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# A New Dose-Finding Design for Bivariate Outcomes

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Summary. For some drugs, toxicity events lead to early termination of treatment before a therapeutic response is observed. That is, there are three possible outcomes: toxicity (therapeutic response unknown), therapeutic response without toxicity, and no response with no toxicity. The optimal dose is the dose that maximizes the probability of the joint event, response, and no toxicity. The optimal safe dose is the dose, from among the doses with toxicity rate less than the maximum tolerable level, that maximizes the probability of response and no toxicity. We present a new sequential design to maximize the number of subjects assigned in the neighborhood of the optimal safe dose in a dose-finding trial with two outcomes.

Key words: Dose-finding studies; Optimal dose; Phase I trial; Random walk; Up-and-down design.

## 1. Introduction

The primary purpose of a phase I clinical trial is to find the dose with the probability of toxicity equal to the maximum tolerable level (often 0.2 or 0.3). The response rate at the dose established in a phase I trial is then evaluated in a phase II trial. For some drugs, however, toxicity events lead to early termination of treatment before response is observed. One of the examples is D-d4FC, a new antiviral reverse transcriptase inhibitor that has activity against HIV that is resistant to other reverse transcriptase inhibitors. This drug has begun its initial testing in humans. One of the possible "toxicities" of D-d4FC is a detectable level of 5 flurouracil (5FU), a compound used in chemotherapy with significant bone marrow and mucosal toxicity. Measurable levels of 5FU at a given dose of D-d4FC would lead to discontinuation of treatment. To study such drugs, we define optimal safe dose in the following way. First, designate the joint event of a response and no toxicity as a success. Then restrict the considered doses to those for which the population toxicity rate is below the maximum tolerable level. The optimal safe dose is the dose that maximizes the probability of success under the toxicity restriction.

Figure 1 illustrates a possible relationship between the maximum tolerated dose, a dose that has maximum tolerable level of toxicity, and the optimal dose. The maximum of the success curve is achieved to the left of the maximum tolerated dose (MTD), hence the optimal safe dose coincides with the optimal dose. Another possible relationship is when the maximum of the success curve is achieved to the right of the MTD, in which case the optimal safe dose coincides with the MTD.

In this article, we develop a sequential dose-finding design with the goal of assigning more subjects in the neighborhood of the optimal safe dose. We formulate the problem and present competing approaches in Section 2. The proposed design is described in Section 3. Group modifications and estimation of the optimal safe dose are discussed in Section 4. We present simulation results in Section 5 and discussion in Section 6.

## 2. Notation and Review of the Existing Literature

Consider the situation where there is a fixed ordered set of dose levels $d_j$, $j \in \{1, \ldots, K\}$. Let $Q(d)$ be the probability of toxicity at $d \in \{d_1, \ldots, d_K\}$. We assume that $Q(d)$ is an increasing function of dose. Let $P(d)$ be the probability of response without toxicity, the probability of success, and $S(d)$ be the probability of no toxicity and no response, $Q(d) + P(d) + S(d) = 1$. Finally, let $\Gamma$ be the maximum tolerable level of toxicity. The optimal dose is dose $d^*$ that maximizes $P(d)$ over the set of doses such that $Q(d) \leq \Gamma$, that is, $P(d^*) = \max_{d \in \{d_1, \ldots, d_K\} \,\&\, Q(d) \leq \Gamma} P(d)$.

Li, Durham, and Flournoy (1995) have acknowledged the need to develop designs to find the dose that maximizes the probability of the joint event, response, and no toxicity in dose-finding trials. They gave sufficient conditions for the existence of the optimal dose. Kpamegan and Flournoy (2001) suggested a nonparametric adaptive allocation scheme, the optimizing up-and-down design that tends to allocate more subjects in the neighborhood of the optimal dose. Subjects are assigned in pairs at adjacent doses. The first pair of subjects is treated with doses ($d_1$, $d_2$). Suppose the most recent pair of subjects was allocated to doses ($d_j$, $d_{j+1}$), $j \in \{1,2, \ldots, K-1\}$. The next pair of subjects is assigned to

(i) *doses* ($d_{j-1}$, $d_j$) if a success was observed at $d_j$ and no success at $d_{j+1}$,
(ii) *doses* ($d_{j+1}$, $d_{j+2}$) if no success was observed at $d_j$ and a success at $d_{j+1}$,
(iii) *doses* ($d_j$, $d_{j+1}$) otherwise.

