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Adaptive Isotonic Estimation of the Minimum Effective and Peak Doses in the Presence of Covariates

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Abstract

We consider a problem of estimating the minimum effective and peak doses in the presence of covariates. We propose a sequential strategy for subject assignment that includes an adaptive randomization component to balance the allocation to placebo and active doses with respect to covariates. We conclude that either adjusting for covariates in the model or balancing allocation with respect to covariates is required to avoid bias in the target dose estimation. We also compute optimal allocation to estimate the minimum effective and peak doses in discrete dose space using isotonic regression.

Keywords

Dose-ranging; Minimum effective dose; Peak dose; Phase II trials; Up-and-down designs

1. Introduction

High precision of estimation of doses of interest in dose-ranging studies is essential for evaluating a drug. The minimum effective dose (MED) and the peak dose are the two doses of most interest. The MED is the smallest dose with a discernible useful effect (ICH E4 Guideline, 1994). The MED is often defined as the lowest dose with response significantly different (referring to statistical significance) from placebo. Alternatively, it can be defined in continuous dose space as the dose with mean response equal to $\mu_0 + \eta$, where μ_0 is the mean response on placebo and η is the minimum clinically important difference. The MED does not exist if mean response at all doses in the range studied is less than $\mu_0 + \eta$. The peak dose, also sometimes referred to as the maximum useful dose, is the maximum dose beyond which no further beneficial effect is seen (ICH E4 Guideline, 1994). Locating the peak dose is usually of interest after the drug has been shown to be efficacious. The peak dose is the lowest dose on the plateau of a dose-response curve. Mathematically, in continuous dose space we define the peak dose as the lowest dose with mean response of $\mu_{\max} - \gamma$, where $\mu_{\max}$ is the maximum mean response and γ is a small constant.

There is a long history of adaptive dose-finding methods for estimating a dose with a certain mean response for binary (e.g. Wetherill, 1963; O'Quigley et al., 1990; Babb et al., 1998) and for continuous outcomes (e.g. Eichhorn and Zacks, 1973; Ivanova and Kim, 2009). All of these methods have been developed under the assumption that the mean response is

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strictly increasing with dose. When the dose-response curve plateaus near the value of the mean response of interest, the goal is usually to find the lowest dose on the plateau. Cheung (2008) pointed out that existing methods might not be appropriate in this case. For example, the CRM converges to one of such doses and not necessarily the lowest one; the stationary distribution of a group design (Wetherill, 1963) will be uniformly spread across all target doses (Xiao and Ivanova, 2011). That is, many existing adaptive methods will not work well for estimating the peak dose, the lowest dose on the plateau. Also, many of existing methods were not designed for the case when finding the target dose requires estimating mean responses at other doses. For example, finding the location of the MED requires estimation of placebo response.

We make the assumption that the mean response is non-decreasing with dose. Such isotonic assumptions are made in most of dose-finding trials. For a non-decreasing curve, using the isotonic assumption usually leads to increased efficiency in estimation of the target dose compared to a trial where this assumption is not utilized. Our investigation shows that this is especially true if the dose-response curve is non-decreasing and has a plateau. Isotonic estimates were successfully used in adaptive dose finding by Conaway et al. (2004); Yuan and Chappell (2004); and recently by Li et al. (2008) and Bekele et al. (2008) in the context of a Bayesian dose-finding trial.

Often there is a set of known covariates that are believed to be associated with response to treatment. Our motivating example is a recent Phase II dose-finding trial conducted by a large pharmaceutical company where it was believed that in- and out-patient status were associated with therapeutic response to treatment. A number of adaptive designs address the problem of estimating the target dose for each level of covariate (e.g., O'Quigley and Paoletti, 2003; Ivanova and Wang, 2006). Both the MED and the peak dose are defined using a reference dose, placebo or the highest dose. When defined this way, the target dose will not depend on covariates as long as effects of dose and covariates are additive (no interaction). In dose-finding trials the role of covariates is similar to that in a comparative multi-arm trial: balancing with respect to covariates is preferred (Atkinson, 1999) for validity and to increase efficiency of estimation. Balancing is more challenging in the context of an adaptive dose-finding trial compared to a parallel group study. We describe how to randomize subjects to doses in the course of an adaptive trial while balancing allocations with respect to known covariates.

2. Optimal allocation for estimating the MED and peak doses

2.1 Notation

Let $\{d_0,\ldots, d_K\}$ be the set of ordered dose levels selected for a trial with d_0 denoting placebo and d_K denoting the highest dose, for example, the maximum tolerated dose established in earlier trials. Let n be the total sample size and n_i be the number of subjects assigned to d_i by the time a total of n subjects have been assigned, $n_0 + \ldots + n_K = n$. Let Y_{ij} denote the response of the jth subject assigned to d_i, $j = 1, 2,\ldots, n_i$, $i = 0, 1,\ldots, K$, and let x_{ij} be a $K\times 1$ vector of covariates associated with that subject. We assume the linear model

$$Y_{ij}=\mu_i+x_{ij}'\beta+\varepsilon_{ij}, i=0, 1, \ldots, K, j=1, 2, \ldots, n_i. \quad (1)$$

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

The MED is defined as the dose with mean response $\mu_0 + \eta$, where $\eta > 0$ is the minimum clinically important difference specified before the trial. The peak dose is defined as the

lowest dose with mean response $\mu_K - \gamma$, where γ, $\gamma \geq 0$, reflects the proximity to the highest mean response. For example, in a seven-dose trial with true mean response at the seven doses of (0.2, 0.21, 0.25, 0.5, 0.74, 0.79, 0.8), the MED defined with $\eta = 0.35$ is d_3, while the peak dose defined with $\gamma = 0.06$ is dose d_4.

