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Designing clinical trials to test disease-modifying agents— application to the treatment trials of Alzheimer's disease

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Abstract

Background—Therapeutic trials of disease-modifying agents on Alzheimer's disease (AD) require novel designs and analyses involving switch of treatments for at least a portion of subjects enrolled. Randomized start and randomized withdrawal designs are two examples of such designs. Crucial design parameters such as sample size and the time of treatment switch are important to understand in designing such clinical trials.

Purpose—The purpose of this article is to provide methods to determine sample sizes and time of treatment switch as well as optimum statistical tests of treatment efficacy for clinical trials of disease-modifying agents on AD.

Methods—A general linear mixed effects model is proposed to test the disease-modifying efficacy of novel therapeutic agents on AD. This model links the longitudinal growth from both the placebo arm and the treatment arm at the time of treatment switch for these in the delayed treatment arm or early withdrawal arm and incorporates the potential correlation on the rate of cognitive change before and after the treatment switch. Sample sizes and the optimum time for treatment switch of such trials as well as optimum test statistic for the treatment efficacy are determined according to the model.

Results—Assuming an evenly spaced longitudinal design over a fixed duration, the optimum treatment switching time in a randomized start or a randomized withdrawal trial is half way through the trial. With the optimum test statistic for the treatment efficacy and over a wide spectrum of model parameters, the optimum sample size allocations are fairly close to the simplest design with a sample size ratio of 1:1:1 among the treatment arm, the delayed treatment or early withdrawal arm, and the placebo arm. The application of the proposed methodology to AD provides evidence that much larger sample sizes are required to adequately power disease-modifying trials when compared with those for symptomatic agents, even when the treatment switch time and efficacy test are optimally chosen.

Limitations—The proposed method assumes that the only and immediate effect of treatment switch is on the rate of cognitive change.

Conclusions—Crucial design parameters for the clinical trials of disease-modifying agents on AD can be optimally chosen. Government and industry officials as well as academia researchers should consider the optimum use of the clinical trials design for disease-modifying agents on AD

in their effort to search for the treatments with the potential to modify the underlying pathophysiology of AD.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder of the brain characterized by an insidious onset of memory deterioration, progressive cognitive deterioration, emergence of neuropsychiatric symptoms and behavioral disturbances, impairment of activities of daily living, and loss of independent function. There are in general two types of therapeutic clinical trials in the search of agents that can treat people with AD: symptomatic and disease-modifying clinical trials. The former includes these for symptomatic agents with a primary objective of improving cognition, function, and global measures or deferring decline over a short period of time. The latter consists of those for disease-modifying agents which strive to show that the course of AD has been altered and the rate of disease progression has been slowed. Complex trial designs have been proposed to allow definite distinctions between symptomatic and disease-modifying clinical trials in AD [1–3]. These designs in general require the switch of treatments in the middle of follow-up for at least a proportion of subjects originally randomized to either placebo or active treatment.

One such design is the randomized start design [4]. All patients in the design eventually will receive the active treatment, but are randomized to two treatment groups that begin the active drug at different times. During the initial time period of the study one group receives active drug and the other placebo. After an interval of time sufficient to demonstrate a difference in performance on the efficacy measure between the two groups, the placebo group switches to the active drug. If the patients who begin active drug late 'catch up' with those who begin the active drug at baseline, the treatment effect is assumed to be symptomatic. If there is no 'catch-up', it is assumed that the effect of the drug is disease-modifying. Often, in order to preserve the blinding of patients and investigators to the active drug, a second randomization may be performed to the initial placebo group so that a proportion of patients will maintain on placebo throughout the trial. Figure 1 presents the expected longitudinal cognitive growth profiles of a randomized start design.

Another design to identify disease modification is the randomized withdrawal design [4]. This design involves an initial period of double-blinded, placebo-controlled, parallel-arm treatment that is sufficient in duration to establish a difference in effect between the active drug and placebo. Following this period, all those who initially receive active drug are switched to placebo. Both initial groups are then assessed in parallel over a further period of time. If the group that is withdrawn from active drug then regresses on the measure of efficacy to, or towards, the level of the group that receives only placebo, a purely symptomatic effect is assumed. On the other hand, if the group withdrawn from the active drug maintains some gains on the efficacy measure relative to the placebo group, it is assumed that the drug has some effects on the biology of the disease. In order to preserve the blinding of patients and investigators to the active drug, a second randomization may be performed to the initial active drug group so that a proportion of patients will maintain on active drug throughout the trial.

The looming crisis of public health due to AD mandates fast development of novel disease-modifying treatments for the disease. Although clinical trials for disease-modifying agents have been widely discussed in the AD research community [1–4,5–9], the analytic and design complications of such trials remain poorly understood. Because of the novel analytic and design features involved in the randomized start and the randomized withdrawal trials, it is important to obtain optimum design parameters to guide the future clinical trial design for

testing disease-modifying compounds on AD. These optimum design parameters must be based on reasonable statistical models that appropriately fit the longitudinal cognitive changes specific to the randomized start and the randomized withdrawal designs. In fact, existing work on statistical designs and analyses of clinical trials on AD are almost entirely focused on symptomatic agents or preventive agents for which the standard randomized and placebo controlled parallel trials are used on patients with AD or on subjects at risk of AD [10–12]. The standard crossover designs in which subjects are randomized to receive a sequence of treatments over time [13,14] are also different from the randomized start and the randomized withdrawal designs because both allow some of the subjects receiving only the treatment or placebo throughout the entire trial. This paper aims first to provide a reasonable statistical model to analyze data from clinical trials for disease-modifying agents on AD and hence to lay the analytic foundation to optimally determine design parameters such as treatment switch times and sample sizes. Further, using reported statistics from published symptomatic trials on AD, we will demonstrate the practical application of our proposed methodology by applying it to optimally design disease-modifying trials on AD in this paper. Finally, we point out that, although we will focus on the disease-modifying trials on AD in this paper, the proposed methodology applies to much more general trials in which either randomized start or randomized withdrawal designs are employed.

The Model and the optimum design parameters

The most commonly used primary efficacy cognitive endpoint in therapeutic trials of AD is the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) [15], which results in a composite score of 0 to 70. Traditionally, the ADAS-cog has been treated as a continuous measure in the analyses of clinical trials for symptomatic agents. Analysis of response profiles, repeated measures analysis of variance, and the general linear mixed models are the most commonly used statistical models to determine the sample sizes and durations of clinical trials. In the following, we propose a method of analyzing clinical trials for disease-modifying agents, i.e., these with a randomized start design or a randomized withdrawal design. Our focus is on trials with a randomized start design, though it is straightforward to generalize the proposed methodology to trials with a randomized withdrawal design.

Let Y be the score of ADAS-cog tested at time points $t_1, t_2, \dots, t_k$ in a disease-modifying trial with a randomized start design. Let $Y_j^u = (y_{j1}^u, y_{j2}^u, \dots, y_{jk}^u)^t$ be the vector of longitudinal measurements of the j -th subject from the treatment group u . We use $u=tt$ and pp to represent the group of subjects who are in the treatment arm and placebo arm throughout the trial, respectively, and let $u=pt$ represent the group of subjects who initially receive the placebo and then switch to the active treatment. We assume that for either the placebo or the treatment arm, their effects on the longitudinal changes in the mean response can be modeled by a linear trend over time and therefore the slope over time can be used to describe the rate of change. We further assume that when subjects switch from the placebo to the active treatment, the only effect of this switch on the longitudinal growth pattern is through the rate of cognitive change. Figure 1 presents the expected rate of cognitive progression for subjects under different treatment arms. The major objective here is to compare the rate of change (i.e., the slope) over time between the treatment and the placebo arm. This comparison is complicated by the fact that it must include subjects who switch from the placebo to the treatment in the middle of the trial to maximize the statistical power.

For each treatment arm that does not change over time, i.e., $u=tt$ or pp , we assume a standard two-stage random effects model [16] with an individual linear growth curve for ADAS-cog, i.e., for subject j ,

$$Y_{ji}^u = \beta_{0j}^u + \beta_{1j}^u t_i + e_{ji}^u, \quad (1)$$

where β_{0j}^u and β_{1j}^u are subject-specific baseline cognitive score (i.e., at $t=0$) and the rate of cognitive change, respectively, and e_{ji}^u 's are assumed to be independent and identically distributed as a normal distribution with mean 0 and variance σ_e^2 . Across subjects within a treatment arm, the subject specific rates of change (β_{1j}^u 's) in ADAS-cog are further assumed to follow another normal distribution with mean β_1^u and variance σ_u^2 for group $u=tt$ or pp , and are independent of e_{ji}^u 's σ

For subject j who is in the placebo arm initially and then switches to the active treatment arm (i.e., $u=pt$) at time t_{k0} ($1 < k_0 < k$, assumed the same for all subjects), similar to the piecewise random coefficients models proposed in [17], we assume that the immediate and only effect of treatment switch is that the expected progression of ADAS-cog for subjects right after the switch follows the same rate of change as these in the active treatment arm throughout the trial (i.e., $u=tt$). Therefore, the longitudinal growth profile of ADAS-cog can be modeled by

$$Y_{ji}^{pt} = \beta_{0j}^{pt} + \beta_{1j}^b (t_i - t_{k0})^- + \beta_{1j}^a (t_i - t_{k0})^+ + e_{ji}^{pt}, \quad (2)$$

where $(t_i - t_{k0})^+ = t_i - t_{k0}$ if $t_i \geq t_{k0}$, and 0 otherwise, and $(t_i - t_{k0})^- = t_i - t_{k0}$ if $t_i \leq t_{k0}$, and 0 otherwise. β_{1j}^b and β_{1j}^a are the subject specific rate of change before and after the treatment switch time, respectively. For this specific group of subjects, we assume that across subjects, $(\beta_{1j}^b, \beta_{1j}^a)$ follows a bivariate normal distribution with mean $(\beta_1^{pp}, \beta_1^{tt})$ and covariance matrix

$$\begin{pmatrix} \sigma_{pp}^2 & \rho \sigma_{pp} \sigma_{tt} \\ \rho \sigma_{pp} \sigma_{tt} & \sigma_{tt}^2 \end{pmatrix}.$$

In order to establish the efficacy of the active treatment for AD, the major interest is in the estimation of mean rates of change from the active treatment and the placebo, i.e., $(\beta_1^{pp}, \beta_1^{tt})$. For each treatment arm that does not change over time (i.e., $u=pp$ or $u=tt$), let n_u be the sample size within group u . The simple least squares estimate $\widehat{\beta}_{1j}^u$ to the subject-specific rate of change in ADAS-cog for subject j within treatment group u is given by Equation (5) in the Appendix. Notice that $\widehat{\beta}_{1j}^u$ follows a normal distribution with mean β_1^u and variance δ_u^2 , as given by Equation (6) in the Appendix. Let β_1^u be the mean estimated rate of change for subjects receiving either active treatment or placebo throughout the trial (i.e., $u=tt$ and pp). It is clear that the difference on the mean estimated rate of change from subjects whose treatments are not switched throughout the trial (i.e., $\beta_1^{tt} - \beta_1^{pp}$) is an unbiased estimator to the effect size of the active treatment (i.e., $\beta_1^{tt} - \beta_1^{pp}$).

For subject j who begins with the placebo and then switches to the active treatment, i.e., $u=pt$, the simple least squares estimate to the rate of change before and after the change time t_{k0} ($1 < k_0 < k$) can be similarly obtained as $\widehat{\beta}_{1j}^b$ and $\widehat{\beta}_{1j}^a$ (please see Equation (7) and (8) in the Appendix), respectively. Notice that the estimated rates of change before and after the treatment switch (i.e., $(\widehat{\beta}_{1j}^b, \widehat{\beta}_{1j}^a)$) follow a bivariate normal distribution with mean rates

$(\beta_1^{pp}, \beta_1^{tt})$ and covariance matrix Σ_{pt} , the latter of which is given by Equation (9) in the Appendix. For subject j , compute the difference on the rates of change before and after the treatment switch $\Delta\hat{\beta}_{1j} = \hat{\beta}_{1j}^{tt} - \hat{\beta}_{1j}^{pp}$. The variance of $\Delta\hat{\beta}_{1j}$, σ_{Δ}^2 , is given by Equation (10) in the Appendix. Let n_{pt} be the sample size of subjects who begins with the placebo and then switches to the active treatment. Let $\Delta\hat{\beta}_1$ be the mean estimated difference on the rate of change in ADAS-cog before and after the treatment switch, which is another unbiased estimator to the effect size of the active treatment (i.e., $\beta_1^{tt} - \beta_1^{pp}$). For any constant weight $0 < c < 1$, combine the two unbiased estimators and let $T_c = c(\bar{\beta}_1^{tt} - \bar{\beta}_1^{pp}) + (1 - c)\Delta\hat{\beta}_1$. It is clear that T_c is still an unbiased estimator to the effect size of the active treatment ($\beta_1^{tt} - \beta_1^{pp}$). The variance of T_c , $\sigma_{T_c}^2$, is given by Equation (12) in the Appendix. A test statistic for testing the efficacy of the active treatment (i.e., $H_0: \beta_1^{tt} = \beta_1^{pp}$ against $H_a: \beta_1^{tt} - \beta_1^{pp} = d \neq 0$) is $z_c = T_c / \sigma_{T_c}$, which follows a standard normal distribution when the null hypothesis is true. The test therefore rejects the null hypothesis of no efficacy difference between the active treatment and the placebo when $|z_c| > z_{\alpha/2}$ at a significance level of α ($0 < \alpha < 1$), where $z_{\alpha/2}$ is the upper $\alpha/2$ percentile from the standard normal distribution. The power function $P(d)$ of the test, as a function of the effect size (i.e., d), is given by Equation (13) in the Appendix. Therefore, the sample sizes required to achieve a statistical power of $(1 - \gamma)$ ($0 < \gamma < 1$) are the solutions to n_{tt} , n_{pp} , and n_{pt} such that $P(d) = 1 - \gamma$.

