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Sample size calculation for non-compliance randomized trials with repeated measurements in binary data

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Abstract

When we have difficulty in recruiting patients into a randomized clinical trial (RCT), we may consider taking more than one measurement per patient to reduce the number of patients needed to achieve a desired power. In this paper, we consider a double blind RCT with two courses of treatment per patient. At each course, a patient assigned to the experimental treatment could switch to receive the placebo if the patient declined his/her assigned (experimental) treatment, and a patient assigned to the placebo could switch to receive the experimental treatment if the patient refused his/her assigned (placebo) treatment as well. Sample size calculation without accounting for this non-compliance can be inadequate when we apply the standard procedure of intention-to-treat analysis for non-compliance trials to test no treatment effect. Based on the simple additive risk model proposed elsewhere, we have incorporated the initial probability of compliance, the dependence of patient's selection of a treatment on his/her previous response, and the variation of probabilities of response between patients into sample size determination. We have included a quantitative discussion that provides an insight into the effect of various parameters on the minimum required sample size. We have also noted the situation in which taking repeated measurements per patient can be most effective to reduce the number of patients needed to maintain a given power.

Keywords: Sample size calculation; Power; Repeated measurements; Non-compliance randomized trials; Binary data

1. Introduction

When the cost of obtaining an additional patient is relatively high as compared to that of obtaining an additional measurement from the same patient or when patients are relatively difficult to recruit into a randomized clinical trial (RCT), we may consider taking more than one measurement from each patient to save the number of patients needed to achieve a desired power or to reduce the total expense of a trial. Furthermore, the data with repeated measurements may also arise in practice due to the natural recurrent characteristics of the underlying disease. For example, consider the double blind RCT of studying the effect of macrophage colony-stimulating factor (M-CSF) (Sato, 2001; Matsuyama, 2002; Ohno et al., 1997) on reducing febrile neutropenia incidence (which can occur recurrently) in acute myeloid leukemia patients. Each patient was given either M-CSF or placebo for two weeks after the completion of the consolidation chemotherapy at three courses and the incidence of febrile neutropenia on the patient was then recorded

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in each of these courses. Other examples of diseases with recurrent symptoms include multiple opportunistic infections in patients with acquired immunodeficiency syndrome, hospitalizations due to drug-associated disease symptoms in drug users, asthma, and multiple injuries in aging studies. Since there were some patients who might not comply with their assigned treatments throughout the trial, sample size calculation without incorporating this non-compliance based on the commonly-used intention-to-treat (ITT) test (Brunner and Neumann, 1985; Sommer and Zeger, 1991; Gillings and Koch, 1991; Bernhard and Compagnone, 1989; Mark and Robins, 1993; Lui and Lin, 2003) could lead us to obtain a statistically non-significant result simply due to inadequate power (Sato, 2000). In fact, the magnitude of the relative loss of power due to an even moderate extent (say, 10%) of non-compliance for both comparison groups can be, as noted later in this paper, substantial ($\approx$ 25%). Thus, it is essentially useful and important to develop a sample size formula accounting for patient non-compliance under a double blind RCT with repeated measurements.

Based on the simple additive risk model proposed elsewhere (Sato, 2000, 2001; Matsuyama, 2002), we have incorporated the initial probabilities of compliance, the dependence of patient's selection of a treatment on his/her previous response, and the variation of probabilities of response between patients into sample size calculation. On the basis of ITT analysis, we have developed a sample size formula for a double blind non-compliance RCT with two measurements per patient under a simple additive risk model (Sato, 2001; Matsuyama, 2002). We have included a quantitative discussion that provides an insight into the effect of various parameters on the minimum required sample size. We have noted the situation in which taking repeated measurements can be most effective to reduce the number of patients needed to maintain a desired power. Some discussions on sample size calculation for repeated measurements with assuming complete compliance for all patients appear elsewhere (Lui, 1991, 1997; Lui and Cumberland, 1992).

2. Notation and sample size determination

Consider comparing an experimental treatment ($g = 1$) with a placebo ($g = 0$) in a double blind RCT, in which $n_g (g = 1, 0)$ patients are randomly assigned to the respective treatment group g. In this paper, we focus our discussion on the situations in which each patient has two courses of treatment. Following Sato (2001) and Matsuyama (2002), we assume that the response of a given patient is unrelated to the treatment status of other patients, and is also not directly affected by the treatment assigned, but rather by the treatment actually received. These two assumptions are called the stable unit treatment value and exclusion restriction assumptions (Rubin, 1978; Angrist et al., 1996). In a double blind RCT, in which neither physicians nor patients know what treatment a patient actually receives. Thus, these assumptions should be generally plausible. At each course, each patient prior to taking his/her responses would receive the assigned treatment if which he/she accepted, and would receive the other treatment, otherwise. Let Y_{ijg} denote the random variable of response for patient i $\left(i = 1, 2, \ldots, n_g\right)$ at course j $(j = 1, 2)$ assigned to treatment g, and $Y_{ijg} = 1$ if the patient has a positive response, and $= 0$, otherwise. Based on the additive risk model suggested elsewhere (Sato, 2000, 2001), we assume that the probability $P\left(Y_{ijg} = 1|Z_{ijg}, M_{ijg}\right) = p_{ijg} + \delta Z_{ijg}$ for $j = 1, 2$, where M_{ijg} denotes all the underlying medical history and conditions up to the course j of patient i assigned to treatment g $(g = 1, 0)$, p_{ijg} denotes the underlying probability of positive response if patient i receives the placebo and is a function of M_{ijg}; δ represents the excess effect due to the experimental treatment over the placebo; and $Z_{ijg} = 1$ if patient i in course j assigned to treatment g actually received the experimental treatment ($g = 1$) prior to observing the response Y_{ijg}, and $= 0$, otherwise. In other words, for a given patient i assigned to treatment g at course j, he/she will have either the probability p_{ijg} of positive response if he/she takes the placebo or the probability $p_{ijg} + \delta$ of positive response if he/she takes the experimental treatment. Because the effect of M_{ijg} is incorporated through p_{ijg}, we may simplify the notation by omitting M_{ijg} from $P\left(Y_{ijg} = 1|Z_{ijg}, M_{ijg}\right)$ and expressing this as $P\left(Y_{ijg} = 1|Z_{ijg}\right)$. Note that the underlying probability p_{ijg} of positive response, like other unknown confounding covariates, are expected to be balanced through randomization. Thus, on the basis of the exclusion restriction assumption, we can assume that the underlying probabilities p_{i1g} $(g = 1, 0)$ of positive response for a randomly selected patient if he/she were actually to receive the placebo at course 1 between two comparison groups follows the same unspecified probability density function with mean $E\left(p_{i1g}\right) = \pi_1$ and variance $Var(p_{i1g}) = \sigma^2_{p_1}$ (Sato, 2001; Matsuyama, 2002). Note further that because the underlying probability of response p_{i2g} at course 2 is likely to be positively correlated to p_{i1g} at course 1, we assume that $p_{i2g} = p_{i1g} + \varepsilon^{(1,2)}_{ig}$, where $\varepsilon^{(1,2)}_{ig}$ denotes the random effect due to the difference in patient's basic conditions between courses 1 and 2 and is assumed to be independent of p_{i1g}. Thus, the covariance between p_{i1g} and p_{i2g} is $\sigma^2_{p_1} > 0$. Following Sato (2001), we also