2.2 Isotonic estimation of the target dose

Let $\widehat{\mu}^U = \left(\widehat{\mu}_0^U, \ldots, \widehat{\mu}_K^U\right)$ be the vector of unconstrained maximum likelihood estimates (MLE) obtained from model (1), and let Σ be its covariance matrix. The constrained MLE, $\hat{\mu} = (\hat{\mu}_0, \ldots, \hat{\mu}_K)$, is the estimator that maximizes the likelihood based on model (1) under the restriction $\hat{\mu}_0 \leq \ldots \leq \hat{\mu}_K$. When the components of $\left(\widehat{\mu}_0^U, \ldots, \widehat{\mu}_K^U\right)$ are independent, the constrained MLEs can be computed by applying the pool adjacent violator algorithm to the unconstrained estimates (Robertson et al., 1988). That is, if $\widehat{\mu}_0^U \leq \ldots \leq \widehat{\mu}_K^U$, $\hat{\boldsymbol{\mu}} = \widehat{\boldsymbol{\mu}}^U$; otherwise, the data from adjacent doses where the assumption of monotonicity is violated are pooled (see Robertson et al., 1988, or Stylianou and Flournoy, 2002, for more details). In presence of covariates the pool adjacent violator algorithm applied to unconstrained MLEs will not yield the constrained MLEs and might result in estimates with increased mean squared error (Hwang and Peddada, 1994). A projection approach that takes covariance into account (Silvapulle and Sen, 2005) cannot be used here since the covariance is unknown. We computed constrained MLEs directly by maximizing the likelihood in (1) under restriction.

Further, we define two estimators based on $\hat{\boldsymbol{\mu}}$. The first will be referred to as the *lowest dose* estimator and is defined as the lowest dose on the plateau of doses with the estimated mean response closest to the target. This estimator is suitable for estimating the peak dose. For example, if $\hat{\boldsymbol{\mu}}$ = (0.22,0.22,0.45,0.45,0.76,0.76,0.76), the estimated mean response closest to $\hat{\mu}_6 - \gamma = \hat{\mu}_6 - 0.06 = 0.7$ is $\hat{\mu}_4 = \hat{\mu}_5 = \hat{\mu}_6 = 0.76$, and the lowest dose estimator will select d_4 as the estimated peak dose. The second estimator is referred to as the *closest dose* estimator and is suitable for estimating the MED. It selects the lowest dose among doses with the mean response closest to the target if their estimated mean is higher than the target; and selects the highest of the doses if their estimated mean is lower than the target. In the example above, when estimating the MED with $\eta = 0.3$ the estimated mean response closest to $\hat{\mu}_0 + 0.3 = 0.52$ is $\hat{\mu}_2 = \hat{\mu}_3 = 0.45$, and the closest dose estimator will select the highest dose on the plateau, d_3, as the estimated MED since $0.45 < 0.52$.

2.3 Optimal allocation to estimate the MED and peak dose

When developing an adaptive allocation it is important to know which fixed allocation is the most efficient for estimating the target dose. An optimal design is an allocation that optimizes a certain criterion with respect to the proportion of subjects $(w_0, \ldots, w_K)$, $w_i \geq 0$, assigned to each dose, $(d_0, \ldots, d_K)$. The classical optimal design (Pukelsheim, 1993) in continuous dose space optimizes a criterion such as the volume of the confidence ellipsoid (D-optimal design) or the average variance of parameter estimates (A-optimal design). With discrete dose space, it is most natural to maximize the probability of correct selection of the target dose. Since in most dose-finding trials we work with a set of doses that have been selected before the trial, we are concerned with identifying the optimal proportions $(w_0, \ldots, w_K)$. In most cases, the optimal design depends on the true model parameters that are not known. This is true in the case of isotonic estimation as well.

In the result below $s = 0$ and $\nu = \eta$ when the MED is being estimated; $s = K$ and $\nu = -\gamma$ when the peak dose is being estimated. The following is true (the proof is in Appendix).

Proposition—The probability of correctly selecting the target dose defined as the dose with mean response equal to $\mu_s + \nu$, $s \in \{0, K\}$ by applying the closest dose or the lowest dose estimator to the weighted average of components of $\hat{\boldsymbol{\mu}}^U$ depends only on $\{w_i\}$, $\left\{(\mu_i - \mu_s)\sqrt{n}/\sigma\right\}$ and $(n/\sigma^2)\Sigma$.

When the pool adjacent violator algorithm is used, the resulting isotonic estimates are weighted averages of components of $\hat{\boldsymbol{\mu}}^U$, hence it follows from the Proposition that the optimal weights are a function of $\left\{(\mu_i - \mu_s)\sqrt{n}/\sigma\right\}$ and $(n/\sigma^2)\Sigma$. If the components of $\hat{\boldsymbol{\mu}}^U$ are uncorrelated, the optimal weights are a function of $\left\{(\mu_i - \mu_s)\sqrt{n}/\sigma\right\}$ only.

Consider the problem of estimating a dose with mean response ν, where ν is a known constant. We use a two-step approach to compute the optimal design. In the first step we determine which support points have non-zero weight. Then, compute optimal weights for these support points. In the first step, for given $\left\{\mu_i\sqrt{n}/\sigma\right\}$ we compute the optimal design numerically using the Nelder-Mead simplex algorithm (Nelder and Mead, 1965). In all dose-response scenarios the optimal design for the lowest dose estimator is at most a three-point design with allocations to $d_{\tau-1}$, d_τ, and $d_{\tau+1}$, where d_τ is the true target dose. Moreover, unless $\mu_{\tau+1} - \mu_\tau$ is very large, the optimal design for the lowest dose estimator is a two-point design with allocations to $d_{\tau-1}$ and d_τ. Since in the peak dose estimation a dose-response curve plateaus and $\mu_{\tau+1} - \mu_\tau \le \gamma$, where γ is small, the optimal design to estimate the peak dose using the lowest dose estimator is a three-point design with allocation to $d_{\tau-1}$, d_τ and d_K, where d_τ is the true peak dose. For the closest dose estimator, the optimal design is at most a three-point design with non-zero weights at the true target dose, d_τ, the dose right below, $d_{\tau-1}$, and the dose right above, $d_{\tau+1}$. Therefore the optimal design to estimate the MED using the closest dose estimator is at most a four-point design with allocation to d_0, $d_{\tau-1}$, d_τ, and $d_{\tau+1}$, where d_τ is the true MED.