Notice that the total spacing or the duration of the trial, the number of repeated measures on the outcome variable, the time spacing of the repeated measures, and the time when the delayed treatment group switches from placebo to the active treatment all impact the statistical power and therefore the sample sizes.

In designing clinical trials for testing potential disease-modifying agents on AD, if the linear growth model is a valid statistical model and that the logistic and practical factors allow, an increase of either the study duration or the frequency of repeated measures will in general decrease the within-subject variability and improve the precision of parameter estimates or the statistical power in the test on the rate of change over time. However, if a significant serial correlation across the repeated measures on the same subjects exists, naively assuming independence of within-subject error terms in our longitudinal model (1) could lead to overestimating the value of increasing the number of measurements. Although the choice of measurement times, $t_1, t_2, \dots, t_k$ should theoretically be chosen to minimize the variance of the estimated difference on the rate of change between the treatment arm and the placebo arm, many economic, logistic, or subject-specific factors constrain the choice of trial duration, $t_k - t_1$. In addition, the validity of the assumed statistical model also constrains the choice of trial duration $t_k - t_1$ in the sense that a linear growth or a piecewise linear growth for the delayed treatment group over time might not be a reasonable assumption with a very long study duration. Similarly, the number of repeated measures in a longitudinal study might also be constrained by many practical factors and it may be impossible for the designers of the study to freely choose the number of repeated measures. As a result, many longitudinal studies are restricted to relatively short duration with a pre-determined number of repeated measures which is not chosen statistically based on an optimal design. Given that the duration of the trial (i.e., $t_k - t_1$) and the number of measurements per subject (i.e., k) are typically chosen by some non-statistical reasons, and assuming an evenly spaced

longitudinal design among the repeated measures, the variance (i.e., σ_{Δ}^2 , see Equation (10) in the Appendix) for the estimated difference on the rates of change before and after the treatment switch can be further simplified through the simplified function B as given by Equation (11) in the Appendix. Because function B is inversely related to the power of the test on the rate of change over time, the optimal design should choose the treatment switch

time k_0 such that B is minimized over all possible choices. It can be mathematically proven that if an odd number of evenly spaced assessments are designed, then the optimum time k_0 for switching the treatment is the assessment half way through the trial, whereas if an even number of evenly spaced assessments are designed, then the optimum time k_0 for switching the treatment is either one of the middle two assessments through the trial.

On the other hand, if the duration of the trial $t_k - t_1$ and the number of measurements k per subject can be statistically chosen, then designers are confronted with a practical question about which parameter, the duration of the trial $t_k - t_1$ or the number of evenly spaced repeated measures k , affects more on the precision of the estimated rates of change over time as well as the statistical power in the test of treatment efficacy. In general, because the square of the trial duration, i.e., $(t_k - t_1)^2$, appears in the denominator of variance $\delta_{u,u}^2 = pp$, tt , and B (therefore σ_{Δ}^2 , see Equations (10) and (11) in the Appendix), and the number of measurements per subject, i.e., k appears approximately linearly in the denominator of $\delta_{u,u}^2 = pp$, tt , and B , the increase of trial duration $t_k - t_1$ is more important than the increased number of repeated measures k in enhancing the precision of the estimated rates of changes. This very fact was also observed by van Belle [18].

Although for each constant weight $0 < c < 1$, $z_c = T_c / \sigma_{T_c}$ provides a valid statistical test for the efficacy of disease-modifying agents. The optimum test on the treatment efficacy in this family of test statistics relies on the optimum estimation to the difference on the rate of change in ADAS-cog (i.e., $\beta_1^{tt} - \beta_1^{pp}$). Let $n = n_{tt} + n_{pp} + n_{pt}$ be the total sample size. Let $\lambda_u = n_u / n$ be the proportion of sample size for each treatment group $u = pp$, tt , and pt . It is clear that $\lambda_{pp} + \lambda_{tt} + \lambda_{pt} = 1$. It is also straightforward to show that the variance of T_c is minimized when

$$c = \frac{\sigma_{\Delta}^2}{\left(\sigma_{\Delta}^2 + \frac{\lambda_{tt}\delta_{tt}^2}{\lambda_{pt}} + \frac{\lambda_{pp}\delta_{pp}^2}{\lambda_{pt}} \right)}. \quad (3)$$

Therefore the proposed test statistic with this optimum c provides the most powerful test. For a clinical trial with a sample size ratio of 1:1:1 among group $u = pp$, tt , and pt , assuming that the study is evenly spaced with quarterly assessments for a total of k assessments and that $\sigma_{pp}^2 = \sigma_e^2 = \sigma_{tt}^2$. Table 1 shows the optimum weight c as a function of the treatment change time t_{k_0} ($1 < k_0 < k$ (optimally chosen) when the correlation ρ between the rates of change before and after the treatment switch is assumed 0.5. We also found that the optimum c is only minimally changed when the correlation ρ varies in a wide interval between 0.2 and 0.8.

Even if the optimum weight c is chosen to obtain the minimum variance estimator to the effect size of the active treatment (i.e., $\beta_1^{tt} - \beta_1^{pp}$), this optimum estimator depends on the choice of sample sizes n_{pp} , n_{tt} , and n_{pt} . Given a total sample size of n for the clinical trial, another important design issue is how to allocate the sample size into different treatment arms, i.e., $\lambda_u, u = pp, tt, pt$, in a randomized start design. In order to find the optimum sample size allocations $\lambda_u, u = pp, tt, pt$, such that $\sigma_{T_c}^2$ as given by Equation (12) in the Appendix (c is optimally chosen) is minimized with respect to the choices of $\lambda_u > 0, u = pp, tt, pt$, and subject to $\lambda_{pp} + \lambda_{tt} + \lambda_{pt} = 1$, the Lagrangian multiplier method is applied to give the optimum sample size allocations as

$$\lambda_u = \frac{\delta_u \sqrt{\sigma_\Delta}}{\sqrt{\sigma_\Delta}(\delta_{pp} + \delta_{tt}) + \sqrt{\delta_{pp}^3 + \delta_{tt}^3}}, \quad (4)$$

