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Alzheimer's & Dementia

Featured Article

Statistical advances in clinical trials and clinical research

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Abstract

Introduction: New treatments for neurodegenerative disease are urgently needed, and clinical trial methods are an essential component of new drug development. Although the parallel-group study design for neurological disorder clinical trials is commonly used to test the efficacy of a new treatment as compared to placebo, it does not efficiently use information from the on-going study to increase the success rate of a trial or to stop a trial earlier when the new treatment is indeed ineffective.

Methods: We review some recent advances in designs for clinical trials, including futility designs and adaptive designs.

Results: Futility designs and noninferiority designs are used to test the nonsuperiority and the noninferiority of a new treatment, respectively. We provide some guidance on using these two designs and analyzing data from these studies properly. Adaptive designs are increasingly used in clinical trials to improve the flexibility and efficiency of trials with the potential to reduce resources, time, and costs. We review some typical adaptive designs and new statistical methods to handle the statistical challenges from adaptive designs.

Discussion: Statistical advances in clinical trial designs may be helpful to shorten trial times and benefit more patients being treated with a better treatment during the discovery of new therapies for neurological disorders. Advancing statistical underpinnings of neuroscience research is a critical aspect of the core activities supported by the Center of Biomedical Research Excellence award supporting the Center for Neurodegeneration and Translational Neuroscience.

Keywords: Adaptive designs; Clinical trials; Futility design; Neurological disorders; Proper statistical inference

1. Introduction

In clinical trials for neurological disorders, a parallel group study is commonly used to assess the efficacy of a new treatment as compared to the placebo group [1–4]. Patients are randomized to either the treatment arm(s) or the placebo arm following a prespecified randomization schedule. At the end of the study, the change of the primary outcome from the end to the baseline, calculated from the treatment arm, is compared with that from the placebo arm to make a conclusion whether the new treatment has sufficient efficacy to move to the next phase for further investigation. The primary outcome to assess the cognitive performance can be measured by established assessment tools, such as the Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog), the Unified Parkinson's Disease Rating Scale (UPDRS), Clinical Dementia Rating, and the ALS Functional Rating Scale-revised (ALSFRSr). The commonly used parallel-group design is able to study the efficacy of the new treatment with the influential covariates being balanced during the randomization step; however, it may not be efficient

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for the purpose of rapidly screening out nonpromising treatments or identifying the most promising treatments [1,5–10].

Futility designs are widely used in early phase neurological disorder trials to screen out new treatments that are highly unlikely to produce successful results [11–15]. Futility designs can be used in a single-arm study with the threshold estimated from historical controls or in a parallel-group study with a nonsuperiority alternative hypothesis [16–18]. The purpose of the futility design is to screen out an unpromising treatment with fewer patients and a much shorter study time period. As compared to the futility design, the commonly used parallel-group study is used to test the superiority of the new treatment over the placebo. In this article, we review the difference between the futility design and the noninferiority design which is also widely used in clinical trials to test the noninferiority of a new treatment. We also provide some guidance on the proper usage of such designs [19–24].

In recent years, adaptive designs have been introduced and used in trials for neurological disorders to reduce resource use and time [25–28]. There are a few definitions for an adaptive design. In 2010, the Food and Drug Administration published a draft guidance document on adaptive designs and defined an adaptive design as "a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study" [29].

Adaptive designs provide opportunities to modify or change the trial during the study while maintaining the validity and integrity of the trial. These opportunities are prespecified when certain conditions are met. In 2008, Chow and Chang [27] reviewed 10 adaptive designs used in clinical trials, including an adaptive randomization design that allows modification of randomization schedules; a group sequential design that allows early stopping due to futility, efficacy, or both; a sample size re-estimation design allowing sample size adjustment; a pick-the-winner design; an adaptive dose-finding design; a biomarker-adaptive design; an adaptive treatment-switching design; an adaptive seamless design; a hypothesis-adaptive design; and a multiple adaptive design. In this article, we review the following two commonly used adaptive designs in neurological disorder trials. The response-adaptive randomization design uses the patients' responses from the current on-going study to modify the assignment probabilities to each treatment arm, with more patients being treated by the better arms. The response-adaptive randomization design belongs to the adaptive randomization design that also includes treatment-adaptive randomization and covariate-adaptive randomization [27]. The other adaptive design discussed in this article is the adaptive dose-finding design that increases the accuracy of the estimation for the maximum tolerated dose or minimum effective dose [30].

Studies designed by an adaptive method may introduce new challenges in data analysis. It is important that intended statistical analysis should guide the study design [23,31,32]. For this reason, new statistical analysis approaches to analyze the data from adaptive designs properly are also discussed. Review of novel, efficient, and proper statistical approaches in neuroscience research is an important service of the Data Management and Statistics Core of the Center for Neurodegeneration and Translational Neuroscience supported by the Center of Biomedical Research Excellence award from the National Institute of General Medical Sciences.

2. Futility designs

The futility design, also known as the nonsuperiority design, can be used to screen out a new treatment candidate who is not promising for further investigation. It can be implemented in a single-arm study or a parallel group study to investigate the efficacy of a new experimental treatment. Suppose μ_e and μ_c are the primary outcome of a new experimental treatment group and the control group in a parallel group study. For a single-arm study, we may use the same notation μ_c to represent the estimated value from historical data. Let $\Delta = \mu_e - \mu_c$ be the difference between the two groups.

For clinical trials in neurology, the primary outcome of interest to measure disease symptoms is often computed from some well-established assessment tools, for example, ADAS-Cog, UPDRS, and ALSFRSr. The change of these measurements from the end of a study to the baseline (post–pre) is often used as the primary outcome, for example, $\mu_e = \mu_{e1} - \mu_{e0}$, where μe_1 and μ_{e0} are the outcome of patients from the treatment group at the end and at baseline, respectively. It should be noted that a treatment with a smaller increase (slowing disease progression) or a larger decrease (improving the disease symptoms) in the outcome is considered as a better treatment in some assessment tools (e.g., ADAS-Cog, UPDRS), whereas it is reversed when others are used (e.g., ALSFRSr).

When ADAS-Cog or UPDRS is used to measure the disease symptom, suppose δ_0 is the maximum allowable progression threshold, the statistical hypotheses for the futility design are presented as

$$H_0 : \Delta \leq \delta_0 \text{against } H_a : \Delta > \delta_0, \quad (1)$$

where δ_0 is a clinically meaningful threshold to measure the disease symptom [33–35]. For example, a clinical trial to assess the effectiveness of coenzyme Q10 and GPI-1485 in PD [36] was designed as a futility study with $\delta_0 = -3.19$, which is 30% of the total UPDRS change of participants in the placebo group from the Deprenyl and Tocopherol Antioxidant Therapy of Parkinsonism trial (DATATOP), $\mu_c = 10.65$. This trial is designed as a single-arm futility study with the hypotheses: