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On clinical trials with a high placebo response rate

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ABSTRACT

The basic problem that causes the frequent failure of a standard randomized parallel placebo-controlled clinical trial with a high placebo response rate is the underestimation of the treatment effect by the observed relative treatment difference. A two-period sequential parallel enrichment design has been proposed where the first period is a standard parallel design and at the end of the first period, the placebo non-responders are identified and re-randomized in the second period. Based on such a design, available methods have primarily focused on testing either the first period treatment null hypothesis or the global null hypothesis defined as the joint period 1 and period 2 treatment effect null hypothesis by a test statistic which is either derived from a combined statistic or defined directly as a weighted z-score where the weights are functions of some population and design parameters satisfying certain power optimality criterion. However, in some cases, it is not clear what their combined statistics are estimating and in others, the combined statistics are estimating the apparent treatment effect; but generally, there is no discussion of the need to provide a proper assessment of the treatment effect for the intended study population. It should be clear that an appropriate assessment of the treatment effect for the intended study population is critical for the benefit/risk analysis as well as the proper dosage recommendation. Any benefit/risk analysis and dosage recommendation that are based on an apparent treatment effect from a standard parallel design such as the first period of a sequential parallel enrichment design tend to underestimate the benefit/risk ratio which in turn may lead to overdosing recommendation. It is the purpose of this paper to introduce the concept of an adjusted treatment effect which is derived by adjusting the apparent treatment effect from the first period of a sequential parallel enrichment design with information from the second period subject to a consistency condition. The adjustment properly compensates for the high placebo response rate. It is proposed that this adjusted treatment effect should be used to assess the treatment effect for the intended study population and should be the basis for the benefit/risk analysis and the dosage recommendation.

1. Introduction

The basic reason for the failure of many standard randomized parallel placebo-controlled clinical trials with high placebo response rate is that the observed relative treatment difference only provides an estimate of an apparent treatment effect since the treatment effect has been diminished by the presence of a substantial proportion of placebo responders in the population. The full treatment effect cannot be directly estimated by the relative treatment difference. An appropriate assessment of the full treatment effect is critical for making a risk/benefit analysis and dosage recommendation. The primary purpose of this paper is to propose a method for adjusting the apparent treatment effect to account for the high placebo response rate within the framework of a doubly randomized delayed start (DRDS) design as discussed in Liu et al. [1] which improves upon the earlier sequential parallel design (SPD) of Fava et al. [2].

2. Background

2.1. The sequential enrichment design

The problem of a high placebo response rate in clinical trials

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occurs in several therapeutic areas, but it is most often observed in trials involving subjects with psychiatric disorders. In these populations of subjects with psychiatric disorders, the placebo response rate has been estimated to vary from 30% to 50%. Trials in these therapeutic areas often failed because in a standard randomized parallel placebo-controlled trial, the observed relative treatment difference only provides an estimate of an *apparent* treatment effect which does not reflect the full treatment effect due to the dilution resulting from the presence of a substantial proportion of placebo responders. This problem has been known for quite some time. Temple [3] had suggested an enrichment design whereby subjects responding to placebo in a run-in period are excluded from a second period during which placebo non-responders are re-randomized to treatment and placebo in a parallel design. The purpose of Temple's enrichment design is merely to show that the treatment is effective in some subpopulation and in this case in the subpopulation of placebo non-responders. However, one problem with this enrichment design is that the claim of treatment effectiveness cannot be readily extended to the entire intended study population. Another problem with this design is that if the treatment is to be indicated for the enriched subpopulation, then in actual clinical practice, a patient has to be given placebo first to verify his/her placebo response status before the treatment can be prescribed; however, this would entail an ethical dilemma.

