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Choosing Alzheimer's disease prevention clinical trial populations

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ABSTRACT

To assist investigators in making design choices, we modeled Alzheimer's disease prevention clinical trials. We used longitudinal Clinical Dementia Rating Scale Sum of Boxes data, retention rates, and the proportions of trial-eligible cognitively normal participants age 65 and older in the National Alzheimer's Coordinating Center Uniform Data Set to model trial sample sizes, the numbers needed to enroll to account for drop out, and the numbers needed to screen to successfully complete enrollment. We examined how enrichment strategies affected each component of the model. Relative to trials enrolling 65-year-old individuals, trials enriching for older (minimum 70 or 75) age required reduced sample sizes, numbers needed to enroll, and numbers needed to screen. Enriching for subjective memory complaints reduced sample sizes and numbers needed to enroll more than age enrichment, but increased the number needed to screen. We conclude that Alzheimer's disease prevention trials can enroll elderly participants with minimal effect on trial retention and that enriching for older individuals with memory complaints might afford efficient trial designs.

1. Introduction

Clinical trials continue to target earlier stages of Alzheimer's disease (AD) because of concern that later intervention might not effectively slow progression because of established pathological burden (Sperling et al., 2011a). The earliest test of a potential intervention is through primary prevention trials that enroll volunteers with no clinical or biological sign of disease. Previous AD primary prevention trials encountered challenges related to slow enrollment, high screen failure rates, loss to follow-up, and fewer than expected cases of dementia (DeKosky et al., 2008; Meinert et al., 2009; Sano et al., 2008; Vellas et al., 2012), despite strategies to enrich for age (DeKosky et al., 2008), family history of disease (ADAPT Research Group et al., 2007; Sano et al., 2008), or memory complaints (Vellas et al., 2012). Trial designs that incorporate single continuous outcomes of global cognitive and functional performance, rather than time to event designs, might alleviate some of these challenges (Aisen et al., 2011; Richard et al., 2012) and have been endorsed by regulatory agencies for trials of those at greatest risk for AD dementia (Center for Drug Evaluation and Research, 2013; Kozauer and Katz, 2013).

The Clinical Dementia Rating (CDR) Sum of Boxes (CDR-SB) (Morris, 1993) measures within-patient clinical change assumed to represent brain disease, rather than normal aging (Morris et al., 1991), and has been proposed as a potential single primary outcome measure for use in predementia AD trials (Aisen et al., 2011; Kozauer and Katz, 2013). We used data from healthy control participants in the National Alzheimer's Coordinating Center Uniform Data Set (NACC UDS) to model AD trials that enroll cognitively normal participants and use the CDR-SB as a single outcome. We examined how enrichment strategies will affect the rates of trial retention and screen failure. We hypothesized that using older minimum ages of enrollment and other enrichment strategies would reduce required sample sizes but would also increase the rates of screen failure and drop out.

2. Methods

2.1. Participants

The NACC UDS is a repository for longitudinal data collected from approximately 30 current or previously National Institute on Aging-funded AD Centers nationwide (www.alz.washington.edu; Beekly et al., 2007; Morris et al., 2006). The NACC UDS was initiated in 2005. These analyses examined data collected on or before December 1, 2012.

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2.2. Study inclusion criteria

We examined the proportion of NACC UDS participants enrolled as cognitively normal healthy control subjects at baseline that was eligible for AD prevention clinical trial criteria and the criteria that most often resulted in ineligibility. To examine eligibility, we developed a set of inclusion criteria, adapted from previous AD prevention trials (DeKosky et al., 2008; Vellas et al., 2012). Participants must have been enrolled as healthy control subjects, be age 65–90, score above 26 on the Mini Mental State Examination (MMSE; Folstein et al., 1975) and have a global CDR score of 0. To permit accurate examination of long-term follow-up rates, only data from participants who had a baseline visit before June 1, 2008 (and thus were eligible for at least 3 annual follow-up visits) were included.

Exclusion criteria were recent or active cardiovascular disease (e.g., heart attack, atrial fibrillation); presence of a pacemaker (because most AD trials include magnetic resonance imaging); medical conditions that might cause or contribute to cognitive impairment, including vitamin B12 deficiency, thyroid disease, alcohol or other substance abuse, Parkinson's disease, seizures, or traumatic brain injury; history of stroke; Hachinski ischemia scale score >4; and Geriatric Depression Scale score >6. For the medical conditions, patients were not excluded if the condition was characterized as remote or inactive. For vitamin B12 and thyroid deficiency, this was assumed to separate patients with a current active condition from those with a previous diagnosis adequately treated. The use of the following concomitant medications was exclusionary: lithium, anti-Parkinsonian medications, monoamine oxidase (MAO)-B inhibitors, tricyclic antidepressants and other anticholinergic drugs (including diphenhydramine), stimulants (i.e., modafinil and methylphenidate), narcotic analgesics, first generation antipsychotics, atypical antipsychotics, anticonvulsants, and approved AD therapies.

