Adaptive dose-finding

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Abstract. The peak dose is the maximal dose beyond which additional benefit is unlikely. We propose an adaptive design to efficiently estimate the peak dose in a dose-finding trial when the dose-response curve can be assumed to be non-decreasing. At each step the peak dose is estimate by fitting a linear model adjusted for a set of known covariates with model coefficients subject to order restriction. Simulations show that the new adaptive strategy is by far superior to equal allocation.

Keywords. Minimum effective dose, peak dose, isotonic regression.

1 Introduction

High precision of estimation of doses of interest in dose ranging studies is essential for the future development of the drug. Among the doses of interest is the peak dose, a maximal dose beyond which additional benefit would be unlikely to occur (ICH E4 guideline). The peak dose is the lowest dose on the plateau of a dose-response curve. There is a long history of adaptive dose-finding methods for estimating a dose with a certain mean response when outcome is binary (Wetherill, 1963; O'Quigley, Pepe and Fisher, 1990; Babb, Rogatko and Zacks, 1998) and for continuous outcomes (Eichhorn and Zacks, 1973; Ivanova and Kim, 2009). Most of these methods have been developed for oncology trials. A number of adaptive strategies for dose-response studies in non-oncology setting have been recently proposed (Berry et al., 2001; Miller, Guilbaud, Dette, 2007; Ivanova, Bolognese, Perevozskaya, 2008; Ivanova et al., 2009). Yet, we are not aware of any publications addressing adaptive estimation of the peak dose.

Often there is a set of known covariates that are believed to be associated with response to treatment. In a recent proof of concept study conducted by a large pharmaceutical company, it was believed that in- an out-patient status was associated with therapeutic response to treatment. If the goal is to estimate the dose with a certain mean response the target doses will be possibly different for each level of the covariate, as in Innocenti et al. (2004) example, and can also be different from the target dose defined based on the population mean response. The goal can be to find all of these doses or, for example, only the one based on the population mean response. Often the target dose is defined as the dose with the mean response equal to the mean response of some other dose (placebo or the highest dose) plus or minus a constant. In this case, if the mean response is modeled with identity link function and a linear model with covariates, the target doses coincide.

In most dose-finding trials one can assume monotonicity of the dose-response curve. In a dose-finding trial where mean responses are believed to follow an isotonic model (for example, non-decreasing or umbrella shape) using isotonic assumption usually leads to increased efficiency in the estimation of the target dose compared to a trial where this assumption is not utilized, especially if the dose-response curve has a long plateau. Isotonic estimates were successfully used in the past (Conaway, Dunbar, Peddada, 2004; Yuan and Chappell, 2004). The presence of covariates presents a challenge in estimation of the adjusted mean response under isotonic assumptions. Restricted maximum likelihood estimates may perform unsatisfactory in terms of mean squared error (Lee, 1988) especially in the context of model (1) when the dose-response curve is flat or when the curve has long plateau (Betcher and Peddada, 2009). Betcher and Peddada (2009) proposed isotonic estimator that performs well in the presence of covariates. We adapt their estimator to use in the proposed adaptive dose-finding design.

2 Computing isotonic estimates of mean responses

Let $D = \{d_1, ..., d_K\}$ be the set of ordered dose levels selected for a trial with d_K denoting the highest dose. The highest dose can be the maximum tolerated dose established in earlier trials. Let n_i be the number of subjects assigned to d_i, and let Y_{ij} denote the response of the jth subject, $j = 1, 2, ..., n_i$, assigned to d_i, $i = 1, 2, ..., K$. Let x_{ij} be a $K \times 1$ vector of covariates associated with the jth subject assigned to the ith dose. Consider a linear model

$$Y_{ij} = \mu_i + x_{ij}'\beta + \varepsilon_{ij}, i = 1,2,...,K, j = 1,2,...,n_i. \quad (1)$$

Here μ_i is the mean response at d_i, β is the regression parameter associated with covariate vector x_{ij} and $\varepsilon_{ij} \sim N(0, \sigma^2)$.

We define the peak dose statistically, as the lowest dose with the mean response no less than $\mu_K - \gamma$, where γ, $\gamma > 0$, is close to 0. For example, in a 7-dose trial with sigmoid dose-response curve that yields mean responses at 7 discrete doses of (0.3,0.3,0.4,0.5,0.6,0.6,0.6), the peak dose is dose d_5 for any $\gamma < 0.05$; if mean responses are (0.3,0.3,0.3,0.3,0.3,0.3,0.3), the peak dose is dose d_1.

Let $\hat{\mu}_1^U, ..., \hat{\mu}_K^U$ be the estimates of the mean response from fitting a linear model (1), where U stands for an unrestricted estimator. We assume that $\mu_1 \le ... \le \mu_K$. Below we describe how to compute restricted estimates $\hat{\mu}_1, ..., \hat{\mu}_K$, $\hat{\mu}_1 \le ... \le \hat{\mu}_K$, following the algorithm of Betcher and Peddada (2009). Let Σ be the covariance matrix of $\boldsymbol{\mu}^U = (\hat{\mu}_1^U, ..., \hat{\mu}_K^U)$. First, we describe how to compute the restricted estimator $\left(\mu_i^{(i,j)}, \mu_j^{(i,j)}\right)$ with $\mu_i^{(i,j)} \le \mu_j^{(i,j)}$ from an unrestricted estimator $\left(\mu_i^U, \mu_j^U\right)$ with covariance matrix Σ_{ij}:

$$\left(\mu_i^{(i,j)}, \mu_j^{(i,j)}\right)^T = \begin{cases} (\hat{\mu}_i^U, \hat{\mu}_j^U), & \text{if } \hat{\mu}_j^U \le \hat{\mu}_j^U \\ \dfrac{1^T \Sigma_{ij}^{-} \hat{\mu}^U}{1^T \Sigma_{ij}^{-} 1}(1,1)^T, & \text{if } \hat{\mu}_i^U > \hat{\mu}_j^U \end{cases} \quad (2)$$