In the second step of the optimal design calculations, we use the normal cumulative distribution function to compute optimal weights. The optimal weights to estimate the peak dose are computed based on $\left\{(\mu_\tau - \mu_K)\sqrt{n}/\sigma\right\}$ and $\left\{(\mu_{\tau-1} - \mu_K)\sqrt{n}/\sigma\right\}$. The probability of correctly selecting d_i as the estimated target dose is equal to

$$P = \Pr\left\{\hat{\mu}^U_{\tau-1} < \hat{\mu}^U_\tau < \hat{\mu}^U_K \cap \hat{\mu}^U_{\tau-1} + \hat{\mu}^U_\tau < 2\left(\hat{\mu}^U_K - \gamma\right) < \hat{\mu}^U_\tau + \hat{\mu}^U_K\right\} + \Pr\left\{\hat{\mu}^U_K < \hat{\mu}^U_\tau \cap \hat{\mu}^U_{\tau-1} + \hat{\mu}^U_{\tau,K} < 2\left(\hat{\mu}^U_{\tau,K} - \gamma\right)\right\},$$

where $\hat{\mu}^u_{\tau,K}$ denotes the sample mean of a pooled sample obtained at d_τ and d_K. Equivalently,

$$\begin{aligned} P = {} & \Pr\left\{\left(\hat{\mu}^U_{\tau-1} - \hat{\mu}^U_K\right) - \left(\hat{\mu}^U_\tau - \hat{\mu}^U_K\right) < 0 < \hat{\mu}^U_K - \hat{\mu}^U_\tau < 2\gamma < \left(\hat{\mu}^U_K - \hat{\mu}^U_\tau\right) + \left(\hat{\mu}^U_K - \hat{\mu}^U_{\tau-1}\right)\right\} \\ & + \Pr\left\{0 < \hat{\mu}^U_\tau - \hat{\mu}^U_K \cap 2\gamma < \hat{\mu}^U_\tau \frac{W_\tau}{w_\tau + w_K} + \hat{\mu}^U_K \frac{w_K}{w_\tau + w_K} - \hat{\mu}^U_{\tau-1}\right\}. \end{aligned} \quad (2)$$

Note that the expression to the right of 2γ can be written as a function of $(\hat{\mu}^U_{\tau-1} - \hat{\mu}^U_K, \hat{\mu}^U_\tau - \hat{\mu}^U_K)$. The vector $(\hat{\mu}^U_{\tau-1} - \hat{\mu}^U_K, \hat{\mu}^U_\tau - \hat{\mu}^U_K)$ follows a bivariate normal distribution with mean vector $(\mu_{\tau-1} - \mu_K, \mu_\tau - \mu_K)$ and a covariance matrix with diagonal $\sigma^2/n\,(1/w_{\tau-1} + 1/w_K, 1/w_\tau + 1/w_K)$ and off-diagonal element $-\sigma^2/(w_K n)$. The probability P is computed using the cumulative function of the multivariate normal distribution. The optimal allocation $(w_{\tau-1}, w_\tau, w_K)$ is the one that maximizes P over $(w_{\tau-1}, w_\tau, w_K)$, $0 \le w_K \le 1$, $k = \tau - 1, \tau, K$. Figure 1 displays $(w_{\tau-1}, w_\tau, w_K)$ plotted against total sample size for

$(\mu_{\tau-1}, \mu_\tau, \mu_K) = (0.5,0.74,0.8)$ with $\sigma = 0.25$. This mean vector is one of the scenarios in Bretz et al. (2005) (Table 1, scenario 5). The optimal allocation for sample sizes larger than those in a typical trial is displayed to illustrate that, for the set-up considered, the optimal allocation proportion to $d_{\tau-1}$ gets smaller and the allocations to d_τ and d_K increase as $\sigma^2/\sqrt{n}$ gets smaller. This is because μ_τ is closer to μ_K than it is to $\mu_{\tau-1}$, therefore it is more efficient to spend resources on distinguishing between μ_τ and μ_K, than between μ_τ and $\mu_{\tau-1}$. The probability of correctly identifying the target dose in the range of sample sizes of interest for optimal allocation is similar to equal allocation to the three doses with minimum relative efficiency of

$$\min_{n\in[20,100]} P(1/3, 1/3, 1/3)/P(w_{\tau-1}^{opt}, w_\tau^{opt}, w_K^{opt}) = 0.99.$$

That is, to estimate the peak dose well, we need to assign about equal number of subjects to the peak dose, the dose right below it, and the highest dose with no assignments to other doses. Interestingly, unbalanced allocation with many more subjects assigned to the peak dose is only beneficial when the standard error of the estimated mean is very small compared to the difference between means. Also, in estimation of the peak dose, increased allocation to the doses on the plateau other than the peak and the high dose, substantially decreases the precision of the estimate of the peak dose.

The optimal weights for the four-point design for estimating the MED are calculated similarly. Figure 2 displays $(w_0, w_{\tau-1}, w_\tau, w_{\tau+1})$ plotted against total sample size for $(\mu_0, \mu_{\tau-1}, \mu_\tau, \mu_{\tau+1}) = (0.2,0.25,0.5,0.74)$ with $\sigma = 0.25$ (Table 1, scenario 5). The conclusion is similar, allocating approximately equal numbers of subjects to each of the four doses yields good quality of estimation of the target dose. As $\sigma^2/\sqrt{n}$ gets smaller, the allocation proportions to $d_{\tau-1}$ and $d_{\tau+1}$ decreases and the allocations to d_0 and d_τ increase.

