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Optimal treatment allocation and study duration for trials with discrete-time survival endpoints

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ABSTRACT

Studies on event occurrence may be conducted in experiments, where one or more treatment groups are compared to a control group. Most of the randomized trials are designed with equally sized groups, but this design is not always the best one. The statistical power of the study may be larger with unequal sample sizes, and researchers may want to place more participants in one group relative to the other due to resource constraints or costs. The optimal designs for discrete-time survival endpoints in trials with two groups, where different proportions of subjects in the experimental group are taken into account, can be studied using the generalized linear model. Applying a cost function, the optimal combination of the number of subjects and periods in the study and the optimal allocation ratio can be found. It is observed that the ratio of the recruitment costs in both groups, the ratio of the recruitment cost in the control group to the cost of obtaining a measurement, the size of the treatment effect, and the shape of the survival distribution have the greatest influence on the optimal design.

1. Introduction

The aim of experiments is to compare the effectiveness of one or more new treatments relative to a standard treatment or no treatment at all. Experiments are often conducted in the social and medical sciences with the aim to develop better medication, surgery or therapy for patients, to develop better teaching material and methods for pupils, to develop better employment and welfare projects for the poor and unemployed, and so forth.

Experiments are often expensive, time consuming, they require the expertise of scientists and supportive staff, and the willingness of subjects to participate. It is therefore important to detect an effect of a treatment with sufficient probability, provided such an effect exists indeed in the population. This probability is called the statistical power and it increases with the size of the study. Sample size calculations can be found in standard textbooks, such as Cohen (1988), Chow et al. (2008), and Julious (2010).

Most sample size formula assume equal allocation of subjects across treatment conditions but there are various reasons for the use of unequal randomization (Dumville et al., 2006; Torgerson and Torgerson, 2008):

- cost: when one of the treatments is more expensive than another one, then researchers might allocate more participants to the least expensive treatment to recruit in total larger number of participants without increasing the costs of the study;
- 'learning curve': allocating more participants to a group receiving a new treatment helps learning faster about the innovation;

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- ethical reasons: when a new treatment might have harmful side effects for participants, researchers should recruit fewer participants to that treatment group than to a control group.

From a statistical point of view using a design with unequally sized treatment groups may be beneficial if it results in a higher power for the test on treatment effect as compared to a design with equally sized treatment groups. This issue has been already presented in the statistical literature, for instance, by Schouten (1999), Moerbeek and Wong (2008), Liu (2003), Dette (2004), Zhu and Wong (2000). The common feature of these papers is that they focus on trials where the outcome variable is measured at one point in time. Sample size formula for longitudinal studies, but with equal allocation, can be found in Raudenbush and Liu (2000), Galbraith and Marschner (2002), Moerbeek (2008), Tekle et al. (2008).

A type of an outcome variable that may be encountered in longitudinal trials is a survival outcome that measures whether and when events occur in time and whether event occurrence depends on treatment condition and relevant covariates. Sample size and power calculations for continuous-time survival analysis are presented by Sposto and Krailo (1987), Kalish and Harrington (1988), Collet (2003), Machin et al. (2006), Hosmer et al. (2008), or Julious (2010).

Unfortunately, these sample sizes cannot be straightforwardly used in trials where event occurrence is measured on a discrete scale using thicker intervals like months or years. Reasons for measuring event occurrence in discrete time are extensively discussed in Singer and Willett (2003) and include memory failure in retrospective studies, and the fact that some events can only occur at a few points in time. For instance, graduation from university can occur at only a small number of preset times during the academic year. Also, it will not always be feasible or practical to follow subjects continuously. In a smoking prevention intervention that aims to prevent and delay the onset of experimental smoking, for instance, it is impractical to contact all subjects on a daily basis to ask if they have started smoking that day. Instead, subjects will be contacted on a regular basis, say once each month.

So far, not much research has been conducted on the design of trials with discrete-time survival endpoints. The relation between statistical power and sample size for such trials with fixed study duration is presented by Jóźwiak and Moerbeek (2012a), and the effect of sample size and varying study duration on power is investigated in Jóźwiak and Moerbeek (2012b). In both papers trials with equally sized groups are considered. The key conceptual difference between the two papers and the current one is that now we take unequal allocation ratios into account. The aim of the current paper is to provide a more thorough study of the design of trials with discrete-time survival endpoints. We aim to study the optimal sample size, allocation across treatments, and study duration. Study duration is directly related to the number of measurements since with discrete-time survival analysis a measurement is taken at the end of each time period. As is obvious statistical power increases with the number of subjects and study duration but these two quantities are often restricted by financial recourses. Therefore we take into account a cost constraint in the calculation of our optimal design. This constraint also allows for unequal costs across treatment conditions.

2. Model for discrete-time survival data

In this section, we present the discrete-time survival model for longitudinal trials where subjects are followed over multiple time periods. For a more extensive introduction to this model we refer to Singer and Willett (2003).

We take trials with maximum duration of p_{max} time intervals into account, but subjects may be followed over $p = 1,2,\ldots,p_{max}$ periods and increasing the number of periods results in an increased duration of the study. So, p_{max} is the maximum number of time periods that can be used and p is the number of time periods at hand. In choosing p_{max} researchers should take the duration of a trial and frequency of observation into consideration, and p can be chosen as a fixed or a random number. We assume all the periods are of equal and fixed length, because in such case it is easier to compare baseline hazard probabilities across periods. In each time period a binary response variable that records event status is observed. It takes the value 1 if the event occurs or 0 if it does not occur. The outcome for the ith subject in the kth ($k = 1,\ldots,p$) period is denoted as Y_{ik} which is used for analysis until and including time period k if the ith subject either experiences the event or drops out from the trial in the kth time period, or until time p if the subject completes the trial experiencing the event in the pth period or does not experience the event during the course of the trial. The risk of experiencing the event in the kth period depends on the duration of the period and the underlying continuous-time survival function that is defined as $S(t) = P(T > t)$, where T is a continuous random variable for time.

Assuming that the event has not occurred in the previous periods, the discrete-time hazard probability for period k is defined as $h(t_k) = P(T = t_k | T \geq t_k)$ with T as a discrete random variable. So it is a conditional probability and it is obtained as $h(t_k) = (S(t_{k-1}) - S(t_k))/S(t_{k-1})$, where $S(t_k)$ is the discrete-time survival function at the end of period k and $t_k = k/p_{max}$. By definition, the survival is equal to 1 at the beginning of the trial ($S(t_0) = 1$).

To model the hazard probability for subject i in period k, the generalized linear model (GLM) with logit link function is used:

$$g(h(t_{ik})) = \text{logit } h(t_{ik}) = \log \frac{h(t_{ik})}{1 - h(t_{ik})} = \sum_{k=1}^{p} \alpha_k D_{ik} + \beta Z_i, \tag{1}$$

where g is the logit link function. The variable Z_i relates to the treatment group: $Z_i = 0$ for the control condition and $Z_i = 1$ for the experimental condition. Its related regression coefficient β is the treatment effect on the logit scale and it is assumed to be constant across time periods. That is, we assume a proportional odds model. Coefficient β may depend on the time intervals'