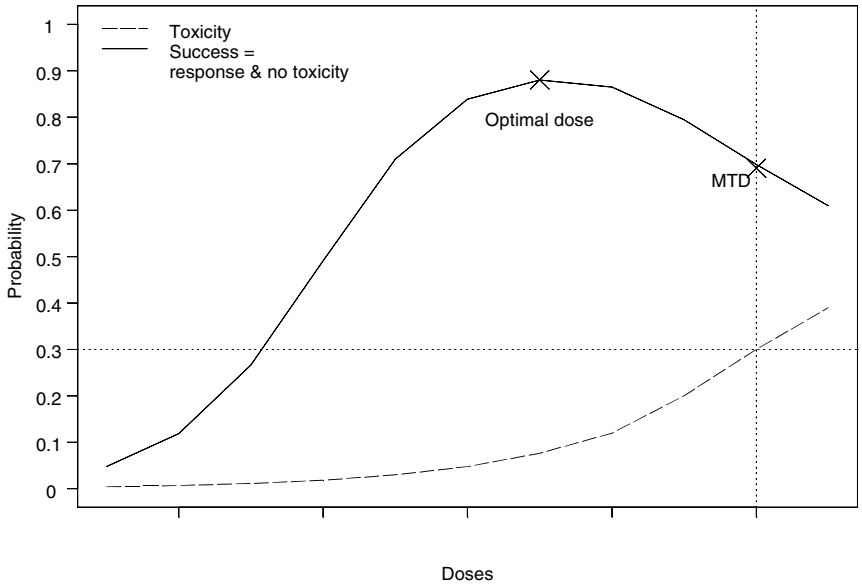


**Figure 1.** One possible relationship between the optimal dose and the maximum tolerated dose. The optimal dose is the dose that maximizes the probability of the joint event, response, and no toxicity. The MTD is the dose with the probability of toxicity equal to the maximum tolerable level (0.3).

Appropriate adjustments are made at the lowest and the highest doses. That is, the pair is treated at $(d_1,\ d_2)$ instead of $(d_0,\ d_1)$, and $(d_{K-1},\ d_K)$ instead of $(d_K,\ d_{K+1})$.

Thall, Inoue, and Martin (2002) considered the problem of determining the infusion time having the highest probability of success in a dose-finding trial in oncology. Success was defined as survival to 50 days, with recovered white blood cell count and no severe liver toxicity. Five infusion times were chosen for the study. A Bayesian approach was used, with adaptive randomization among five infusion times, according to their posterior success probabilities.

O'Quigley, Huges and Fenton (2001) considered the problem of finding a safe dose with satisfactory success rate, which is similar to the problem of finding the optimal safe dose. Attention is restricted to doses for which the toxicity rate is below the maximum tolerable level $\Gamma = 0.3$. In this restricted dose space, the method finds a dose where the probability of success is at least 0.7. Note that this dose might not exist. The algorithm starts at the second lowest dose. The initial maximum tolerable level is set at $\Gamma = 0.1$, with $\Delta\Gamma$ equal to 0.1. Two success rates, $p_0$ and $p_1$, with $p_0 < p_1$, are specified. If $d_i$ is the current dose level, $H_0$: $P(d_i) < p_0$ is tested against $H_1$: $P(d_i) > p_1$. "Inability to conclude in favor of either hypothesis leads to further experimentation. Conclusion in favor of $H_0$ leads to level $d_i$, and all lower levels, being removed from further experimentation. At this point, the target toxicity level is changed from $\Gamma$ to $\Gamma + \Delta\Gamma$," (O'Quigley et al., 2001). Since the essence of this methodology is the use of the sequential probability ratio test (SPRT) at increasing dose levels, we refer to this method as the "repeated SPRT method."

## 3. A New Design to Find the Optimal Safe Dose

### 3.1 *Definition of the New Design*

We first define an allocation procedure that tends to assign more subjects in the neighborhood of the optimal dose. The new design is in the spirit of the play-the-winner design (Zelen, 1969), in that it repeats the dose if a success is observed. The dose is decreased if toxicity is observed, and increased in case of no response and no toxicity. The first subject is assigned to dose $d_1$. Suppose the most recent subject was allocated to level $d_j$, $j \in \{1, \ldots, K\}$. Assign the next subject to

(i) *dose* $d_{j-1}$ if the most recent subject had toxicity,
(ii) *dose* $d_j$ if the most recent subject had response and no toxicity (that is, "success"),
(iii) *dose* $d_{j+1}$, if the most recent subject had no response and no toxicity.

Appropriate adjustments are made at the lowest and the highest doses.

According to the proposed allocation procedure, the dose is reduced every time toxicity is observed. For a wide class of models, this design assigns only a small fraction of subjects to doses with high rate of toxicity. If the problem is to find the dose with maximum success probability from among the doses with tolerable level of toxicity, that is, the optimal safe dose, then the allocation scheme above is adjusted by monitoring the marginal probability of toxicity using Bayesian methods. The dose-toxicity relationship is modeled with $Q(d_j) = \alpha_j^a$, $j \in \{1, \ldots, K\}$, where $(\alpha_1,\ \alpha_2, \ldots, \alpha_K)$ are fixed in advance, and parameter $a$ has density taken to be $g(a) = \exp(-a)$

(O'Quigley, Pepe, and Fisher, 1990). The distribution is updated using Bayes' theorem as data become available. Let $\hat{a}$ be the current posterior mean of $a$. Let $d_\Gamma(\hat{a}) \in \{d_1, \ldots, d_K\}$ be the maximum dose level at which the estimated probability of toxicity is less than $\Gamma$. The next subject is assigned to the dose that is the smaller of $d_\Gamma(\hat{a})$ and the dose prescribed by the allocation procedure introduced in the beginning of this section.