Optimal allocations in Section 2 were computed under the assumptions of independence among unconstrained estimates. When covariates are present the unconstrained estimates are no longer independent, and optimal allocations are computed under a given correlation structure. Our simulation study of trials with covariates yielded similar optimal designs: three or four point designs with balanced allocation are nearly optimal.

3. Adaptive design to estimate the MED and peak doses

3.1 Adaptive strategy to estimate the MED and the peak dose

In Section 2 we computed the optimal design for estimating the MED and peak doses. As is the case for most parametric models, the optimal allocation depends on the true model. For isotonic model, one needs to know the location of the target dose to construct the optimal design. Therefore our adaptive strategy will be to locate the target dose and to make allocations to the target dose and other two or three key doses approximately equal. We use this as a guideline to design an adaptive strategy. Ivanova and Kim (2009) introduced a dose-finding design based on t-statistic to locate the dose with a certain mean response. We modify their strategy to target optimal (or nearly optimal) allocation. According to the t-statistic design, subjects can be assigned in groups or one at a time. Assume that the most recent assignment was to dose d_i. Let T_i be the test statistic testing H_0: $\mu_i - (\mu_0 - \eta) = 0$ against the two-sided alternative computed using constrained MLEs $\hat{\mu}_i$, $\hat{\mu}_K$ and the estimated common variance from linear model (1).

Then,

i. If $T_i \le -\Delta$, the next group of subjects is assigned to doses d_{i+1};

ii. If $-\Delta < T_i < \Delta$, the next group of subjects is assigned to doses d_i;

iii. If $T_i \ge \Delta$, the next group of subjects is assigned to doses d_{i-1}.

Applying this rule when the current dose is d_1 or d_K might cause the dose assignment to be outside $\{d_1,\ldots,d_K\}$. Thus for $i = 1$ or K, when the rule would cause a treatment to be outside of the dose levels, the current dose is repeated instead.

To estimate the MED, we set $\Delta = 0$, in the above design in which case the adaptive rule will allocate to either d_{i-1} or d_{i+1} after allocating d_i. If $\mu_\tau = \mu_0 - \eta$, the limiting allocation for the t-statistic design is allocating to $d_{\tau-1}$, d_τ, and $d_{\tau+1}$ with proportion (0.25,0.5,0.25). This proposed strategy provides acceptable balance in allocations to $d_{\tau-1}$, d_τ, and also allows the design to "move fast" among doses in the early stages of the trial (Ivanova and Kim, 2009).

To estimate the peak dose, one needs to make sure that the design converges to the lowest dose on the plateau and also that the allocation close to optimal is achieved. We accomplish this by a choice of Δ and by modified the decision rule in the design. To make sure that the design reaches the lowest dose of the plateau, we replace the action "if $-\Delta < T_i < \Delta$, repeat the dose" in the design described above with the action "if $-\Delta < T_i < \Delta$, assign next subject to d_{i-1} with some probability ϕ or repeat the dose with probability $1 - \phi$ while keeping Δ strictly above 0. Ivanova and Kim (2009) pointed out that it is advantageous to have small Δ in the beginning of the trial for "fast movement" with larger Δ later in the trial. For example, a trial with 8 cohorts and 3 subjects per cohort yielded the optimal $\Delta = 0.45$ for the first 2 cohorts and $\Delta = 1.05$ for the cohorts 3–8 (Ivanova and Kim, 2009). Following this suggestion, we propose setting $\Delta_{n_i} = 3/[1+\exp(3 - 0.05n_i)]$. Defining Δ_{n_i} in such a way makes Δ equal to about 0.5 for small n_i, equal to about 1.0 when $n_i = 46$; Δ_{n_i} tends to 3.0 when n_i goes to infinity. The choice of the value ϕ is guided by the optimal allocation for estimating of the peak dose. The value of $\phi = 1$ results in equal allocation (which is nearly optimal) to the target dose and a dose level right below in the limit, therefore we set $\phi = 1$ in the adaptive strategy. This results in a simple allocation strategy for estimating a target dose when dose-response curve is assumed to be non-decreasing: increase the dose if $T_i \le -\Delta_{n_i}$, where n_i is the number of subjects assigned to dose d_i so far; otherwise decrease the dose.

3.2 Covariate adjusted randomization

In a dose-ranging study subjects are usually assigned in cohorts. In a trial estimating the MED, at each step a dose is adaptively chosen from $\{d_1,\ldots,d_K\}$ and some subjects in a cohort are randomized to placebo d_0. In a trial estimating the peak dose some subjects in each cohort are randomized to d_K and some to one of $\{d_1,\ldots, d_{K-1}\}$. To ensure balanced allocation between d_0 (or d_K) and the estimated target dose we propose to keep the allocation to d_0 approximately equal to the allocation to a dose with the most assignments. In the remainder of this section we will use the estimation of the MED as an example. In order to achieve balance in assignments with respect to covariates between d_0 and the current dose recommended by the adaptive strategy based on the data available so far, we propose to use a method similar to minimization (Taves 1974; Pocock and Simon 1975). For ease of presentation, we describe the method for a single covariate with two levels $x = 0$ and $x = 1$. Let $n_{ix}(t)$ be the number of subjects assigned to dose d_i, $i = 0,\ldots,K$, with the covariate level x, $x = 0, 1$, right after subject t has been assigned, and let $n_i(t) = n_{i0}(t) + n_{i1}(t)$, that is, $\sum_{i=0}^{K}\sum_{x=0}^{1} n_{ix}(t) = \sum_{i=0}^{K} n_i(t) = t$. Let dose d_i be the current dose. A new subject, subject $t + 1$, entering the study will be assigned to either d_i or to placebo d_0. Define the measure of discrepancy (MD) as follows

$$MD = W\left|n_0(t+1) - \max_{i=1,\ldots,K} n_i(t+1)\right| + \left|\frac{n_{0x}(t+1)}{n_0(t+1)} - \frac{n_{ix}(t+1)}{n_i(t+1)}\right| \frac{n_i(t+1)n_0(t+1)}{n_i(t+1)+n_0(t+1)}$$

