specific consideration: the impact on participant recruitment. It is unknown how these 2 designs will impact recruitment timelines. Also unknown are the factors that might explain why one design is more appealing than the other. Participants' views cannot entirely settle the competing ethical, clinical, and resource considerations, but they do provide an important perspective on how, on a person-by-person basis, they settle these issues. Absent empirical data, trialists, institutional review boards, and funders can only speculate over how blinded versus transparent designs impact enrollment, or simply implement these designs and learn from the efforts.

Transparent enrollment preclinical AD trials require people to learn risk information for a disease for which no treatment exists or may ever exist. But compared to blinded enrollment trials, these trials require fewer participants and closely approximate how clinicians will diagnose and treat sporadic preclinical AD (Burns and Klunk, 2012). If transparent enrollment trials suffer from slow recruitment, then, despite smaller overall sample sizes, these trials may be less efficient than those using blinded designs. Here, we test the hypothesis that a preclinical AD trial with transparent enrollment will have poorer recruitment than one with blinded enrollment. A secondary aim was to identify clinical and trial factors associated with willingness to enroll. We chose to study persons with interest in AD research because they approximate the kinds of persons who would be recruited for a preclinical AD trial.

2. Methods

2.1. Participants and recruitment

Participants were required to be aged 65 years or older, able to complete the study in English, and to have shown interest in AD and AD prevention research, as evidenced by at least 1 of the following activities: attendance at community education events on AD; enrollment in the UCLA AD Research Center (ADRC) potential participants registry (Grill and Galvin, 2014) or another research registry; referral by a community liaison; self-referral by e-mailing the UCLA ADRC.

Exclusion criteria included a previous diagnosis of dementia, mild cognitive impairment, or another neurological disease; previous diagnosis of psychiatric disease; or auditory or visual impairments that prevented the conduct of the study interview. All criteria were assessed by self-report. Participants received a $25 gift card to a national retail store for their participation.

2.2. Study design

A research assistant completed a face-to-face interview with all participants. After being read a primer on AD, participants were given the choice of reading or having read to them an informed consent form (ICF) describing a hypothetical AD prevention clinical trial. Using a single sequence of random assignment based on computer-generated random numbers, participants were randomized to consider an ICF that described a trial that did (transparent enrollment design) or did not (blinded enrollment design) require disclosure of amyloid positron emission tomography (PET) results to learn trial eligibility and participate.

Both ICFs described the purpose of amyloid PET, based largely on the materials being used in an ongoing preclinical AD trial(Sperling et al., 2014): "this scan allows doctors to detect amyloid plaques in the brain of a living person"; "the scan tells whether amyloid level is elevated or not; people with Alzheimer's disease have elevated amyloid levels"; "about 30% of people with normal memory and thinking have elevated amyloid levels." The blinded enrollment ICF stated "the results of this scan will not be shared"; the transparent enrollment ICF stated "only persons who demonstrate elevated levels of beta amyloid in their brain on the amyloid PET scan will be eligible for this study."

Both ICFs described a 36-month, double-blind, 1:1 randomized study requiring visits at the medical center every 6 months. The aim of the study was to test an oral anti-amyloid therapy with risks including dizziness, headache, nausea, and vomiting, and in more rare occurrences bleeding in the stomach. Listed study procedures included blood draws, cognitive testing, 5 magnetic resonance imaging scans, and 3 PET scans. The ICF stated that genetic testing for the apolipoprotein E genotype would be performed but that results would not be returned to the participant. The hypothetical trial design was based on preliminary data and intended to elicit an approximately 50% willingness to participate (Grill et al., 2013).

The research assistant used a scripted interview guide to review the ICF. When discussing the screening process, 1 additional phrase was included for participants randomized to consider a transparent enrollment design: "Lastly, in this study, only persons who demonstrate elevated levels of beta amyloid in their brain on the amyloid PET scan will be eligible to participate." Confirmatory questions ensured participant understanding. If a participant was unable to provide the correct answers, the research assistant rereviewed the hypothetical ICF and confirmed their understanding. Additional questions that addressed the role of amyloid PET in determining eligibility were asked in the transparent enrollment arm, including: "Suppose you were to enroll in this study, would you want to learn your amyloid PET results?" The study materials can be obtained by e-mailing the corresponding author.

2.3. Measurements

2.3.1. Willingness to participate in a prevention trial

Willingness to participate was assessed with a single question: "How likely would you be to enroll in the described Alzheimer's disease prevention trial?" Responses were provided using a 6-point Likert scale from "extremely unlikely" to "extremely likely."

2.3.2. Factors associated with willingness

2.3.2.1. Importance of trial factors. Subjects used a 6-point Likert scale from "extremely unimportant" to "extremely important" to rate the importance of 7 factors in the decision whether to enroll: frequency of visits, location of visits, length of the study, requirement of a study partner, study risks, likelihood of receiving placebo, and required procedures.

2.3.2.2. Incentives for participation. Participants rated 6 potential incentives as making them much less likely to enroll, somewhat less likely to enroll, no difference, somewhat more likely to enroll, or much more likely to enroll. The incentives included receiving overall study results, reports of personal blood test results at each visit, personal genetic testing results, personal cognitive testing results at each visit, financial compensation at each visit, and personal estimates of risk for getting AD.

2.3.2.3. AD Knowledge Scale. This validated 30-item true or false questionnaire assesses the level of understanding related to AD (Carpenter et al., 2009). Higher scores represent greater knowledge.

2.3.2.4. Research Attitude Questionnaire. This validated 7-item, 5-point Likert scale survey (range 7–35) assesses community-dwelling volunteers' attitudes toward research (Rubright et al., 2011). Higher scores represent a more favorable attitude toward research.