for $u = pp, tt$, and $\lambda_{pt} = 1 - \lambda_{pp} - \lambda_{tt}$. Assuming a clinical trial with a total of k evenly spaced assessments and that $\sigma_{pp}^2 = \sigma_{tt}^2 = \sigma^2$ (therefore, $\lambda_{pp} = \lambda_{tt}$). Table 2 shows the optimum allocations (in %) of the total sample size with the optimum weight c as a function of the number of measurements k per subject, the ratio of between and within subject variances $r = \sigma^2 / \sigma_e^2$, and the correlation ρ between the rates of change before and after the treatment switch. It is interesting to observe that the optimum sample size allocations over a wide spectrum of parameters in Table 2 are fairly close to the simplest design with a sample size ratio of 1:1:1 among the treatment arm, the delayed treatment arm, and the placebo arm. For a 3-year trial with quarterly assessments under a randomized start design, Figure 2 presents the ratio of optimum sample sizes between the arms with and without treatment switch (i.e., $\lambda_{pt} / \lambda_{pp} = \lambda_{pt} / \lambda_{tt}$) against the ratio of between and within subject variances (i.e., $r = \sigma^2 / \sigma_e^2$) for several choice of the correlation (i.e., ρ) between the rates of change before and after the treatment switch.

Missing data almost always happen in longitudinal clinical trials. In general, the impact of missing data on sample size determination is difficult to quantify precisely because of the complexity in the patterns of missingness. The proposed model is likelihood based, and therefore is only valid when the missing data mechanism is missing at random (MAR) [19]. Under the assumption of MAR, the simplest conservative approach to account for the missing data in sample size determination is to first compute the sample sizes required assuming all subjects have the complete data, and then adjust the sample sizes based on an estimated rate of attrition accordingly.

Application to clinical trials for disease-modifying agents on AD

During the past dozen years, several agents have been approved that enhance cognition and global function of AD patients, and recent advances in understanding AD pathogenesis has led to the development of numerous compounds that might modify the disease process. A wide array of anti-amyloid and neuroprotective therapeutic approaches are under investigation on the basis of the hypothesis that amyloid beta (A β) protein plays a pivotal role in disease onset and progression and that secondary consequences of A β generation and deposition, including tau hyperphosphorylation and neurofibrillary tangle formation, oxidation, inflammation, and excitotoxicity, contribute to the disease process [20]. Interventions in these processes with agents that reduce amyloid production, limit aggregation, or increase removal might block the cascade of events comprising AD pathogenesis. Reducing tau hyperphosphorylation, limiting oxidation and excitotoxicity, and controlling inflammation might be beneficial disease-modifying strategies. Potentially neuroprotective and restorative treatments such as neurotrophins, neurotrophic factor enhancers, and stem cell-related approaches are also under investigation [20]. It is anticipated that these promising agents and treatments will soon be tested for their ability to modify the disease process of AD through well designed clinical trials. We therefore apply our proposed methodology to estimate sample sizes under a variety of scenarios for hypothetical future trials of disease-modifying agents on AD. We assume that a design of randomized start will be used and the sample size ratio is 1:1:1 between the treatment arm, the delayed treatment arm, and the placebo arm. We also assume that the optimum design for the time of treatment switch is used for the delayed treatment arm. Finally, we assume that the trial assesses patients quarterly. The statistical test (i.e., with test statistic z_c) on the

difference of the rate of change is optimally chosen as indicated in Table 1. None of the published symptomatic trials reported the estimates to individual variance components associated with the rates of cognitive change σ_{pp}^2 , σ_{tt}^2 , or the within-subject variance σ_e^2 . However, pooling multiple estimates from several reported symptomatic treatment trials on AD provides information on these variance components which can be used to design future disease-modifying trials on AD. Because essentially all these reported trials were analyzed by treating change from the baseline on ADAS-cog as the primary cognitive endpoint, the variation associated with such endpoints is therefore a function of the length of follow-up. Most published symptomatic treatment trials on AD followed patients for a duration ranging from 4 weeks to 1 year [21,22], and the reported variance for the change from baseline on ADAS-cog in the placebo arm also spanned a wide range [21,22]. Assuming a linear growth pattern of ADAS-cog over time, the annual rate of change on ADAS-cog (i.e., the slope) can then be estimated (mostly through extrapolation) by the reported mean difference from baseline divided by the follow-up time (in years). Therefore the standard deviation for the estimated annual rate of change can be estimated by the reported standard deviation on the change from baseline (call it SD) divided by the number of years in follow-up. Linking this to the two-stage random effect model (1) (i.e., with 2 time points, i.e., baseline and the end of the trial) and assuming that $\sigma_{pp}^2 = \sigma_{tt}^2 = \sigma^2$, we have

$$\frac{SD^2}{L^2} = \frac{2\sigma_e^2}{L^2} + \sigma^2,$$

where $L (= t_k - t_1)$ is the number of years in follow-up from a reported symptomatic trial. We identified two recent symptomatic trials that reported the necessary statistics from the placebo group for estimating σ^2 and σ_e^2 . Aisen et al. [23] reported the effects of Rofecoxib or Naproxen in treating AD for a 1-year trial. Out of a sample of 111 subjects receiving the placebo, the mean 1-year change from baseline on ADAS-cog is 5.7 points with an estimated $SD=8.2$ points. Therefore $8.2^2 = 2\sigma_e^2 + \sigma^2$. Rogers et al. [24] reported that for patients at least 50 years old with mild to moderate uncomplicated AD, an estimated mean change of ADAS-Cog from baseline in a 24-week (i.e., 0.46-year) trial is 1.82 with an

estimated standard deviation of 6.06 [24]. Therefore, $\frac{6.06^2}{0.46^2} = \frac{2\sigma_e^2}{0.46^2} + \sigma^2$. Solving these equations, we obtain $\sigma^2 = 38.71$ and $\sigma_e^2 = 14.27$. Assuming a randomized start design for a 2-year or 3-year clinical trial with quarterly assessments and $\sigma_{pp}^2 = \sigma_{tt}^2 = \sigma^2$, for a selected set of effect size (i.e., the difference on the annual rate of change on ADAS-cog between the active treatment and the placebo, $d = \beta_1^{tt} - \beta_1^{pp}$), and the correlation ρ between $(\beta_{1j}^b, \beta_{1j}^a)$ from the delayed treatment group, Table 3 presents the total sample sizes required to detect a selected set of effect sizes typically reported in the literature with a statistical power of 80%. The optimum treatment switch time was used in the computation of Table 3. The optimum test statistic $z_c = T_c / \sigma_{T_c}$ was used (i.e., with optimum weight c). For a 3-year trial with quarterly assessments under a randomized start design, Figure 3 presents the total sample size against the effect size (i.e., $d = \beta_1^{tt} - \beta_1^{pp}$) to be detected with 80% statistical power for several choice of the correlation (i.e., ρ) between the rates of change before and after the treatment switch.