Here W is the weight similar to the weight used in minimization; we used $W = 0.5$ in the simulation study. The value of MD is computed assuming that subject $t + 1$ is assigned to d_i, and then computed assuming that subject $t + 1$ is assigned to d_0. The subject is assigned to the dose with the smaller value of MD. In the case when the values of MD are the same, the subject is randomized to one of the doses with equal probability. When there are no covariates, this strategy is still useful as it helps to keep the number of subjects assigned to placebo approximately equal to the number of subjects assigned to the estimated target MED.

4. Simulation study

Our simulation study investigates the effect of balancing assignments to doses with respect to covariates, adjusting for covariates, doing both or neither. Also, we are comparing adaptive strategies with equal allocation. Simulation results are based on 5000 simulation runs. Table 1 displays seven scenarios from Bretz et al. (2005) that we considered. A two-level covariate, in-patient with $x = 0$, $\Pr(x = 0) = 0.4$, and out-patient with $x = 1$, with covariate effect $\beta = 0.5$ was considered. To estimate the MED defined as the dose with the mean response equal to $\mu_0 + 0.35$ we used the adaptive strategy described in Section 3.1; to balance with respect to covariates we used the algorithm described in Section 3.2. Unless specified otherwise the simulations were performed with balancing with respect to covariates and adjusting for covariates in the analysis.

It is useful to have a lead-in phase with equal number of assignments to all doses. Such lead-in phase ensures that all doses are tested and provides data for initial estimation of the MED. The estimated MED after the lead-in is used as a starting dose for the adaptive design. Forty two subjects, 26% of the total sample size of 162, were assigned in the lead-in phase, 6 subjects to each dose. We have investigated various choices of the size of lead-in and lead-ins with 25%–50% of the total sample size performed well as far as estimation of the target dose. We used 26% because we wanted to explore the impact of the number of cohorts on adaptive design performance.

It is always desirable to stop the trial for futility if a drug is not beneficial, that is, if the null hypothesis H_0: $\mu_K = \mu_0 + \eta$, $\eta = 0.35$, is rejected in favor of one-sided alternative $\mu_K < \mu_0 + \eta$. Looks for futility were performed at each interim and at the final analysis. Given the goals of a Phase II trial, we suggest setting the probability of rejecting an efficacious drug at 0.05 or lower. The Pocock stopping boundary was used in sequential monitoring to minimize the expected sample size if the treatment is not effective. If the trial was stopped early for futility or futility was established during the final analysis none of the doses was selected as the estimated MED.

Table 2 displays the proportion of trials in which the true MED was selected as the estimated MED. In adaptive design, after lead-in subjects were assigned in 5 cohorts, 24 subjects per cohort. That is, there were 5 interim and one final analysis. Data were generated from scenarios in Table 1 with $\sigma = 0.25$. We report results when balancing with respect to covariates, adjusting for covariates, neither or both were performed. The results where the allocation was balanced with respect to covariates but covariates were ignored in the analysis, and where the allocation was not balanced but covariates were used in the analysis were only slightly worse than those for adaptive design with balancing and adjusting. These findings were consistent across various numbers of analyses and for both the MED and the

peak dose estimation. Thus, one needs to least balance assignments with respect to covariates or adjust for covariates in the analysis. It is interesting to note that balancing with respect to and adjusting for covariates when $\beta \neq 0$ yielded very similar quality of estimation to the case where covariate effect was 0. On the other hand, it is clear from the comparison of the adaptive adjusted design and adaptive design with no balancing or adjustment, that disregarding covariates that are associated with the outcome in design and analysis have negative effect on quality of estimation of the target dose. Compared with equal allocation, adaptive design yields much higher probability of selecting the correct MED.

Table 3 displays results for the average sample size at the estimated target dose. Adaptive design assigns more subjects on average to the estimated target dose, which increases the power of comparisons that involve the estimated target dose. Adaptive design assigns about twice as many subjects to the estimated target dose on average compared to equal allocation in all non-null scenarios. As far as futility stopping, all trials were stopped for futility in the null scenario, scenario 1, and the average sample size in scenario 1 was 63. For the equal allocation, in the null scenario futility was declared at the end of every trial after 160 patients were treated. None of trials was stopped early for futility in scenarios 2–7.

To study the effect of the number of interim analyses on the design performance we performed simulations with the total of 2 analyses where two doses were selected in stage 2, and adaptive design with 3 analyses (2 cohorts of size 60), 4 analyses (3 cohorts of size 40), 6 analyses (5 cohorts of size 24), 9 analyses (8 cohorts of size 15) and 13 analyses (12 cohorts of size 10). Each trial had a lead-in phase with a total of 42 subjects equally allocated to 7 doses. The average (over non-null scenarios) percent selection of the target dose was 0.84, 0.87, 0.88, 0.88, 0.88 and 0.89, respectively. The average sample size at the estimated target dose (averaged over non-null scenarios) was 38, 39, 44, 44, 43 and 43. Regardless of the number of analysis, the probability of stopping early for futility was 1 in the null scenario, the average sample size was 117, 84, 72, 62, 58 and 58 for 2, 3, 4, 6, 9, and 13 analysis correspondingly. None of the trials was stopped early for futility in scenarios 2–7.