### 3.2 *Stationary Distribution*

We first assume that the new design is applied without the toxicity restriction. The design induces a Markov chain, and thus the stationary treatment distribution exists (Kemeny and Snell, 1960). Let $N_j(n)$ be the number of subjects assigned to dose $d_j$ by the time $n$ subjects have been assigned. Then, $\pi = (\pi_1, \ldots, \pi_K) = \lim_{n\to\infty}(N_1(n)/n, \ldots, N_K(n)/n)$, where the limit is in probability, is the stationary distribution.

THEOREM. *If $\lambda_k = S(d_{k-1})/Q(d_k)$, $k \in \{2, \ldots, K\}$, is a decreasing sequence, then the stationary distribution $\pi$ is log-concave. Furthermore, if $\lambda_2 < 1$, the mode is at dose $d_1$. If $\lambda_2 \geq 1$, let $d_k$, $k \in \{2, \ldots, K\}$, be the largest dose such that $\lambda_k \geq 1$. If $\lambda_k > 1$ the mode is at $d_k$; if $\lambda_k = 1$, the mode spans $d_{k-1}$ and $d_k$.*

Proof of the theorem is in the Appendix.

COROLLARY. *If $S(d)$ is a decreasing function of a dose and $Q(d)$ is increasing with dose, the stationary distribution is log-concave.*

The corollary immediately follows from the Theorem, since the sequence $\lambda_k$, $k \in \{2, \ldots, K\}$ is decreasing.

Table 1 presents all four scenarios from O'Quigley et al. (2001). The stationary distributions without toxicity restriction for these scenarios are shown in Table 2. For all four scenarios, the sequence $(\lambda_2, \lambda_3, \lambda_4)$ is decreasing, so that the above Theorem applies, and the stationary distribution is log-concave. Note that, for all four scenarios, the mode of the stationary distribution coincides with the optimal dose.

Now assume that a toxicity restriction is in place. Then, the stationary distribution is calculated on the subset of tolerable doses in a similar way. Assume that the conditions of the Corollary are satisfied. Let $d_\tau$ be the mode of the stationary distribution, and let $d^*$ be the optimal safe dose. The question is how close $d^*$ is to $d_\tau$,, or how close the probabilities of success are at the two doses. It can be shown that $\max[P(d^*) - P(d_\tau)] \leq \Gamma$. Here, the maximum is taken over all increasing functions $Q(d)$ and all decreasing functions $S(d)$, $S(d) + Q(d) + P(d) = 1$. In fact, if dose levels $\{d_1, \ldots, d_K\}$ are chosen wide apart, $d^*$ and $d_\tau$ are close or coincide.

**Table 1**
*Four scenarios with four doses from O'Quigley et al.* (2001)

| | $d_1$ | $d_2$ | $d_3$ | $d_4$ |
|---|---|---|---|---|
| **Scenario 1** | | | | |
| $Q(d_j)$ | 0.06 | 0.17 | 0.25 | 0.30 |
| $P(d_j)$ | 0.20 | 0.70 | 0.60 | 0.50 |
| **Scenario 2** | | | | |
| $Q(d_j)$ | 0.13 | 0.30 | 0.40 | 0.50 |
| $P(d_j)$ | 0.70 | 0.50 | 0.50 | 0.40 |
| **Scenario 3** | | | | |
| $Q(d_j)$ | 0.00 | 0.05 | 0.15 | 0.30 |
| $P(d_j)$ | 0.10 | 0.30 | 0.70 | 0.50 |
| **Scenario 4** | | | | |
| $Q(d_j)$ | 0.00 | 0.00 | 0.10 | 0.14 |
| $P(d_j)$ | 0.20 | 0.30 | 0.50 | 0.70 |

**Table 2**
*Stationary distributions for the new design, with groups of size* 1 (ND 1)*, groups of size* 2 (ND 2)*, and groups of size* 3 (ND 3)*, calculated for the scenarios in Table* 1

| | $d_1$ | $d_2$ | $d_3$ | $d_4$ |
|---|---|---|---|---|
| **Scenario 1** | | | | |
| ND 1 | 0.11 | 0.50 | 0.26 | 0.13 |
| ND 2 | 0.04 | 0.72 | 0.19 | 0.05 |
| ND 3 | 0.06 | 0.68 | 0.20 | 0.06 |
| **Scenario 2** | | | | |
| ND 1 | 0.52 | 0.30 | 0.15 | 0.03 |
| ND 2 | 0.71 | 0.23 | 0.06 | 0.00 |
| ND 3 | 0.68 | 0.25 | 0.07 | 0.00 |
| **Scenario 3** | | | | |
| ND 1 | 0.01 | 0.13 | 0.57 | 0.29 |
| ND 2 | 0.00 | 0.04 | 0.77 | 0.19 |
| ND 3 | 0.00 | 0.06 | 0.73 | 0.21 |
| **Scenario 4** | | | | |
| ND 1 | 0.00 | 0.04 | 0.25 | 0.71 |
| ND 2 | 0.00 | 0.00 | 0.11 | 0.89 |
| ND 3 | 0.00 | 0.00 | 0.13 | 0.87 |

