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Optimizing parameters in clinical trials with a randomized start or withdrawal design

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ABSTRACT

Disease-modifying (DM) trials on chronic diseases such as Alzheimer's disease (AD) require a randomized start or withdrawal design. The analysis and optimization of such trials remain poorly understood, even for the simplest scenario in which only three repeated efficacy assessments are planned for each subject: one at the baseline, one at the end of the trial, and the other at the time when the treatments are switched. Under the assumption that the repeated measures across subjects follow a trivariate distribution whose mean and covariance matrix exist, the DM efficacy hypothesis is formulated by comparing the change of efficacy outcome between treatment arms with and without a treatment switch. Using a minimax criterion, a methodology is developed to optimally determine the sample size allocations to individual treatment arms as well as the optimum time when treatments are switched. The sensitivity of the optimum designs with respect to various model parameters is further assessed. An intersection–union test (IUT) is proposed to test the DM hypothesis, and determine the asymptotic size and the power of the IUT. Finally, the proposed methodology is demonstrated by using reported statistics on the placebo arms from several recently published symptomatic trials on AD to estimate necessary parameters and then deriving the optimum sample sizes and the time of treatment switch for future DM trials on AD.

1. Introduction

Many clinical trials require a switch of treatments in the middle of the studies, and yet are not conducted through a standard crossover design. Examples include disease-modifying (DM) trials on chronic diseases such as Alzheimer's disease (AD) that strive not only to establish the symptomatic efficacy for novel treatments in improving cognition, function, and global measures or deferring decline over a relatively short period of time, but also to demonstrate that the course of AD has been altered and the rate of disease progression has been slowed (Cummings, 2006; Aisen, 2006; Citron, 2004; Mani, 2004) over a relatively long period of time. DM trials have been widely discussed in the AD research community (Leber, 1997; Sampaio, 2006; Whitehouse et al., 1998; Cummings et al., 2007). Clinicians have conceptualized designs of DM trials to allow a definite distinction from the symptomatic trials (Cummings, 2006; Aisen, 2006; Citron, 2004). These designs in general require a switch of treatments in the middle of trials for at least a proportion of subjects originally randomized to either placebo or active treatment. One such design is the randomized start design (Mani, 2004). All patients in the design eventually will receive the active treatment, but are randomized to two treatment groups that begin the active drug at

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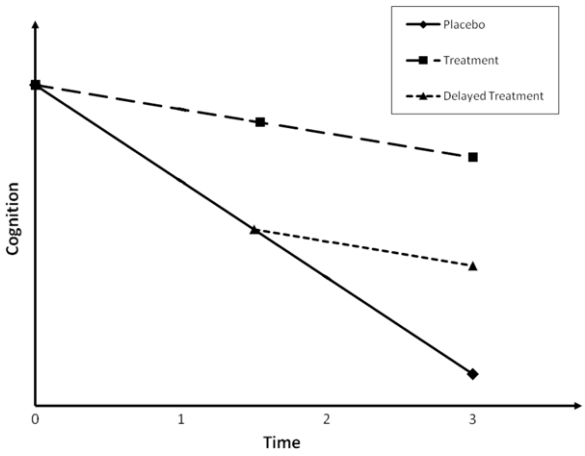

Fig. 1. Expected cognitive progression in a simple disease modifying trial on AD.

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 the symptomatic efficacy for the active drug, 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 DM. Another DM design is the randomized withdrawal design (Mani, 2004), which differs from the randomized start design only in that subjects initially on active drug are switched to placebo in the second phase. If the group withdrawn from the active drug maintains gains on the efficacy measure relative to the placebo group, it is assumed that the drug is DM. In both DM designs, in order to preserve the blinding, a second randomization must be performed to the initial placebo (or active drug) arm so that a proportion of patients will maintain on placebo (or active drug) throughout the trial. Fig. 1 presents the expected longitudinal cognitive growth profiles of a randomized start design on AD. To date, all FDA-approved treatments to AD have been entirely based on their efficacy for treating symptoms (Kryscio et al., 2004; Ringman et al., 2009; Andrieu et al., 2006), partly because the design and analyses to establish the DM effectiveness of these treatments as well as many emerging ones (Salloway et al., 2008) have not been fully established.

This paper focus on the DM trial with a randomized start or withdrawal design for which only three repeated efficacy assessments are planned: one at the baseline, one at the end of the trial, and the other at the time when the treatments are switched. We formulate the DM hypothesis and propose a method to test the hypothesis, derive optimal sample size allocations to different treatment arms and the optimum time of treatment switch, and assess the sensitivity of these designs. Finally, we present optimum designs of future DM trials on AD using the reported statistics from recently published symptomatic trials.

2. A model for DM trials with a randomized start design

2.1. Estimating DM efficacy and testing the DM hypothesis

We will discuss our methodology by focusing on the DM trials on AD with a randomized start design, and point out that our proposed methods apply to many similar clinical trials on other diseases that require a switch of treatments in the middle of the trial (i.e., randomized withdrawal design). We use Y to denote the primary efficacy outcome in DM trials on AD (Cummings, 2008). The Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog, Rosen et al., 1984) has been the most commonly used primary cognitive outcome in symptomatic trials of AD. Recently, many modalities of biomarkers have now shown promising ability to track the disease progression, including magnetic resonance imaging-based brain volumes (Storandt et al., 2009), diffusion tensor imaging-based measures of white matter microstructure (Head et al., 2004), cerebrospinal fluid (Fagan et al., 2006), and molecular imaging of cerebral fibrillar amyloid with positron emission tomography using the [^{11}C] benzothiazole tracer, Pittsburgh Compound-B (Mintun et al., 2006).

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 use $u = pt$ to represent the group of subjects who initially receive the placebo and then switch to the active treatment. Assume that $y_j^u(t)$ is the observation of Y at time t for the j-th subject from treatment group u. Let t_1, t_2, t_3 be the three time points for repeated measures of Y in a DM trial with a randomized start design, where $t_1 = 0$ is the baseline, t_3 is the time of the final assessment, and t_2 is the time for the treatment switch. Let $y_{ji}^u = y_j^u(t_i)$, $i = 1, 2, 3$, and let $Y_j^u = (y_{j1}^u, y_{j2}^u, y_{j3}^u)^t$ (superscript t means matrix transpose) be the vector of longitudinal measurements of the j-th subject from treatment group u. Because the DM design requires the establishment of both symptomatic efficacy prior to the treatment switch and the DM efficacy after the treatment switch, the first objective is to compare the change from the