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D-optimality of unequal versus equal cluster sizes for mixed effects linear regression analysis of randomized trials with clusters in one treatment arm

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ABSTRACT

The efficiency loss due to varying cluster sizes in trials where treatments induce clustering of observations in one of the two treatment arms is examined. Such designs may arise when comparing group therapy to a condition with only medication or a condition not involving any kind of treatment. For maximum likelihood estimation in a mixed effects linear regression, asymptotic relative efficiencies (*RE*) of unequal versus equal cluster sizes in terms of the *D*-criterion and D_s-criteria are derived. A Monte Carlo simulation for small sample sizes shows these asymptotic *RE*s to be very accurate for the D_s-criterion of the fixed effects and rather accurate for the *D*-criterion. Taylor approximations of the asymptotic *RE*s turn out to be accurate and can be used to predict the efficiency loss when planning a trial. The *RE* usually will be more than 0.94 and, when planning sample sizes, multiplying both the number of clusters in one arm and the number of persons in the other arm by $1/RE$ is the most cost-efficient way of regaining the efficiency loss.

1. Introduction

Trials evaluating the effect of an intervention are often characterized by observations being correlated within clusters. A well-known case is group or cluster randomized trials (Donner and Klar, 1994; Raudenbush, 1997), where groups (e.g. schools or general practices) are assigned to one of the several treatment conditions. In these designs groups are the units of assignment. Observations may also be clustered when individuals are the units of assignment. This may occur when the treatment itself induces clustering, such as in individually randomized group treatment trials (Pals et al., 2008), where treatments are given to groups of individuals. In such trials interactions between persons within a group may lead to observations being correlated (Bauer et al., 2008; Roberts and Roberts, 2005). It is quite common that the clustering occurs in only one of the treatment arms, such as when group therapy is compared to a condition involving no kind of intervention (e.g. Bauer et al., 2008; Heller-Boersma et al., 2007; Pisinger et al., 2005) or to a condition involving only medication (e.g. Dannon et al., 2004; Haugli et al., 2001).

Even if the treatment is given on an individual basis, instead of groupwise, the treatment may induce clustering. This may occur if several patients are treated by the same therapist. Since it is likely that patients of the same therapist will be treated in a more similar way than patients treated by different therapists (Pals et al., 2008; Roberts, 1999), observations within each therapist will be clustered. Also in this case clustering may occur in only one of the two treatment arms, such as when treatment is contrasted with a waiting-list condition (e.g. Ladouceur et al., 2000; Thompson et al., 1987; Van Minnen et al., 2003) or with a pharmacological or placebo condition (e.g. Jarrett et al., 1999).

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Starting from a particular cost function Moerbeek and Wong (2008) examined optimal designs and derived sample size formulas in case there is clustering in one of two treatment arms. The present study extends their study by examining clusters that are of unequal size. Unequal cluster sizes may be due to variation in actual cluster size, but also due to nonresponse or dropout of subjects, and therefore is a common situation. The efficiency loss due to variation in cluster sizes when focussing on the estimation of the treatment effect has already been examined (Candel and Van Breukelen, 2009). The present study will examine the efficiency loss when considering the ensemble of all model parameters involved. Also the efficiency loss for the subset of all fixed parameters, among which the treatment effect, and the efficiency loss for the subset of all variance components, will be considered. In randomized trials the fixed parameters are usually of primary interest. The standard errors of the fixed effect estimators, however, are a function of the variance components. Furthermore, variance component estimation in itself may be relevant, such as in quality control studies where the variance in health outcomes between clusters (e.g. general practices, therapists or therapy groups) is examined (e.g. Van Berkestein et al., 1999). This motivates studying the efficiency loss also for the variance components. The efficiency criteria that are examined in this paper, are known as the D-criterion and, in case of a subset of parameters, as the D_s-criterion (Atkinson et al., 2007). For each criterion the issue is how much efficiency is lost due to varying cluster sizes and how to compensate for this loss.