Here Σ_{ij}^{-} is a generalized inverse of Σ_{ij}. Then, $\hat{\mu}_1, ..., \hat{\mu}_K$ are computed in the following way:

Step 1. Consider one of the doses d_i, $i = 1,\ldots,K$. For $j = 1, 2, \ldots, i - 1$ compute $\mu_i^{(j,i)}$ from the pair $\left(\mu_j^U, \mu_i^U\right)$ with $\mu_j^{(j,i)} \le \mu_i^{(j,i)}$ using (2); for $j = i+1, \ldots, K$ compute $\mu_i^{(i,j)}$ from the pair $\left(\mu_i^{(i,j)}, \mu_j^{(i,j)}\right)$ with $\mu_i^{(i,j)} \le \mu_j^{(i,j)}$. Then compute

$$\mu_i^{AVE} = \frac{\Sigma_{j=1,...,i-1} \alpha_j \hat{\mu}_i^{(j,i)} + \Sigma_{j=i+1,...,K} \alpha_j \hat{\mu}_i^{(i,j)}}{\Sigma_{j=1,...,i-1,i+1,...,K} \alpha_j},$$

where α_j is the jth diagonal element of the covariance matrix Σ.

Repeat the procedure described above for all $i = 1,\ldots, K$ to obtain $(\mu_1^{AVE}, ..., \mu_K^{AVE})$. Note that $(\mu_1^{AVE}, ..., \mu_K^{AVE})$ is not necessarily isotonic.

Step 2. Obtain an isotonic vector of estimates $(\hat{\mu}_1, ..., \hat{\mu}_K)$ recursively as follows:

$$\hat{\mu}_K = \mu_K^{AVE}$$
$$\hat{\mu}_i = \min(\mu_i^{AVE}, \hat{\mu}_{i+1}) \quad i = K-1, K-2, ..., 1$$

3 Adaptive design to find the peak dose

The peak dose is defined as the lowest dose with the mean response equal to $\mu_K - \gamma$. Ivanova and Kim (2009) suggested a dose-finding design based on *t*-statistic to estimate the dose with a certain mean response. In case when the dose-response curve plateaus and there are several doses on the plateau with the mean response equal to the target value, the *t*-statistic design will select one of these doses, and not necessarily the lowest one. The same is true of other similar methods such as groups designs (Wetherill, 1963) and the continual reassessment method (O'Quigley et al., 1990). We propose a design that is in the spirit of the *t*-statistic design. The new design selects the lowest dose with the target mean response and utilizes the estimator defined in Section 2. The new design is defined below.

The total number of subjects in the trial is fixed and is equal to *N*. Subjects can be assigned in groups or one at a time. Assume that the most recent assignment was to dose d_j. Let T_j be the test statistic testing H_0: $\mu_j - (\mu_K - \gamma) = 0$ against the two-sided alternative computed using $\hat{\mu}_j$, $\hat{\mu}_K$ defined in Section 2 and the estimated common variance from the linear model (1) . Then,

(i) If $T_j \le -\Delta$, the next group of subjects is assigned to doses d_{j+1};

(ii) If $-\Delta \le T_j \le \Delta$, the next group of subjects is assigned to dose d_j with probability φ and d_{j-1} with probability 1 - φ;

(iii) If $T_j > \Delta$, the next group of subjects is assigned to doses d_{j-1};

Applying this rule when the current dose is d_1 to d_K might cause the dose assignment to be outside *D*. Thus for $j = 1$ or *K*, when the rule would cause a treatment to be outside of the dose levels, the current dose is repeated instead. We call this strategy the modified *t*-statistic design.

Here φ, $0 < \varphi < 1$, and $\Delta > 0$ are the design parameters. We used $\varphi = 0.5$. The choice of parameter Δ was discussed in detail in Ivanova and Kim (2009). If the estimated dose is computed by interpolation $\Delta = 0$ is recommended, otherwise $\Delta = 1.0$ is recommended.

Covariate adjusted randomization within this design can be accomplished by using minimization algorithm (Pocock and Simon 1975).

4 Simulation study

We performed a simulation study to investigate the performance of the modified *t*-statistic design with balancing randomization assigning $\pi = 0.30$ of the subjects to the highest dose. The total number of subjects in the trial was 160 with design parameters $\Delta = 1.0$ and $\varphi = 0.5$. We performed simulations for equal allocation with the same balanced randomization and $\pi = 0.30$ of the subjects assigned to the highest dose. In both adaptive trial and trial where equal allocation was used, the estimated peak dose at the end of the trial was the lowest dose among all doses (including the highest) with the smallest $\left|\hat{\mu}_j - \hat{\mu}_K - \gamma\right|$. Simulation study shows that adaptive design provides better precision in estimating the peak dose than equal allocation. It also yields an increased allocation to the peak dose, which is beneficial if hypothesis testing is planned after the trial.

5 Discussion

We describe an adaptive dose-finding design to estimate the peak dose. The proposed adaptive strategy can be also used to estimate the minimum effective dose, when it is defined as the dose with the mean response equal to placebo plus some constant. Logistics of the fully sequential adaptive design can be prohibitive. One can derive a two-stage adaptive strategy from the proposed fully sequential

strategy. Our simulations show that two stage strategy that assigned half of the sample in each stage is more efficient than a single stage design.

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