## 4. Practical Considerations

### 4.1 *Group Modifications*

Assignment in groups is often used for logistic and other considerations. We present a group modification of the new design, with group sizes of two and three. Modifications with other group sizes can be obtained similarly. The first group of subjects is assigned to dose $d_1$. Suppose the most recent group was allocated to level $d_j$, $j \in \{1, \ldots, K\}$. Assign the next group to

(i) *dose* $d_{j-1}$ if two or more subjects in the most recent group had toxicity,
(ii) *dose* $d_{j+1}$ if two or more subjects in the most recent group had the outcome of no toxicity and no response,
(iii) *dose* $d_j$ otherwise.

Appropriate adjustments are made at the lowest and the highest doses.

Statements similar to the Theorem of Section 3.2 can be formulated for the above group modifications of the new design. Table 2 displays the stationary distributions for group modifications calculated for the four scenarios in Table 1. The stationary distribution is more concentrated around $d_\tau$ when subjects are assigned in groups. Simulation results for group designs are discussed in Section 5.

4.2 *Stopping Rules and Estimation of the Optimal Safe Dose*

Fixing sample size in advance simplifies the logistics of the trial. However, a trial that defines a stopping rule and allows a random sample size can save resources. First, consider the problem when the treatment is not considered promising unless there is a safe dose with probability of success no less than a specified value. For example, O'Quigley et al. (2001) were looking for a dose with success rate of 0.7 or higher. In this case, success probability at each dose can be monitored with the sequential probability ratio test (Wetherill and Glazebrook, 1986). Let $p_0$ and $p_1$, with $p_0 < p_1$, be two values for the probability of success considered unsatisfactory and satisfactory, respectively. Let $\varepsilon_1$ be the desired probability of concluding that the success rate is higher than $p_1$ when, in fact, it is equal to $p_0$. Also, let $\varepsilon_2$ be the desired probability of concluding that the success rate is lower than $p_0$ when, in fact, it is equal to $p_1$. Then, according to the sequential probability ratio test, sampling is continued as long as

$$\log \frac{\varepsilon_2}{1-\varepsilon_1} < X_i(n) \log \frac{p_1}{p_0} + [N_i(n) - X_i(n)] \log \frac{1-p_1}{1-p_0} < \log \frac{1-\varepsilon_2}{\varepsilon_1},$$

where $X_i(n)$ is the number of successes observed at dose $d_i$ by the time $n$ subjects were treated. If the upper boundary is crossed, we conclude in favor of hypothesis $P(d_i) > p_1$, while if the lower boundary is crossed, we conclude in favor of hypothesis $P(d_i) < p_0$. When the new design is used, the current lowest dose is eliminated as soon as the lower boundary of the SPRT is crossed. The trial is stopped as soon as the upper boundary is crossed for any safe dose and that dose is declared to be a dose with a satisfactory success rate.

If the satisfactory success rate is not specified and the sample size is fixed, the question is how to estimate the optimal safe dose after the trial. We suggest the following estimation procedure. Let $N$ be the total sample size in the trial divided by the number of doses. That is, $N$ is the average number of subjects assigned to a dose. At the end of the trial, compare proportions of successes at the doses with at least $N$ subjects assigned. The dose with the highest proportion of successes and tolerable toxicity rate is declared the optimal safe dose.

## 5. Design Comparisons

We first compare the new design with the repeated SPRT, and the optimizing design of Kpamegan and Flournoy (2001), for four scenarios from O'Quigley et al. (2001), Table 1. A model $Q(d_j) = \alpha_j^a$, with $(\alpha_1, \ldots, \alpha_4) = (0.05, 0.10, 0.2, 0.3)$, is used to estimate toxicity with both the new and optimizing designs. The maximum tolerable level, $\Gamma$, is set to 0.3. The stopping rule based on the SPRT, with $p_0 = 0.4$, $p_1 = 0.6$, $\varepsilon_1 = \varepsilon_2 = 0.075$, and starting dose $d_2$, is used with all the designs. The maximum allowable number of subjects per trial is 100. If the maximum number of subjects is reached, the optimal safe dose is estimated as described in Section 4.2, with