Discussion

Searching for potential disease-modifying agents to treat AD has been a top priority in AD research. We proposed a general linear mixed effect model to test the disease-modifying efficacy of novel therapeutic compounds on AD. This model links the longitudinal growth

from both the placebo arm and the treatment arm at the time of treatment switch for individuals whose treatment has been changed and allows the potential correlation on the rate of cognitive change before and after the treatment switch. Based on this model and the resulting optimum designs, we proposed a method of determining sample sizes to adequately power the clinical trials for testing potential disease-modifying agents on AD. We provided the optimum time for treatment switch of such trials according to the model as well as the best linear unbiased estimator to the treatment effect on the rate of change which then offers the optimum statistics for the test of treatment efficacy. We also provided the optimum sample size allocations to different treatment arms. Our results show that clinical trials for disease-modifying agents on AD can be adequately powered and optimized. The proposed methods of sample size determination provide evidence that much larger sample sizes are in general required to adequately power such clinical trials when compared to existing trials for symptomatic agents on AD, even when the treatment switch time and the test statistic for efficacy are optimally chosen. These results are important for government and industry officials as well as for academia researchers when they design optimum clinical trials for disease-modifying agents on AD.

Compared to the existing work in the statistical design of longitudinal clinical trials, our proposed methodology has several unique characteristics and therefore represents some major improvements. First, whereas general methods of sample size calculations were provided under different scenarios for comparing mean slopes on the repeated measures by many authors [25–30], none of these [25–30] specifically dealt with the design of clinical trials involving a switch of treatments, which is the focus of this paper. Second, although much work has been done for the standard crossover designs in which subjects are randomized to receive a sequence of treatments over time [13,14], the randomized start and the randomized withdrawal designs considered here by us are different from the standard crossover designs in the sense that the former allows some of the subjects receiving only one treatment throughout the trials. Jarjoura [31] considered the efficiency of a clinical trial design which did allow crossing control to treatment (i.e., similar to our designs), but no optimal design parameters such as sample sizes and treatment switch times as well as the number of repeated measures were provided in their work. When the efficacy outcome is a rate, Frost et al. [32] provided optimal design parameters in a parallel trial allowing a run-in period during which all subjects would be ‘off-treatment’. The purpose of such a run-in period was to estimate the baseline rate of the outcome which can be subsequently used in final efficacy analyses to increase the statistical power. The design in [32] is therefore different from the designs we studied here in the sense that our designs randomize the subjects at baseline and do not involve a run-in period. Unlike the trials we consider here for which treatments are switched by design, switch of treatments can also happen by non-compliance of subjects in parallel clinical trials, especially in these to estimate the dose-response curves. Through compliance-response regression analyses, Efron and Feldman [33] provided an excellent approach to recover the true dose-response curves.

Analytically, our approaches also differ from these of many authors. Here we assumed a random intercept and random slope model [34] for a repeatedly measured continuous efficacy outcome and derived statistical tests and optimal design parameters based on this model, whereas others were based on GEE either for a continuous outcome [26] or for an ordinal outcome [35], general linear multivariate models (GLMM) [27], and constrained longitudinal data analysis models (cLDA) [28]. Finally, the effect of missing data on design parameters is an extremely important issue and has been the focus of much existing work [36,37]. Although we briefly discussed missing data issues in this paper, our focus is on the optimal design parameters for the randomized start or randomized withdrawal designs. We will fully consider the missing data issue in our future work.

There are some limitations on the proposed methodology. First, there is currently no consensus on the definition of ‘disease-modifying trials’ within the Alzheimer’s disease research community [1], and we have considered here only the randomized start and randomized withdrawal designs. Standard crossover designs (i.e., randomization between treatment sequences pt and tp) and trials randomizing over all 4 possible arms (i.e., including tt , pp , pt , and tp) could be other approaches to establish the efficacy of disease-modifying agents. Second, the proposed statistical model assumes that a linear growth pattern appropriately describes the cognitive progression for both the treatment group and the placebo group and that the only and immediate effect of treatment switch from the placebo to the treatment is on the rate of cognitive change. The derived optimum design parameters are only valid under these rather stringent assumptions. Although similar assumptions have been made in the context of step-stress accelerated life testing [38], they need to be carefully examined before the proposed methodology can be employed to design disease-modifying trials on AD. If pilot data are available, trial designers should first carefully assess the model goodness-of-fit with pilot data before using the optimum design parameters we have proposed. If pilot data are not available but an interim analysis is designed for a trial, then trial designers should check the assumptions with initial data collected and adapt the design if the initial data are not consistent with the assumed parameters in the original design. Third, we have not considered the possible serial correlations on the within-subject error components of the longitudinal model (1). Although our approaches can be easily generalized to the models such as these with an AR(1) structure considered by Chi [14], it would be important in the future work to examine the implications of model specifications in optimum design parameters, especially given the fact that if a significant serial correlation does exist, naively assuming independence of within-subject error terms could lead to overestimating the value of increasing the number of measurements. Finally, we have assumed that trial designers have control over the design parameters such as treatment switching time. In practice subjects may drop out due to toxicity and/or lack of efficacy or switch over to other treatment arm at a random fashion. These will require more complicated models, and the proposed methodology does not address these difficult issues.

In addition to statistically optimizing disease-modifying trials on AD, ethical considerations are important when designing such trials. Both the randomized start design and the randomized withdrawal design require treatment switch for at least a portion of individuals enrolled in the study. If preliminary data prior to the treatment switch indicate efficacy of the novel agent under study, it may not be ethical to then switch individuals from the treatment arm to the placebo. Likewise, similar ethical issue comes out when the preliminary data indicate that the novel treatment is not efficacious or even harmful and patients from the placebo arm have to be switched to the active treatment. Government and industry officials as well as academia researchers should consider not only the optimum use of the clinical trials design for disease-modifying agents on AD but also the potential ethical issues arising from such designs.