Fava et al. [2] proposed a SPD design where subjects are randomized to a treatment group and two placebo groups in the first period. At the end of the first period, the non-responders in one placebo group will be given treatment in the second period, while the non-responders in the other placebo group will continue with placebo in the second period. The subjects in the treatment group in the first period will continue on the treatment in the second Period. It should be noted that in the original proposed SPD design, the randomization in Period 2 refers to the original randomization conducted at the beginning of the first period. The lack of a re-randomization in the second period poses potential imbalance in key covariates between the two placebo non-responder groups at the end of the second period if there is a differential placebo dropout rate between the two placebo arms. Such imbalance may introduce bias and cause difficulty in the statistical inference. Liu et al. [1] proposed a doubly randomized delayed start (DRDS) design which was presented earlier at the 2010 BASS Conference. This DRDS design involves randomizing the subjects to treatment and placebo in the first period and then re-randomizing the placebo non-responders identified at the end of the first period based on some pre-specified response threshold to treatment and placebo in the second period. The terms “delayed start” were used for the obvious application of this design to trials involving progressive diseases. A simple diagram of such a design is depicted in Fig. 1.

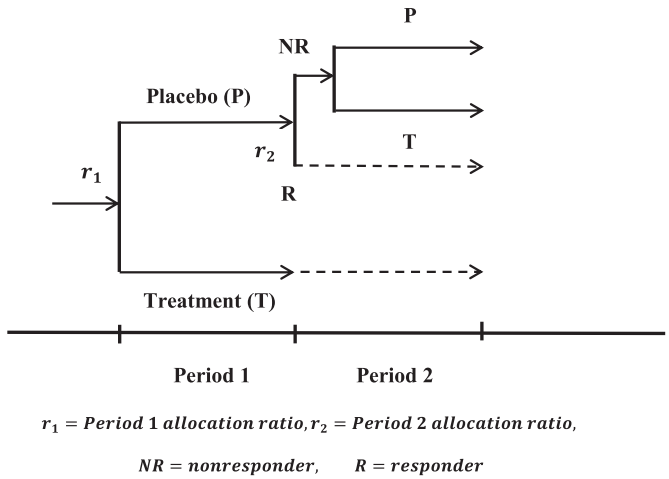

Fig. 1. A basic DRDS design for assessing treatment effect in trials with a high placebo response rate.

Chen et al. [4] considered a SPD design with re-randomization in the second period which they termed a SPD-ReR design. Now, the original SPD design has since also been revised to include re-randomization in the second period. In this paper, the DRDS design may refer to a SPD ReR design or a SPD design with re-randomization if found appropriate, and for convenience, some of the terminologies and notations used in Liu et al. [1] are adopted. The DRDS design has been accepted by the regulatory agencies as an innovative design. However, the regulatory agencies have raised issues with various proposed methods of analysis. In order to address these issues, a new statistical methodology is proposed here that includes the DRDS design and a statistical approach for this design that differs from the currently available methods.

2.2. Some key issues associated with the current methods for a DRDS design

There are a few important conceptual and technical issues related to the problem of a high placebo response rate in a DRDS design that have not been mentioned nor discussed by the previous authors. These basic issues need to be satisfactorily resolved before a DRDS design can be applied to phase 3 trials to obtain the evidence of effectiveness required. These issues will now be discussed and they will be addressed in the new approach to be proposed in Section 4.

2.2.1. Issue 1

The customary view considers the standard randomized parallel double blind placebo-controlled design as the design of choice because the relative treatment difference from such a design reflects the net treatment effect over and beyond what is expected of a placebo which should be minimal for this view to be valid. In a study population that has a substantial proportion of placebo responders, the relative treatment difference is only an apparent treatment difference, because it ignores the mitigating effect of the presence of a high placebo response rate on this treatment difference. This is the primary reason why many such trials have failed in the past. In a DRDS design, this same problem is present in the first period. Therefore, clearly the apparent treatment effect from the first period would be underestimating the full treatment effect. Another problem inherent in the above view is that even if perchance the apparent treatment effect shows the treatment is superior to placebo, any dosage recommendation based on an apparent dose–response relationship would likely lead to overdosing. Hence, for these two reasons alone, an appropriate assessment of the treatment effect adjusting for high placebo response rate is needed.

2.2.2. Issue 2

A problem that is born of the above view is present in the current proposed methods of analysis of a DRDS design. These methods variously proposed to estimate the apparent treatment effect of Period 1 by a combined statistic, which is defined as a weighted combination of the apparent treatment effect of Period 1 and the enriched treatment effect of Period 2 under some assumptions. For example, in Huang and Tamura [5], a score test is derived under the constancy assumption which requires that the enriched treatment effect of Period 2 be equal to the apparent treatment effect of Period 1, while for binary outcome, in Tamura