**Table 3**

*Percent recommendation, allocation proportions, median sample size, 25th and 75th percentiles of the sample size distribution for scenarios* 1–4 (*Table* 1)*. The designs are repeated SPRT with groups of size* 1 (RSPRT 1)*, optimizing design* (OPTIMIZING)*, the new design with groups of size* 1 (ND 1)*, groups of size* 2 (ND 2)*, and groups of size* 3 (ND 3)*. Stopping rule used is based on the SPRT, with* $\varepsilon_1 = \varepsilon_2 = 0.075$.

| | Percent recommendation | | | | Allocation proportions | | | | Sample size | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $d_1$ | $d_2$ | $d_3$ | $d_4$ | $d_1$ | $d_2$ | $d_3$ | $d_4$ | $n$ | {25%; 75%} |
| **Scenario 1** | | | | | | | | | | |
| RSPRT 1 | 0.01 | 0.97 | 0.02 | 0.01 | 0.23 | 0.75 | 0.02 | 0.00 | 24 | {13; 33} |
| OPTIMIZING | 0.00 | 0.95 | 0.05 | 0.00 | 0.24 | 0.48 | 0.26 | 0.02 | 32 | {22; 46} |
| ND 1 | 0.00 | 0.88 | 0.11 | 0.01 | 0.13 | 0.66 | 0.17 | 0.04 | 23 | {14; 35} |
| ND 2 | 0.00 | 0.96 | 0.04 | 0.00 | 0.09 | 0.87 | 0.04 | 0.00 | 20 | {14; 30} |
| ND 3 | 0.00 | 0.94 | 0.06 | 0.00 | 0.07 | 0.86 | 0.06 | 0.01 | 18 | {12; 30} |
| **Scenario 2** | | | | | | | | | | |
| RSPRT 1 | 0.95 | 0.05 | 0.00 | 0.00 | 0.76 | 0.24 | 0.00 | 0.00 | 19 | {14; 27} |
| OPTIMIZING | 0.96 | 0.04 | 0.00 | 0.00 | 0.47 | 0.50 | 0.03 | 0.00 | 32 | {22; 46} |
| ND 1 | 0.89 | 0.09 | 0.02 | 0.00 | 0.60 | 0.31 | 0.08 | 0.01 | 24 | {16; 36} |
| ND 2 | 0.88 | 0.12 | 0.00 | 0.00 | 0.64 | 0.34 | 0.02 | 0.00 | 24 | {18; 38} |
| ND 3 | 0.85 | 0.14 | 0.01 | 0.00 | 0.51 | 0.45 | 0.04 | 0.00 | 27 | {21; 42} |
| **Scenario 3** | | | | | | | | | | |
| RSPRT 1 | 0.00 | 0.00 | 0.95 | 0.05 | 0.05 | 0.44 | 0.44 | 0.07 | 35 | {28; 46} |
| OPTIMIZING | 0.00 | 0.00 | 0.98 | 0.01 | 0.13 | 0.33 | 0.37 | 0.17 | 46 | {32; 62} |
| ND 1 | 0.00 | 0.00 | 0.95 | 0.05 | 0.01 | 0.20 | 0.61 | 0.18 | 25 | {16; 38} |
| ND 2 | 0.00 | 0.00 | 0.98 | 0.02 | 0.01 | 0.22 | 0.72 | 0.05 | 24 | {18; 34} |
| ND 3 | 0.00 | 0.00 | 0.96 | 0.04 | 0.00 | 0.24 | 0.68 | 0.08 | 24 | {18; 36} |
| **Scenario 4** | | | | | | | | | | |
| RSPRT 1 | 0.00 | 0.00 | 0.12 | 0.88 | 0.00 | 0.37 | 0.33 | 0.31 | 46 | {35; 58} |
| OPTIMIZING | 0.00 | 0.00 | 0.28 | 0.72 | 0.10 | 0.24 | 0.40 | 0.26 | 100 | {100; 100} |
| ND 1 | 0.00 | 0.00 | 0.07 | 0.93 | 0.00 | 0.10 | 0.29 | 0.61 | 24 | {16; 36} |
| ND 2 | 0.00 | 0.00 | 0.12 | 0.88 | 0.00 | 0.14 | 0.37 | 0.49 | 32 | {24; 44} |
| ND 3 | 0.00 | 0.00 | 0.10 | 0.90 | 0.00 | 0.15 | 0.33 | 0.52 | 30 | {21; 39} |

**Table 4**
*Percent recommendation, allocation proportions, median sample size, 25th and 75th percentiles of the sample size distribution for scenarios* 1–4 (*Table* 1) *for repeated SPRT with groups of size* 3 (RSPRT 3), *and the new design with groups of size* 3 (ND 3). *Stopping rule used is based on the* SPRT *with* $\varepsilon_1 = \varepsilon_2 = 0.15$.

| | Percent recommendation | | | | Allocation proportions | | | | Sample size | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $d_1$ | $d_2$ | $d_3$ | $d_4$ | $d_1$ | $d_2$ | $d_3$ | $d_4$ | $n$ | {25%; 75%} |
| **Scenario 1** | | | | | | | | | | |
| RSPRT 3 | 0.00 | 0.95 | 0.05 | 0.01 | 0.22 | 0.76 | 0.02 | 0.00 | 16 | {7; 24} |
| ND 3 | 0.00 | 0.94 | 0.06 | 0.00 | 0.07 | 0.88 | 0.05 | 0.00 | 12 | {9; 21} |
| **Scenario 2** | | | | | | | | | | |
| RSPRT 3 | 0.90 | 0.09 | 0.01 | 0.00 | 0.68 | 0.32 | 0.00 | 0.00 | 13 | {10; 19} |
| ND 3 | 0.76 | 0.22 | 0.02 | 0.00 | 0.43 | 0.52 | 0.05 | 0.00 | 21 | {15; 30} |
| **Scenario 3** | | | | | | | | | | |
| RSPRT 3 | 0.00 | 0.02 | 0.93 | 0.05 | 0.05 | 0.46 | 0.44 | 0.05 | 23 | {18; 31} |
| ND 3 | 0.00 | 0.00 | 0.96 | 0.04 | 0.00 | 0.29 | 0.65 | 0.06 | 18 | {12; 27} |
| **Scenario 4** | | | | | | | | | | |
| RSPRT 3 | 0.00 | 0.02 | 0.22 | 0.76 | 0.00 | 0.37 | 0.38 | 0.25 | 33 | {26; 43} |
| ND 3 | 0.00 | 0.00 | 0.17 | 0.83 | 0.00 | 0.19 | 0.37 | 0.44 | 21 | {18; 30} |

$N = 100/4 = 25$ for the new design and $N = 10$ for the optimizing design. Simulation results based on 5000 runs are presented in Table 3. The methodology of O'Quigley et al. (2001) performs better than the new design in scenario 1, and slightly better in scenario 2. This is because, in these two scenarios, the best doses are $d_1$ and $d_2$, and are detected early by the repeated SPRT. The new design yields much smaller median sample size and better, or the same probability of correct selection for scenarios 3 and 4. For example, in scenario 4, the new design uses half the sample size required by the repeated SPRT and has better probability of correct selection. This is because the best dose is $d_4$ and the repeated SPRT requires about 10–15 subjects at each of the lower doses before it reaches $d_4$. The optimizing design of Kpamegan and Flournoy (2001) has the largest sample size in all scenarios considered, and comparable probability of correct selection.

Results for group designs are displayed in Tables 3 and 4. Assigning in groups does not lead to substantial increase in sample size. The new design with groups of size 3 is similar or better than the repeated SPRT with groups of size 3 (Table 4), in all four scenarios except scenario 2.

We also compared the new design with the optimizing design of Kpamegan and Flournoy (2001), in the case where 6 doses are studied (Table 5). Designs were compared with fixed sample sizes of $n = 24$ and $n = 50$. The starting dose was $d_2$ for the new design, and ($d_2$, $d_3$) for the optimizing design. Toxicity was modeled by $Q(d_j) = \alpha_j^a$, with $(\alpha_1, \ldots, \alpha_6) = (0.05, 0.10, 0.2, 0.3, 0.5, 0.7)$, and exponential prior with mean one for parameter $a$. Sample size of 24 was enough for the new design to identify the optimal safe dose well in all three scenarios (Table 5). In scenario 6, the optimal dose is dose 3. Since $\lambda_4 = \lambda_5 = \lambda_6 = 1$, the new design will assign approximately equal number of subjects to doses $d_3$ and higher, in the limit, if the toxicity restriction is not invoked. This explains why the allocation for $n = 50$ is not as peaked around the optimal safe dose as for $n = 24$ when the new design is used. In scenario 7, the dose with the highest success rate has an unacceptable toxicity rate of 0.5, hence the optimal safe dose is dose 2. The combination of the new allocation procedure with Bayesian methods, to monitor toxicity, is effective and results in assigning about 6 out of 24 subjects to doses with high toxicity rate in scenario 7. The optimizing design fails to escalate to the higher doses in scenario 5; however, it performs well in scenario 6, where there are two adjacent doses with high success rates.

## 6. Discussion

We have proposed a new design for dose-finding studies with bivariate outcome, toxicity, and therapeutic response. Several issues remain for future investigation. The first is to find efficient methods of estimating the optimal dose and the optimal safe dose. A nonparametric method, such as isotonic regression (Stylianou and Flournoy, 2002; Ivanova et al., 2003), might work well in estimating the toxicity profile of the agent. Stopping rules in the case when no satisfactory success rate is specified require investigation. It is known that, when adaptive allocation and stopping rules are used, the maximum likelihood estimates of success probabilities can be biased. One needs to know the magnitude of the bias. We considered the case where, if toxicity is observed, response cannot be observed. The methodology still applies if response can be observed irrespective of toxicity; that is, when there are four possible outcomes rather than three. Some improvements to the design might be possible, since more information is available.

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**Table 5**
*Percent recommendation and allocation proportions for scenarios* 5–7. *Designs include optimizing design (OPTIMIZING), and the new design with groups of size* 1 *(ND 1), groups of size* 2 *(ND 2), and groups of size* 3 *(ND 3).*

| | Percent recommendation | | | | | | Allocation proportions | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $d_1$ | $d_2$ | $d_3$ | $d_4$ | $d_5$ | $d_6$ | $d_1$ | $d_2$ | $d_3$ | $d_4$ | $d_5$ | $d_6$ |
| **Scenario 5** | | | | | | | | | | | | |
| $Q(d_j)$ | 0.03 | 0.05 | 0.07 | 0.10 | 0.20 | 0.30 | | | | | | |
| $P(d_j)$ | 0.00 | 0.05 | 0.07 | 0.20 | 0.70 | 0.50 | | | | | | |
| $n = 24$ | | | | | | | | | | | | |
| ND1 | 0.00 | 0.01 | 0.03 | 0.21 | 0.75 | 0.00 | 0.00 | 0.06 | 0.09 | 0.33 | 0.50 | 0.02 |
| ND2 | 0.00 | 0.02 | 0.04 | 0.25 | 0.69 | 0.00 | 0.00 | 0.11 | 0.13 | 0.34 | 0.42 | 0.00 |
| ND3 | 0.00 | 0.01 | 0.04 | 0.31 | 0.64 | 0.01 | 0.00 | 0.13 | 0.15 | 0.36 | 0.35 | 0.01 |
| OPTIMIZING | 0.00 | 0.31 | 0.26 | 0.25 | 0.18 | 0.00 | 0.09 | 0.39 | 0.38 | 0.10 | 0.03 | 0.00 |
| $n = 50$ | | | | | | | | | | | | |
| ND1 | 0.00 | 0.00 | 0.01 | 0.17 | 0.81 | 0.01 | 0.00 | 0.03 | 0.07 | 0.33 | 0.56 | 0.02 |
| ND2 | 0.00 | 0.00 | 0.01 | 0.20 | 0.79 | 0.00 | 0.00 | 0.05 | 0.06 | 0.30 | 0.58 | 0.00 |
| ND3 | 0.00 | 0.00 | 0.01 | 0.21 | 0.78 | 0.00 | 0.00 | 0.06 | 0.08 | 0.33 | 0.53 | 0.00 |
| OPTIMIZING | 0.00 | 0.36 | 0.22 | 0.25 | 0.17 | 0.00 | 0.11 | 0.34 | 0.33 | 0.16 | 0.06 | 0.00 |
| **Scenario 6** | | | | | | | | | | | | |
| $Q(d_j)$ | 0.03 | 0.04 | 0.05 | 0.10 | 0.20 | 0.30 | | | | | | |
| $P(d_j)$ | 0.00 | 0.05 | 0.85 | 0.70 | 0.50 | 0.40 | | | | | | |
| $n = 24$ | | | | | | | | | | | | |
| ND1 | 0.00 | 0.00 | 0.70 | 0.25 | 0.05 | 0.00 | 0.00 | 0.07 | 0.51 | 0.25 | 0.14 | 0.02 |
| ND2 | 0.00 | 0.00 | 0.95 | 0.05 | 0.00 | 0.00 | 0.00 | 0.10 | 0.86 | 0.04 | 0.00 | 0.00 |
| ND3 | 0.00 | 0.00 | 0.92 | 0.07 | 0.01 | 0.00 | 0.00 | 0.13 | 0.80 | 0.06 | 0.01 | 0.00 |
| OPTIMIZING | 0.00 | 0.01 | 0.79 | 0.19 | 0.01 | 0.00 | 0.01 | 0.15 | 0.45 | 0.34 | 0.04 | 0.00 |
| $n = 50$ | | | | | | | | | | | | |
| ND1 | 0.00 | 0.00 | 0.76 | 0.21 | 0.03 | 0.00 | 0.00 | 0.05 | 0.43 | 0.29 | 0.20 | 0.03 |
| ND2 | 0.00 | 0.00 | 0.93 | 0.07 | 0.00 | 0.00 | 0.00 | 0.05 | 0.85 | 0.08 | 0.02 | 0.00 |
| ND3 | 0.00 | 0.00 | 0.89 | 0.10 | 0.01 | 0.00 | 0.00 | 0.07 | 0.78 | 0.12 | 0.03 | 0.00 |
| OPTIMIZING | 0.00 | 0.01 | 0.86 | 0.12 | 0.02 | 0.00 | 0.01 | 0.14 | 0.44 | 0.36 | 0.05 | 0.00 |
| **Scenario 7** | | | | | | | | | | | | |
| $Q(d_j)$ | 0.05 | 0.25 | 0.50 | 0.60 | 0.70 | 0.80 | | | | | | |
| $P(d_j)$ | 0.10 | 0.20 | 0.30 | 0.20 | 0.10 | 0.03 | | | | | | |
| $n = 24$ | | | | | | | | | | | | |
| ND1 | 0.15 | 0.71 | 0.14 | 0.00 | 0.00 | 0.00 | 0.19 | 0.53 | 0.24 | 0.04 | 0.00 | 0.00 |
| ND2 | 0.15 | 0.73 | 0.12 | 0.00 | 0.00 | 0.00 | 0.12 | 0.62 | 0.25 | 0.01 | 0.00 | 0.00 |
| ND3 | 0.14 | 0.73 | 0.13 | 0.00 | 0.00 | 0.00 | 0.12 | 0.59 | 0.27 | 0.02 | 0.00 | 0.00 |
| OPTIMIZING | 0.22 | 0.60 | 0.18 | 0.00 | 0.00 | 0.00 | 0.32 | 0.47 | 0.18 | 0.03 | 0.00 | 0.00 |
| $n = 50$ | | | | | | | | | | | | |
| ND1 | 0.13 | 0.82 | 0.05 | 0.00 | 0.00 | 0.00 | 0.20 | 0.61 | 0.16 | 0.02 | 0.00 | 0.00 |
| ND2 | 0.09 | 0.87 | 0.04 | 0.00 | 0.00 | 0.00 | 0.11 | 0.72 | 0.16 | 0.01 | 0.00 | 0.00 |
| ND3 | 0.09 | 0.87 | 0.04 | 0.00 | 0.00 | 0.00 | 0.14 | 0.68 | 0.17 | 0.01 | 0.00 | 0.00 |
| OPTIMIZING | 0.15 | 0.74 | 0.11 | 0.00 | 0.00 | 0.00 | 0.37 | 0.49 | 0.13 | 0.01 | 0.00 | 0.00 |

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## Résumé

Pour certaines substances l'apparition de manifestations toxiques peut amener à des interruptions précoces de traitement, avant l'apparition d'une réponse thérapeutique. En fait il y a trois résultats possibles : une manifestation toxique sans effet thérapeutique observé, une réponse thérapeutique sans manifestation toxique, et aucun effet ni thérapeutique ni toxique. La dose optimale est la dose qui rend maximum la probabilité d'avoir conjointement un effet thérapeutique et pas de toxicité. La dose maximale sûre est la dose qui maximise la probabilité d'une réponse sans toxicité parmi les doses avec une toxicité inférieure au seuil maximum tolérable. Nous présentons un nouveau protocole séquentiel pour les essais d'escalade de doses avec deux critères de jugement. Ce protocole maximise le nombre de sujets recevant une dose voisine de la dose optimale sûre.

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## Appendix

*Proof of Theorem.* Let $a_k$, $b_k$, and $c_k$ denote the probabilities of decreasing the dose from $d_k$ to $d_{k-1}$, to stay at dose $d_k$, or increase the dose from $d_k$ to $d_{k+1}$. Here, $a_k + b_k + c_k = 1$, for $k \in \{2, \ldots, K-1\}$. The transitional probabilities, $a_{\rm k}$, $b_{\rm k}$, and $c_{\rm k}$, for the play-the-winner up-and-down design are

$$\begin{array}{lll} a_1 = 0, & b_1 = 1 - S(d_1), & c_1 = S(d_1), \\ a_k = Q(d_{\rm k}), & b_k = 1 - Q(d_k) - S(d_k), & c_{\rm k} = S(d_k), \\ a_{\rm K} = Q(d_K), & b_{\rm K} = 1 - Q(d_K), & c_K = 0, \end{array}$$

where $k \in \{2, \ldots, K-1\}$. The stationary distribution can be obtained by solving the balance equations, $\pi_k = \pi_{k-1}\, c_{k-1} + \pi_k\, b_k + \pi_{k+1}\, a_{k+1}$, $k \in \{1, \ldots, K\}$. (Here, for convenience $c_0 = a_{K+1} = 0$.) The solution is

$$\pi_k = \prod_{j=1}^{k} \lambda_j, \quad \lambda_1 = \left(1 + \sum_{k=2}^{K} \prod_{j=2}^{k} \lambda_j\right)^{-1}, \quad \lambda_k = \frac{S(d_{k-1})}{Q(d_k)},$$

where $k \in \{2, \ldots, K\}$. Let $\lambda_2 \geq 1$. Since the sequence of $\lambda_k$, $k = 2, \ldots, K$, decreases, there exist unique index $k$ such that $d_k$ is the largest dose, with $\lambda_k \geq 1$. Then, similarly to Durham and Flournoy (1994), the stationary distribution is log-concave, with either the mode at $d_k$ if $\lambda_k > 1$, or the mode that spans $d_{k-1}$ and $d_k$ if $\lambda_k = 1$. That is, the stationary distribution for the winner up-and-down has a mode at a dose $d_\tau$, for which $S(d_{\tau-1}) > Q(d_\tau)$ and $S(d_\tau) < Q(d_{\tau+1})$. If $\lambda_2 < 1$, the mode is at dose $d_1$.