Abbreviations and symbols

AD	Alzheimer’s disease
$t_1, t_2, \dots, t_k$	Measurement times
$\bar{t}$	Average of measurement times, $t_1, t_2, \dots, t_k$
Y	Efficacy outcome repeatedly measured over time
pp	Placebo arm throughout the trial

tt	Treatment arm throughout the trial
pt	Placebo first and then switched to treatment arm
t_{k0}	Time of switch from placebo to treatment for group $u=pt$ ($1 < k_0 < k$)
n_u	Sample size for group $u=pp$, tt , or pt
n	Total sample size
λ_u	Proportion of sample size for group $u=pp$, tt , or pt
β_{0j}^u	Outcome measure for individuals when $t=0$ for group $u=pp$ and tt
β_{1j}^u	Rate of change for individuals in group $u=pp$ and tt
β_1^u	Mean rate of change for group $u=pp$ and tt
d	Difference on the rate of change between groups $u=pp$ and $u=tt$
σ_u^2	Variance for the rate of change for group $u=pp$ and tt
β_{1j}^b	Rate of change before the treatment switch for individuals in group $u=pt$
β_{1j}^a	Rate of change after the treatment switch for individuals in group $u=pt$
$\Delta\beta_{1j}$	Estimated difference on the rate of change before and after treatment switch for individuals in group $u=pt$
σ_{Δ}^2	Variance for the estimated difference on the rate of change before and after treatment switch for individuals in group $u=pt$
ρ	Correlation between the rates of change before and after the treatment switch for individuals in group $u=pt$
σ_e^2	Within-subject variance on the repeated measures from the same subjects
c	Weight for the test statistic on treatment efficacy
T_c	An unbiased estimator to the effect size of the active treatment with weight c ($0 < c < 1$)
$\sigma_{T_c}^2$	Variance of the test statistic for the efficacy of the active treatment
γ	Probability of Type II error for testing the efficacy of the active treatment

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References

1. Cummings JL. Challenges to demonstrating disease-modifying effects in Alzheimer's disease clinical trials. *Alzheimer's & Dementia*. 2006; 6:263–271.
2. Aisen PS. Commentary on "Challenges to demonstrating disease-modifying effects in Alzheimer's disease clinical trials". *Alzheimer's & Dementia*. 2006; 6:272–274.

3. Citron M. Strategies for disease modification in Alzheimer's disease. *Net Rev Neurosci.* 2004; 5:677–685.
4. Mani RB. The evaluation of disease modifying therapies in Alzheimer's disease: a regulatory viewpoint. *Stat Med.* 2004; 23:305–314. [PubMed: 14716731]
5. Leber P. Slowing the progression of Alzheimer's disease: methodologic issues. *Alzheimer Dis Assoc Disord.* 1997 Suppl 5:S10–S20. [PubMed: 9348423]
6. Sampaio C. Alzheimer disease: disease modifying trials. Where are we? Where do we need to go? A reflective paper. *J Nutr Health Aging.* 2006; 10:113–115. [PubMed: 16554943]
7. Whitehouse PJ, Kittner B, Roessner M, et al. Clinical trial designs for demonstrating disease-course-altering effects in dementia. *Alzheimer Dis Assoc Disord.* 1998; 12:281–294. [PubMed: 9876956]
8. Cummings JL, Doody R, Clark C. Disease-modifying therapies for Alzheimer disease: challenges to early intervention. *Neurology.* 2007; 69:1622–1634. [PubMed: 17938373]
9. Cummings JL. Optimizing phase II of drug development for disease-modifying compounds. *Alzheimers Dement.* 2008; 4:S15–S20. [PubMed: 18631992]
10. Kryscio RJ, Mendiondo MS, Schmitt FA, Markesbery WR. Designing a large prevention trial: statistical issues. *Stat Med.* 2004; 23:285–296. [PubMed: 14716729]
11. Ringman JM, Grill J, Rodriguez-Agudelo Y, Chavez M, Xiong C. Prevention Trials in Persons At-Risk for Dominantly-Inherited Alzheimer's Disease: Opportunities and Challenges. *Alzheimer's & Dementia.* 2009 in press.
12. Andrieu S, Rascol O, Lang T, et al. Methodological issues and statistical analyses. *J Nutr Health Aging.* 2006; 10:116–117. [PubMed: 16554944]
13. Putt ME, Ravina B. Randomized, placebo-controlled, parallel group versus crossover study designs for the study of dementia in Parkinson's disease. *Controlled Clinical Trials.* 2002; 23:111–126. [PubMed: 11943439]
14. Chi EM. Analysis of cross-over trials when within-subject errors follow an AR(1) process. *Biom. J.* 1992; 34:359–365.
15. Rosen WG, et al. A new rating scale for the Alzheimer's disease: *Am J Psychiatry.* 1984; 141:1356–1364. [PubMed: 6496779]
16. Diggle, PJ.; Heagerty, P.; Liang, K-Y.; Zeger, SL. *Analysis of Longitudinal Data.* 2nd ed.. New York: Oxford University Press; 2002.
17. Xiong, C.; Zhu, K.; Yu, K. Statistical modeling in biomedical research: longitudinal data analysis. In: Rao, CR.; Miller, JP.; Rao, DC., editors. *Epidemiology and Medical Statistics.* Amsterdam: Elsevier B.V.; 2008.
18. van Belle, G. *Statistical Rules of Thumb.* 2nd edition. Wiley: John & Sons; 2008.
19. Little, RJA.; Rubin, DB. *Statistical Analysis with Missing Data.* New York: John Wiley; 1987.
20. Salloway S, Mintzer J, Weiner MF, Cummings JL. Disease-modifying therapies in Alzheimer's disease. *Alzheimers Dement.* 2008; 4(2):65–79. [PubMed: 18631951]
21. Qizilbash N, Whitehead A, Higgins J, Wilcock G, Schneider L, Farlow M. for the Dementia Trialists' Collaboration. Cholinesterase inhibition for Alzheimer disease: A meta-analysis of the Tacrine trials. *JAMA.* 1998; 280:1777–1782. [PubMed: 9842955]
22. Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt H-P, van den Bussche H. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. *BMJ.* 2005; 331(7512):321–327. [PubMed: 16081444]
23. Aisen PS, Schafer KA, Grundman M, et al. Effects of Rofecoxib or Naproxen vs Placebo on Alzheimer disease progression: a randomized controlled trial. *JAMA.* 2003; 289:2819–2826. [PubMed: 12783912]
24. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. Donepezil Study Group. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology.* 1998; 50(1):136–145. [PubMed: 9443470]
25. Dawson JD. Sample size calculations based on slopes and other summary statistics. *Biometrics.* 1998; 54:323–330. [PubMed: 9544525]
26. Jung S-H, Ahn C. Sample size estimation for GEE method for comparing slopes in repeated measurements data. *Statistics in Medicine.* 2003; 22:1305–1315. [PubMed: 12687656]

27. Muller KE, LaVange LM, Ramey SL, Ramey CT. Power calculations for general linear multivariate models including repeated measures applications. *Journal of the American Statistical Association*. 1992; 87:1209–1226.
28. Lu K, Mehrotra DV, Liu G. Sample size determination for constrained longitudinal data analysis. *Statistics in Medicine*. 2009; 28:679–699. [PubMed: 19051207]
29. Winkens B, Schouten HJA, van Breukelen GJP, Berger MPF. Optimal number of repeated measures and group sizes in clinical trials with linearly divergent treatment effects. *Contemporary Clinical Trials*. 2006; 27:57–69. [PubMed: 16260188]
30. White IR, Thomas J. Standardized mean differences in individually-randomized and cluster-randomized trials, with application to meta-analysis. *Clinical Trials*. 2005; 2:141–151. [PubMed: 16279136]
31. Jarjoura D. Crossing controls to treatment in repeated-measures trials. *Controlled Clinical Trials*. 2003; 24:306–323. [PubMed: 12757996]
32. Frost C, Kenward MG, Fox NC. Optimizing the design of clinical trials where the outcome is a rate. Can estimating a baseline rate in a run-in period increase efficiency? *Statistics in Medicine*. 2008; 27:3717–3731. [PubMed: 18484598]
33. Efron B, Feldman D. Compliance as an explanatory variable in clinical trials. *Journal of the American Statistical Association*. 1991; 86:9–17.
34. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics*. 1982; 38:963–974. [PubMed: 7168798]
35. Kim H-Y, Williamson JM, Lyles CM. Sample-size calculations for studies with correlated ordinal outcomes. *Statistics in Medicine*. 2005; 24:2977–2987. [PubMed: 16149125]
36. Tu XM, Zhang J, Kowalski J, Shults J, Feng C, Sun W, Tang W. Power analyses for longitudinal study designs with missing data. *Statistics in Medicine*. 2007; 26:2958–2981. [PubMed: 17154250]
37. Galbraith S, Marschner IC. Guidelines for the design of clinical trials with longitudinal outcomes. *Controlled Clinical Trials*. 2002; 23:257–273. [PubMed: 12057878]
38. Xiong C, Milliken G. Step-stress Life-testing with Random Stress-change Times for Exponential Data. *IEEE Transactions on Reliability*. 1999; 48:141–148.

Appendix

For subjects whose treatment do not change over time, i.e., $u=tt$ or pp , the simple least squares estimate to the subject-specific rate of change in ADAS-cog for subject j within treatment group u is given by

$$\widehat{\beta}_{1j}^u = \frac{\sum_{i=1}^k (t_i - \bar{t}) Y_{ji}^u}{\sum_{i=1}^k (t_i - \bar{t})^2}, \quad (5)$$

where $\bar{t} = \sum_{i=1}^k t_i / k$. It is straightforward to derive the variance for the least square estimate $\widehat{\beta}_{1j}^u$ to the rate of change as

$$\delta_u^2 = \sigma_e^2 \left\{ \sum_{i=1}^k (t_i - \bar{t})^2 \right\}^{-1} + \sigma_u^2. \quad (6)$$

For subject j who begins with the placebo and then switches to the active treatment, i.e., $u=pt$, the simple least squares estimate to the rate of change before and after the change time t_{k0} ($1 < k_0 < k$) are

$$\widehat{\beta}_{1j}^b = \frac{\sum_{i=1}^{k_0} (t_i - \bar{t}_p) Y_{ji}^{pt}}{\sum_{i=1}^{k_0} (t_i - \bar{t}_p)^2}, \quad (7)$$

and

$$\widehat{\beta}_{1j}^a = \frac{\sum_{i=k_0}^k (t_i - \bar{t}_t) Y_{ji}^{pt}}{\sum_{i=k_0}^k (t_i - \bar{t}_t)^2}, \quad (8)$$

respectively, where $\bar{t}_p = \sum_{i=1}^{k_0} t_i / k_0$ and $\bar{t}_t = \sum_{i=k_0}^k t_i / (k - k_0 + 1)$. The covariance matrix of $(\widehat{\beta}_{1j}^b, \widehat{\beta}_{1j}^a)$ is

$$\Sigma_{pt} = \begin{pmatrix} \sigma_{pt1}^2 & \rho_{pt} \sigma_{pt1} \sigma_{pt2} \\ \rho_{pt} \sigma_{pt1} \sigma_{pt2} & \sigma_{pt2}^2 \end{pmatrix}, \quad (9)$$

where

$$\sigma_{pt1}^2 = \sigma_e^2 \left\{ \sum_{i=1}^{k_0} (t_i - \bar{t}_p)^2 \right\}^{-1} + \sigma_{pp}^2, \quad \sigma_{pt2}^2 = \sigma_e^2 \left\{ \sum_{i=k_0}^k (t_i - \bar{t}_t)^2 \right\}^{-1} + \sigma_{tt}^2,$$

and

$$\rho_{pt} = \frac{\rho \sigma_{pp} \sigma_{tt} + (t_{k_0} - \bar{t}_p)(t_{k_0} - \bar{t}_t) \sigma_e^2 \left[\sum_{i=1}^{k_0} (t_i - \bar{t}_p)^2 \sum_{i=k_0}^k (t_i - \bar{t}_t)^2 \right]^{-1}}{\sigma_{pt1} \sigma_{pt2}}.$$

The variance of $\Delta \widehat{\beta}_{1j} = \widehat{\beta}_{1j}^a - \widehat{\beta}_{1j}^b$ is

$$\sigma_{\Delta}^2 = \sigma_{pp}^2 + \sigma_{tt}^2 - 2\rho \sigma_{pp} \sigma_{tt} + \sigma_e^2 B, \quad (10)$$

where

$$B = \left\{ \left(\sum_{i=1}^{k_0} (t_i - \bar{t}_p)^2 \right)^{-1} + \left(\sum_{i=k_0}^k (t_i - \bar{t}_t)^2 \right)^{-1} - 2(t_{k_0} - \bar{t}_p)(t_{k_0} - \bar{t}_t) \left[\sum_{i=1}^{k_0} (t_i - \bar{t}_p)^2 \sum_{i=k_0}^k (t_i - \bar{t}_t)^2 \right]^{-1} \right\}. \quad (11)$$

Assuming that $t_k - t_1$ and k are chosen and that an evenly spaced longitudinal design among the repeated measures is used, it is straightforward to prove that

$$\sum_{i=1}^{k_0} (t_i - \bar{t}_p)^2 = \frac{(t_{k_0} - t_1)^2 k_0 (k_0 + 1)}{12(k_0 - 1)},$$

and

$$\sum_{i=k_0}^k (t_i - \bar{t}_t)^2 = \frac{(t_k - t_{k_0})^2 (k - k_0 + 1)(k - k_0 + 2)}{12(k - k_0)}.$$

Therefore B can be simplified as

$$B = \left\{ \frac{12(k_0 - 1)k_0^{-1}}{(t_{k_0} - t_1)^2(k_0 + 1)} + \frac{12(k - k_0)(k - k_0 + 1)^{-1}}{(t_k - t_{k_0})^2(k - k_0 + 2)} + \frac{72(k_0 - 1)(k - k_0)k_0^{-1}(k_0 + 1)^{-1}}{(t_{k_0} - t_1)(t_k - t_{k_0})(k - k_0 + 1)(k - k_0 + 2)} \right\}.$$