2.3. Enrichment strategies

2.3.1. Age

We assessed the effect of limiting trial populations to those at least age 70 or 75.

2.3.2. Apolipoprotein E ε4 carrier status

Apolipoprotein E (ApoE) genotype is a well-described genetic risk factor for AD (Corder et al., 1993). ApoE genotyping was performed locally at National Alzheimer's Coordinating Center AD Centers or at the National Cell Repository for AD, primarily using blood samples. Subjects were divided into those who did and those who did not carry at least 1 ε4 allele.

2.3.3. Education levels

Demographic collection of information as part of the NACC UDS includes the highest level of educational completion for all participants. Education might serve as a surrogate for cognitive reserve and cognitive reserve might protect against cognitive decline (Stern, 2009). We enriched trial models by excluding those assumed to have the greatest cognitive reserve, those with a maximum education level >16 years.

2.3.4. Subjective cognitive complaint

As part of the NACC UDS, the clinician is asked to record whether the participant reports a decline in memory. The accompanying instructions in the NACC UDS Coding Guidebook state that decline refers to cognitive changes in the subject's usual or customary memory function and that changes in behavior, motor, or other nonmemory symptoms should not be considered. We used this single item to categorize participants as having a subjective cognitive complaint.

2.4. CDR-SB

The CDR is an interview-based assessment tool. The researcher separately interviews an informant and the participant and assesses the participant's change relative to their premorbid (in this case, earlier life) performance on 6 domains: memory; orientation; judgment and problem solving; community affairs; home and hobbies; and personal care. Each domain is scored as 0 (no dementia), 0.5 (questionable), 1.0 (mild), 2.0 (moderate), or 3 (severe dementia). Two overall scores can be derived; a global score using a standardized algorithm and a cumulative score summing the boxes. The CDR-SB is a well-described, validated, and reliable measure of change through the course of AD (Morris, 1993; Williams et al., 2009) and has been proposed as a suitable single outcome measure for AD trials in dementia and predementia populations (Aisen et al., 2011; Cedarbaum et al., 2013; Coley et al., 2011; Kozauer and Katz, 2013).

2.5. Data analyses

We examined the mean decline in the CDR-SB at 36 months. Sample size estimates under an assumption of normality and known variance were calculated from an equation used frequently in the literature (Fox et al., 2000; Grill et al., 2013a; Leung et al., 2010; Schott et al., 2010):

$$\text{Sample size} = \left(Z_{1-\beta} + Z_{1-\alpha/2}\right)^2 X \left(2\sigma^2\right)/(\Delta\mu)^2$$

Here, $z_{1-\beta} = 0.842$ to provide 80% power; $z_{1-\alpha/2} = 1.96$ to test at the 5% level; $\Delta\mu$ is the mean change in CDR-SB score relative to baseline, multiplied by the drug effect (0.25) to reflect the estimated mean difference between placebo group change scores and drug group change scores; and σ is the SD of the change scores in the groups (assuming SD is the same in treatment and placebo groups). We report sample sizes per trial arm.

We calculated the retention rate after 36 months in NACC for each modeled population. Those who discontinued study participation, were lost to follow-up, or died during the 3-year interval were considered to have dropped out of the study. Using the specific retention rate and the calculated sample size for each population, we calculated the number needed to enroll for a trial to maintain statistical power at completion. Finally, we examined the proportion of NACC UDS participants who met eligibility criteria for each specific trial model. Using the rates of inclusion and the number needed to enroll, we calculated the number needed to screen.

To assist in the comparison of sample size estimates, we calculated the 95% confidence interval for the sample sizes, numbers needed to enroll, and numbers needed to screen. These confidence intervals were estimated using bootstrap resampling, calculating 10,000 iterations for each scenario. Formal statistical comparisons of model outputs were not performed.

Descriptive statistics (mean, SD, and percentages) were calculated for eligible trial populations. The frequency of each reason for trial ineligibility was also calculated. Groups were compared using χ^2, and Kruskal–Wallis test, as appropriate. Age comparisons were performed on the mutually exclusive age epochs (i.e., 65–69, 70–74, and >75). All analyses were performed using SAS 9.3 (Cary, NC, USA) and R v2.14 (http://www.R-project.org).