In deriving the efficiency loss we assume that the data within each treatment arm are (approximately) normally distributed and are analyzed with mixed effects linear regression. The relative efficiency of unequal versus equal cluster sizes will be derived for the asymptotic case when the model parameters are estimated through maximum likelihood. Furthermore, Taylor approximations of the asymptotic relative efficiencies, that can be of practical use when planning a trial, will be derived. Since in relevant studies (e.g. Calzone et al., 2005; Haugli et al., 2001; Pals et al., 2008; Roberts and Roberts, 2005; Wampold and Serlin, 2000), the number of clusters as well as the cluster sizes themselves are rather small, the asymptotic relative efficiencies and their Taylor approximations will be checked for small samples by an extensive Monte Carlo simulation study, both for maximum likelihood and restricted maximum likelihood estimation. Finally, we will address how to optimally regain the efficiency loss. If we want to minimize the costs involved with a study, should we additionally sample relatively more clusters for one arm or more persons for the other?

The paper is structured as follows. Section 2 presents the mixed effects linear regression model for trials comparing a treatment arm with clustering to a control arm without clustering. In Section 3 the criteria for evaluating the efficiency loss due to varying cluster sizes will be presented. Section 4 will provide explicit expressions for the asymptotic relative efficiencies when comparing equal to unequal cluster sizes, and will also present Taylor approximations for these asymptotic expressions. Section 5 will discuss the design and results of a Monte Carlo simulation that examines the relative efficiency for various cluster size distributions with realistic sample sizes. The accuracy of both the asymptotic relative efficiencies and the Taylor approximations will be discussed. Section 6 explains how to regain the efficiency loss such that the costs of a design are minimized. Section 7 illustrates for an empirical example how to determine sample sizes in case of the D_s-criterion for fixed effects and how to adjust these to repair the efficiency loss that is expected due to varying cluster sizes. The paper closes with some implications for the planning phase of trials.

2. The mixed effects linear regression model

Suppose in a randomized trial cognitive behavioural group therapy is given to patients with a panic disorder, and its effectiveness in terms of anxiety reduction is compared to only receiving medication (e.g. paroxetine) (cf. Dannon et al., 2004). Within the treatment arm we then have K therapy groups, or, more generally, K clusters. In cluster j ($j = 1, \ldots, K$) there are n_j persons, with all persons receiving the treatment. The total number of persons in the treatment arm therefore amounts to $N = \sum_{j=1}^{K} n_j$. In the control arm medication is given and there is no clustering. This condition is denoted as the $K+1$th cluster, consisting of n_{K+1} persons. If the cluster sizes are equal, we have $n_j = n$ for $j = 1, \ldots, K$, but in general not for $j = K+1$ (e.g. when $n_{K+1} = N$).

Let the outcome variable be some quantitative measure of anxiety, such as the Hamilton rating scale for anxiety (cf. Dannon et al., 2004), which is denoted as y_{ij}, for person i in cluster j ($j = 1, \ldots, K+1$). If y_{ij} is (approximately) normally distributed, mixed effects linear regression is an appropriate tool for data analysis. The corresponding analysis model is then as follows (cf. Bauer et al., 2008; Moerbeek and Wong, 2008; Roberts, 1999):

$$y_{ij} = \beta_0 + (\beta_1 + u_{0j} + \varepsilon_{ij})T_{ij} + \delta_{ij}(1 - T_{ij}), \tag{1}$$

where T_{ij} denotes the treatment condition for person i in cluster j, and is coded as 1 for persons in the treatment arm and 0 for persons in the control arm. With this coding scheme, β_0 represents the mean anxiety score of the control condition (i.e. pharmacological treatment) and β_1 represents the treatment effect of group therapy versus medication on anxiety. The terms ε_{ij} and u_{0j} represent a random person and random cluster effect in the treatment arm, which are assumed to be independently normally distributed with variances σ_ε^2 and σ_0^2 respectively. The random person effect in the control arm, δ_{ij}, is also independently normally distributed, with a possibly different variance σ_δ^2. So the model has five parameters that have to be estimated: two fixed regression weights, β_0 and β_1, and three variance components, σ_0^2, σ_ε^2 and σ_δ^2. Estimates of these parameters can be obtained through maximum likelihood (ML). A relevant concept is the intraclass correlation, which is the correlation between outcome measures for two randomly drawn persons from the same cluster in the treatment arm. The intraclass correlation, denoted as ρ, can be expressed in terms of the variance components as: $\rho = \sigma_0^2/(\sigma_0^2 + \sigma_\varepsilon^2)$.