For any constant weight $0 < c < 1$, let $T_c = c(\bar{\beta}_1^t - \bar{\beta}_1^p) + (1 - c) \Delta \hat{\beta}_1$. The variance of T_c is given by

$$\sigma_{T_c}^2 = \frac{c^2 \delta_{pp}^2}{n_{pp}} + \frac{c^2 \delta_{tt}^2}{n_{tt}} + \frac{(1 - c)^2 \sigma_{\Delta}^2}{n_{pt}}. \quad (12)$$

The power function for testing $H_0: \beta_1^{tt} = \beta_1^{pp}$ against $H_a: \beta_1^{tt} - \beta_1^{pp} = d \neq 0$ is

$$P(d) = \Pr(|z_c| > z_{\alpha/2} | H_a) = \sum_{b=0}^1 (-1)^{b+1} \Phi \left((-1)^b z_{\alpha/2} - \frac{d}{\sqrt{\frac{c^2 \sigma_{tt}^2}{n_{tt}} + \frac{c^2 \sigma_{pp}^2}{n_{pp}} + \frac{(1-c)^2 \sigma_{\Delta}^2}{n_{pt}}}} \right), \quad (13)$$

where Φ is the standard normal distribution function, and $z_{\alpha/2}$ is the upper $\alpha/2$ percentile from the standard normal distribution.

Figure 1.
Expected Cognitive Progression for Testing Disease Modifying Agents on AD

Figure 2. Ratio of Optimum Sample Sizes Between the Arms With and Without Treatment Switch in a 3-years Trial With Quarterly Assessments (X axis = ratio of variances=between-subject variance on slope/within-subject variance, Corr = correlation on the rate of change before and after the treatment switch)

Figure 3. Total Sample Size of a 3-years Randomized Start Design with Quarterly Assessments for 80% Statistical Power (Corr = the correlation on the rate of change before and after the treatment switch)

Table 1

Optimum weight c minimizing the variance of the linear unbiased estimator T_c to the treatment effect size $\beta_1^{tt} - \beta_1^{pp}$ (k = the number of quarterly spaced measures per subject, k_0 =the time of treatment switch)

k	k₀	c
5	3	0.83
6	3 or 4	0.82
7	4	0.77
8	4 or 5	0.74
9	5	0.68
10	5 or 6	0.65
11	6	0.60

Table 2

Optimum sample size allocations ($\lambda_{pp}, \lambda_{tt}, \lambda_{pt}$) to treatment groups (in %) as a function of the number of quarterly spaced measures (k), the correlation on the rates of change before and after the treatment switch (ρ), and the ratio of between and within subject variances ($r = \sigma^2 / \sigma_e^2$)

k	ρ	r	($\lambda_{pp}, \lambda_{tt}, \lambda_{pt}$) (in %)
7	0.2	1	(34.8, 34.8, 30.4)
7	0.2	2	(33.9, 33.9, 32.2)
7	0.2	10	(31.9, 31.9, 36.2)
7	0.5	1	(34.7, 34.7, 30.6)
7	0.5	2	(33.6, 33.6, 32.8)
7	0.5	10	(31.1, 31.1, 37.8)
7	0.8	1	(34.5, 34.5, 31.0)
7	0.8	2	(33.3, 33.3, 33.4)
7	0.8	10	(30.0, 30.0, 40.0)
9	0.2	1	(33.8, 33.8, 32.4)
9	0.2	2	(32.9, 32.9, 34.2)
9	0.2	10	(31.3, 31.3, 37.4)
9	0.5	1	(33.6, 33.6, 32.8)
9	0.5	2	(32.4, 32.4, 35.2)
9	0.5	10	(30.3, 30.3, 39.4)
9	0.8	1	(33.2, 33.2, 33.6)
9	0.8	2	(31.8, 31.8, 36.4)
9	0.8	10	(28.7, 28.7, 42.6)
11	0.2	1	(33.0, 33.0, 34.0)
11	0.2	2	(32.2, 32.2, 35.6)
11	0.2	10	(31.1, 31.1, 37.8)
11	0.5	1	(32.6, 32.6, 34.8)
11	0.5	2	(31.5, 31.5, 37.0)
11	0.5	10	(29.9, 29.9, 40.2)
11	0.8	1	(32.0, 32.0, 36.0)
11	0.8	2	(30.6, 30.6, 38.8)
11	0.8	10	(27.9, 27.9, 44.2)

Table 3

Total sample size n of a randomized start design with quarterly assessments and a sample size ratio of 1:1:1 for testing future disease-modifying agents on AD with 80% statistical power (T = the number of years for the entire trial with quarterly assessments, d = the difference on the annual rate of decline for ADAS-cog between the treatment and the placebo, ρ = the correlation on the rates of change before and after the treatment switch)

T	d	ρ	n
2	1.5	0.2	7581
2	1.5	0.5	6945
2	1.5	0.8	6135
2	2.0	0.2	4263
2	2.0	0.5	3909
2	2.0	0.8	3450
2	2.5	0.2	2730
2	2.5	0.5	2502
2	2.5	0.8	2208
2	3.0	0.2	1896
2	3.0	0.5	1737
2	3.0	0.8	1536
2	3.5	0.2	1392
2	3.5	0.5	1278
2	3.5	0.8	1128
2	4.0	0.2	1068
2	4.0	0.5	978
2	4.0	0.8	864
2	4.5	0.2	843
2	4.5	0.4	774
2	4.5	0.8	684
2	5.0	0.2	684
2	5.0	0.5	627
2	5.0	0.8	552
2	5.5	0.2	564
2	5.5	0.5	519
2	5.5	0.8	459
2	6.0	0.2	474
2	6.0	0.5	435
2	6.0	0.8	384
3	1.5	0.2	6099
3	1.5	0.5	5133
3	1.5	0.8	3780
3	2.0	0.2	3432

T	d	ρ	n
3	2.0	0.5	2889
3	2.0	0.8	2127
3	2.5	0.2	2196
3	2.5	0.5	1848
3	2.5	0.8	1362
3	3.0	0.2	1527
3	3.0	0.5	1284
3	3.0	0.8	945
3	3.5	0.2	1122
3	3.5	0.5	945
3	3.5	0.8	696
3	4.0	0.2	858
3	4.0	0.5	723
3	4.0	0.8	534
3	4.5	0.2	678
3	4.5	0.5	573
3	4.5	0.8	420
3	5.0	0.2	549
3	5.0	0.5	462
3	5.0	0.8	342
3	5.5	0.2	456
3	5.5	0.5	384
3	5.5	0.8	282
3	6.0	0.2	384
3	6.0	0.5	321
3	6.0	0.8	237