We also repeated simulations with different values of σ. The probabilities of correct selection of the MED in non-null scenarios were 0.49, 0.37, 0.38, 0.67, 0.65, 0.76 for σ = 0.65 (Table 4). These numbers are to be compared with selection probabilities for equal allocation, 0.39, 0.30, 0.33, 0.58, 0.61, 0.69. Average sample sizes at the estimated MED were 37, 36, 36, 39, 42, 41 for σ = 0.65. The probability of stopping early for futility was 0.6 in scenario 1, with the average sample size of 142. For equal allocation futility was declared in 0.23 of the trials. None of trials was stopped early for futility in scenarios 2–7 when adaptive design was used. When the variability of the outcome was large (σ = 1.3 and larger) while keeping the sample size the same, selection probabilities were low and adaptive design did not bring much benefit compared to equal allocation.

Often patient response is not known prior to assignment of the next cohort. We repeated the simulations under the following staggered entry model: the outcome was available 5 weeks from the start of treatment; the accrual rate was 1, 5, 20, and 40 subjects per week. The adaptation was performed every time when a new cohort was initiated based on all response data available at that point. If no data were available for an adaptation, subjects were randomized equally among all doses including placebo. With total sample size of 162, trials with accrual rate of 40 subjects did not allow any adaptations resulting in equal allocation, and therefore selection probability of the target dose was the same as for equal allocation. As accrual rate increased from 1 to 40, selection probability decreased from that of adaptive design to that of equal allocation. For example, in scenario 2, the correct MED was selected in 0.88, 0.84, 0.82, and 0.76 of the trials with accrual of 1, 5, 20, and 40 subjects per week

respectively. Here and in other scenarios only half of the advantage of adaptive design compared to equal allocation was preserved in trials with accrual rate of 20 subjects per week.

We also performed simulations to estimate the peak dose defined as the lowest dose with the mean response of $\mu_K - \gamma$, where $\gamma = 0.06$. The conclusions were similar to those of the MED. With lead-in phase allocating 6 subjects per dose and four cohorts with 30 patients each, the probabilities of correct selection of the peak dose in non-null scenarios were 0.46, 0.70, 0.55, 0.73, 0.88, 0.95 (Table 4). These results should be compared to 0.38, 0.55, 0.47, 0.66, 0.81, 0.88 for equal allocation. There was almost no additional benefit in estimation when the number of analyses was increased and slight benefit as far as the average sample size at the target dose. For $\sigma = 0.65$, the probabilities of correct selection of the peak dose were 0.27, 0.35, 0.40, 0.51, 0.56, 0.67 for adaptive design (Table 4), and 0.22, 0.31, 0.34, 0.43, 0.50, 0.55 for equal allocation. Simulation study for the peak dose did not include a stopping rule. Estimated peak dose will be normally compared to placebo, therefore requiring increased allocation to both placebo, to stop early for futility, and to the highest dose, to estimate the peak dose better.

We compared our methods to the Normal Dynamic Linear Model (NDLM) (Berry et al., 2001). The NDLM method was simulated using Compass® software (Compass®, Cytel Inc.) based on 5000 trials for each set-up. Though the NDLM allows covariates, we simulated the NDLM without covariates as Compass® does not accommodate covariates. We used allocation rule that minimized the variance of the estimated mean response, the NDLM default values were used to specify the prior. The NDLM was simulated with the same number of cohorts and cohort size as corresponding isotonic designs. Instead of the peak dose defined as the lowest dose with the mean response of $\mu_K - 0.06$, we estimated ED90, as the two doses coincide for all scenarios we considered. In our designs placebo/drug ratio was not fixed, but rather adaptively chosen so that allocation to placebo is approximately equal to allocation to the dose with maximum number of patients. For the NDLM, we performed simulations for various placebo/drug ratios and report results corresponding to the ratio that yielded the best selection probabilities for the NDLM over seven scenarios we considered. Results are presented in Table 4. Results for placebo/drug ratio of 1:2 are reported for the MED estimation and 1:4 ratio for ED90 estimation. As far as allocation to doses the NDLM tends to spread allocation across the dose range and the isotonic designs tend to concentrate assignments near the target dose. Estimation results are presented in Table 4. The NDLM provides similar estimation of the MED compared to isotonic designs, percent selection of the target dose is only by 2% lower on average for the NDLM. For the peak dose estimation, the NDLM is inferior by 14% on average compared to the isotonic design. This can be due to a different definition of the target dose or due to the fact that the NDLM does not rely on isotonic assumption.

5. Conclusions

We investigated various strategies for dose-finding trials with covariates. Our conclusion is that one needs to least balance assignments with respect to covariates or adjust for covariates in the analysis. We propose an algorithm, similar to the method of minimization, to balance allocation with respect to covariates in a dose-finding trial.

We examined sequential strategies to estimate the MED and the peak dose that use the knowledge of the allocation that maximizes the probability of correctly selecting the target dose. In many trials, it is desirable to test the mean response at the target dose against placebo mean response. In this case the optimality criterion for the design can be set as a function of the probability of correct selection of the target dose and the number of subjects

allocated to target. Another possibility is to fix the probability of correct selection at, say, 95% of the optimal and maximize the number of subjects allocated to the target dose.

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Appendix. Proof of the Proposition

The vector of unconstrained MLEs obtained from model (1), $\widehat{\mu}^U = \left(\widehat{\mu}_0^U, \ldots, \widehat{\mu}_K^U\right)$, has multivariate normal distribution with mean vector $\boldsymbol{\mu} = (\mu_0, \ldots \mu_K)$ and variance covariance matrix Σ with $(\sigma^2/n_0, \ldots, \sigma^2/n_K)$ on the diagonal. Let $w_i = n_i/n$, $0 < w_i < 1$, $w_0 + \ldots + w_K = 1$. First we wish to show that when $\mu_s = 0$ and it is known, the probability of correctly selecting the target dose by applying the closes dose or the lowest dose estimator to the weighted average of components of $\hat{\boldsymbol{\mu}}^U$ depends only on vectors $\{w_i\}$, $\left\{\mu_i \sqrt{n}/\sigma\right\}$ and matrix $(n/\sigma^2)\Sigma$. We note that the probability of selecting the correct target dose can be expressed as:

$$\sum_{j=1}^{J} \int_{A_j} \frac{1}{(2\pi)^{(K+1)/2}|\sum|^{0.5}} e^{-(x-\mu)'\sum^{-1}(x-\mu)/2} \prod_{i=1}^{K+1} dx_i, \qquad \text{(A.1)}$$

where the regions A_j, $j = 1, \ldots, J$, are disjoint sets in the sample space each defined by a set of inequalities where the algorithm chooses the correct target dose. For example, when $\widehat{\boldsymbol{\mu}}^U = \left(\widehat{\mu}_{\tau-1}^U, \widehat{\mu}_\tau^U, \widehat{\mu}_K^U\right)$, the two rejoins are shown in formula (2). We note that each of these regions may be expressed as an intersection of solution sets of inequalities where each side of the inequality is a linear combination of the components of $\hat{\boldsymbol{\mu}}^U$ or the absolute value of such a combination, and the coefficients are functions of the $\{w_i\}$. Thus, the regions A_j of the sample space where the closest dose is chosen are given by inequalities of the form described above. We rewrite (A.1) after making the substitution $y_i = \left(x_i \sqrt{n}\right)/\sigma$, $i = 0, \ldots, K$.

$$\sum_{j=1}^{J} \int_{A_j} \frac{1}{(2\pi\sigma^2/n)^{k/2}|\Lambda|^{0.5}} e^{-0.5(y-\frac{\sqrt{n}}{\sigma}\mu)'\Lambda^{-1}(y-\frac{\sqrt{n}}{\sigma}\mu)} \prod_{i=1}^{k} \frac{\sigma}{\sqrt{n}} dy_i = \sum_{j=1}^{J} \int_{A_j} \frac{1}{(2\pi)^{k/2}|\Lambda|^{0.5}} e^{-0.5(y-\frac{\sqrt{n}}{\sigma}\mu)'\Lambda^{-1}(y-\frac{\sqrt{n}}{\sigma}\mu)} \prod_{i=1}^{k} dy_i,$$

where $\Lambda = (n/\sigma^2)\Sigma$ is the covariance matrix for the y_i. This substitution does not change the regions A_j because substituting $(y_i\sigma)/\sqrt{n}$ for x_i in the original inequalities that define the A_j and dividing through by the positive constant $\sigma/\sqrt{n}$ does not change solution set for the inequalities, which now depend only on the w_i and the y_i. Because the y_i will be integrated out, the integral in (3) depends only on the $\{w_i\}$, $\left\{\mu_i \sqrt{n}/\sigma\right\}$ and $(n/\sigma^2)\Sigma$. If μ_s in the definition of the target dose is not known and is being estimated, the result is obtained similarly to the above by considering $\left(\widehat{\mu}_0^U - \widehat{\mu}_s^U, \ldots, \widehat{\mu}_K^U - \widehat{\mu}_s^U\right)$. This is because the density is

from a location-scale family, and the regions of correct selection do not depend on the location. Location is irrelevant to the regions of correct selection because the inequalities that define them are comparisons of isotonic estimates where the coefficients for each observation sum to 1, so shifting all means up by a constant does not change their solution sets.

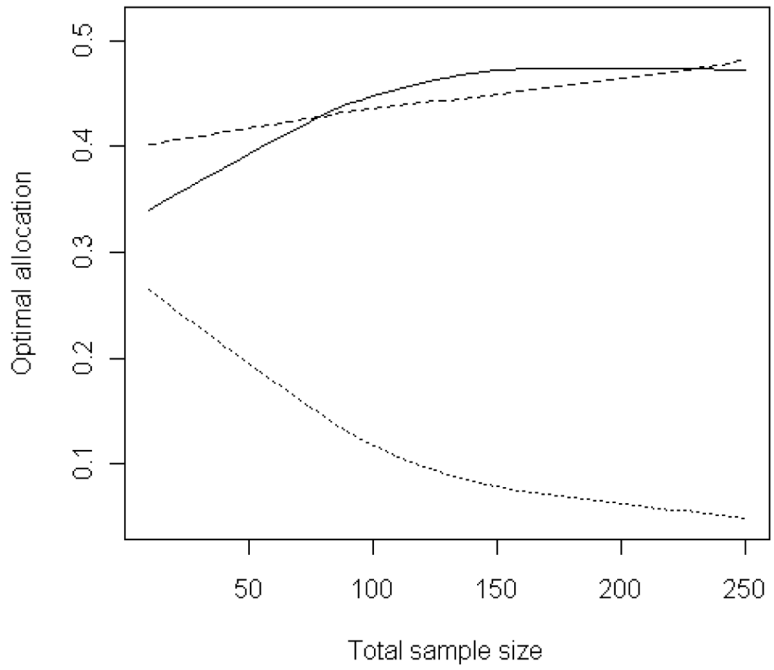

Figure 1.
Optimal allocation to estimate the peak dose. The solid line is the proportion assigned to the true peak dose, d_τ, the dotted line proportion assigned to d_K and the dashed line proportion assigned to $d_{\tau-1}$.

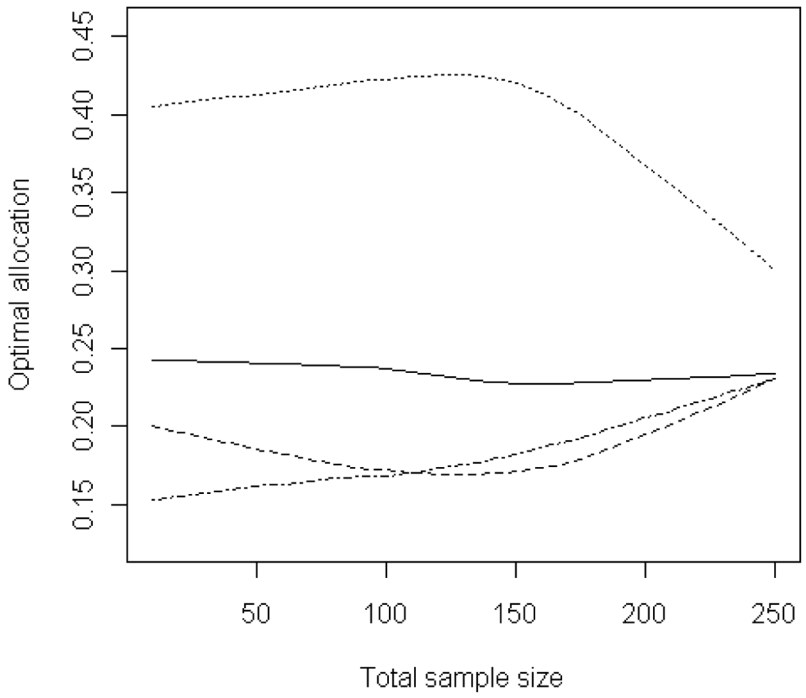

Figure 2.
Optimal allocation to estimate the MED. The solid line is the proportion assigned to the true MED, d_τ, the dotted line proportion assigned to placebo d_0, the dashed line proportion assigned to $d_{\tau-1}$ and the dotted-dashed line to $d_{\tau+1}$

Table 1

Data generating dose response curves, $\boldsymbol{d} = (0,0.05,0.2,0.4,0.6,0.8,1)$

Scenario	Model	Mean Response
1	Constant = 0.2	(0.20,0.20,0.20,0.20,0.20,0.20,0.20)
2	$E_{max} = 0.2+0.7d/(0.2+d)$	(0.20,0.34,0.55,0.67,0.72,0.76,0.78)
3	Linear in log-dose = $0.2+0.6\log(5d+1)/\log(6)$	(0.20,0.27,0.43,0.57,0.66,0.74,0.80)
4	Linear = $0.2+0.6d$	(0.20,0.23,0.32,0.44,0.56,0.68,0.80)
5	Logistic = $0.193+0.607/\{1+\exp[10\log(3)(0.4-d)]\}$	(0.20,0.21,0.25,0.50,0.74,0.79,0.80)
6	Step 1 = $0.2+0.6I(d\geq 0.2)$	(0.20,0.20,0.80,0.80,0.80,0.80,0.80)
7	Step 2 = $0.2+0.3I(d\geq 0.4)+0.3I(d\geq 0.6)$	(0.20,0.20,0.20,0.50,0.80,0.80,0.80)

Table 2

Proportion of trials in which the true MED was selected as the estimated MED 1) in adaptive trial with balancing with respect to a covariate and adjusting for covariate in the analysis (Balance and Adjust), in adaptive trial with only balancing (Balancing only), in adaptive trial with only adjusting (Adjusting only), in adaptive trial without balancing or adjusting for covariate (None), in adaptive trial with no covariate effect ($\beta = 0$) and for equal allocation with balancing and adjusting for covariate.

Scenario	Adaptive, Balancing and Adjusting β = 0.5	Adaptive, Balancing only β = 0.5	Adaptive, Adjusting only β = 0.5	Adaptive, None β = 0.5	Adaptive, None β = 0	Equal allocation, Balancing and Adjusting β = 0.5
2	0.88	0.88	0.87	0.76	0.89	0.76
3	0.78	0.73	0.76	0.62	0.78	0.65
4	0.78	0.73	0.78	0.65	0.78	0.69
5	0.96	0.95	0.95	0.88	0.96	0.94
6	0.91	0.89	0.91	0.83	0.91	0.84
7	0.99	0.99	0.99	0.96	0.99	0.99

Table 3

Average number of subjects allocated to the estimated dose in each design. For comparison, equal allocation design with the same total sample size will have 23 subjects at each dose

Scenario	Adaptive, Balancing and Adjusting β = 0.5	Adaptive, Balancing only β = 0.5	Adaptive, Adjusting only β = 0.5	Adaptive, None β = 0.5	Adaptive, None β = 0
2	43	42	38	39	42
3	42	41	35	37	40
4	42	41	36	38	41
5	46	45	44	44	47
6	46	46	45	45	47
7	47	46	46	46	48

Table 4

Proportion of trials in which the true dose was selected by the proposed isotonic designs (Isot) and the NDLM in trials with no covariate effect

	MED $\sigma = 0.25$		MED $\sigma = 0.65$		Peak, ED90 $\sigma = 0.25$		Peak, ED90 $\sigma = 0.65$	
Scenario	**Isot**	**NDLM**	**Isot**	**NDLM**	**Isot**	**NDLM**	**Isot**	**NDLM**
2	0.89	0.85	0.49	0.54	0.46	0.41	0.27	0.23
3	0.78	0.78	0.37	0.38	0.70	0.78	0.35	0.39
4	0.78	0.79	0.38	0.36	0.55	0.51	0.40	0.41
5	0.96	0.92	0.67	0.59	0.73	0.56	0.51	0.38
6	0.91	0.85	0.65	0.62	0.88	0.71	0.56	0.53
7	0.99	0.97	0.76	0.66	0.95	0.82	0.67	0.44