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# Simultaneously optimizing dose and schedule of a new cytotoxic agent

Thomas M Braun<sup>a</sup>, Peter F Thall<sup>b</sup>, Hoang Nguyen<sup>b</sup> and Marcos de Lima<sup>c</sup>

**Background** Traditionally, phase I clinical trial designs are based upon one pre-defined course of treatment while varying among patients the dose given at each administration. In actual medical practice, patients receive a schedule comprised of several courses of treatment, and some patients may receive one or more dose reductions or delays during treatment. Consequently, the overall risk of toxicity for each patient is a function of both actual schedule of treatment and the differing doses used at each administration.

**Purpose** Our goal is to provide a practical phase I clinical trial design that more accurately reflects actual medical practice by accounting for both dose per administration and schedule.

**Methods** We propose an outcome-adaptive Bayesian design that simultaneously optimizes both dose and schedule in terms of the overall risk of toxicity, based on time-to-toxicity outcomes. We use computer simulation as a tool to calibrate design parameters.

**Results** We describe a phase I trial in allogeneic bone marrow transplantation that was designed and is currently being conducted using our new method. Our computer simulations demonstrate that our method outperforms any method that searches for an optimal dose but does not allow schedule to vary, both in terms of the probability of identifying optimal (dose, schedule) combinations, and the numbers of patients assigned to those combinations in the trial.

**Limitations** Our design requires greater sample sizes than those seen in traditional phase I studies due to the larger number of treatment combinations examined. Our design also assumes that the effects of multiple administrations are independent of each other and that the hazard of toxicity is the same for all administrations.

**Conclusions** Our design is the first for phase I clinical trials that is sufficiently flexible and practical to truly reflect clinical practice by varying both dose and the timing and number of administrations given to each patient. *Clinical Trials* 2007; 4: 113–124. <http://ctj.sagepub.com>

## Introduction

Conventional phase I clinical trials determine the maximum-tolerated dose (MTD) of a new agent by characterizing patient outcome as a binary indicator of whether toxicity occurs within a short-time period from the start of therapy. Generally, the

MTD is the highest dose that does not present a practical limitation to therapy [1–3]. This approach has seen widespread use largely because it facilitates adaptive dose-finding methods that successively use the doses and outcomes of previous patients to select doses for new patients. A limitation of these methods is that they typically base dose-finding on

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a single course of therapy, whereas multiple courses typically are used in medical practice. As a result, the MTD based on a single course of treatment may prove to be overly toxic when given over multiple courses. For example, if conventional dose-finding is done with a fixed schedule consisting of one course when in fact a safe dose  $d^*$  exists with three courses and this combination has substantive anti-disease effect whereas  $d^*$  with only one course does not, then the conventional MTD of one course may lead to the erroneous conclusion in later studies that the agent is ineffective. Similarly, if conventional dose-finding is done with four courses and it turns out that the lowest dose is excessively toxic, then it may be concluded erroneously that the agent is unsafe at any dose simply because shorter schedules were not examined.

Recently, a new phase I method was proposed that determines a maximum-tolerated schedule (MTS), rather than a conventional MTD [4]. The MTS is defined as the maximum number of courses that can be given without causing unacceptable cumulative toxicity. The model and method account for the patients' sequence of administrations and allow the number of courses to vary so that an optimal schedule may be determined. However, while this method allows the number of courses to vary, it requires the dose used in each administration to be fixed. Thus, if the fixed dose is ill-chosen, the MTS may be far from optimal. One may easily imagine examples similar to those given above by switching the roles of dose and schedule.

This paper is motivated by the problems, noted above, that arise in phase I trials when either the schedule is fixed and an MTD is found, or the per-administration dose is fixed and an MTS is found. We propose a new paradigm for phase I clinical trials that simultaneously optimizes both the dose per administration and the overall schedule. The design examines a matrix of possible (dose and schedule) combinations. Each patient is assigned a combination using previous patients' data, with decision criteria based on the posterior under a Bayesian model using time-to-toxicity as the outcome. The goal is to determine a maximum-tolerated dose and schedule (MTDS) in terms of the overall risk of toxicity. Our formulation allows both the dose and the timing of each administration to vary among patients. This accommodates settings where a patient's dose per administration is decreased if a low-grade toxicity is observed, and we also allow a patient's actual doses or administration times to deviate from planned values due to logistical difficulties or human error. Consequently, although the design examines a predetermined matrix of (dose and schedule) combinations, the model allows each patient's treatment to consist of an arbitrary sequence of administration times and a

corresponding sequence of doses, so that the likelihood reflects the actual data in the trial.

Motivating example describes the trial that motivated this research and that will be used for illustration. Probability model presents notation and probability models, including methods for eliciting and calibrating priors. Choosing (dose, schedule) combinations provides criteria for evaluating (dose, and schedule) pairs and rules for trial conduct. Section 5 illustrates the method via simulations as applied to an allogeneic cell transplantation trial, and we conclude with a discussion in Section 6.

## Motivating example

In allogeneic blood or bone marrow cell transplantation (allotx) for treatment of leukemia, a patient (host) receives cells (the graft) from a donor who has been matched on a number of human leukocyte antigen sites. The graft contains T-cells and natural killer cells that coordinate a positive immune response that kills leukemia cells, called a graft versus leukemia (GVL) effect. However, allotx recipients who initially respond to treatment have a substantial risk of disease recurrence due to proliferation of residual leukemia cells. As a result, investigators continue to seek agents that can be given to allotx recipients after they achieve a response in order to reduce the risk of disease recurrence.

Epigenetic DNA changes are reversible modifications of the DNA-histone complex that do not require alterations in nucleotide sequences [5]. Addition of a methyl group to gene promoter areas (DNA methylation) is associated with gene silencing, and abnormal methylation patterns are commonly seen in cancer cells. Hypermethylation of promoter regions appears to suppress genes involved in leukemic cell growth. Methylation is maintained by the enzyme cytosine DNA methyltransferase, with inhibition of this enzyme leading to hypomethylation and subsequent reactivation of tumor suppressor genes. Vidaza<sup>®</sup> (5-azacitidine) inhibits DNA methyltransferase by forming covalent adducts with the enzyme, activating silent genes that may lead to cell death, and also may induce phenotypic modification of the leukemic cells to facilitate immune recognition and potentiation of the donor cells' GVL effect. Vidaza<sup>®</sup> has been approved by the US Food and Drug Administration for the treatment of myelodysplastic syndrome (MDS), a blood cell disease that often progresses to acute myelogenous leukemia (AML). The recommended dose and schedule for MDS patients is 75 mg/m<sup>2</sup> given subcutaneously, daily for seven days, with this seven-day cycle repeated every four weeks. No data exist, however, on what a safe dose and schedule for AML patients might be.

The method described here was motivated by the desire to design a phase I trial to optimize both the schedule and the dose per administration of Vidaza® in AML. The trial currently is ongoing at M.D. Anderson Cancer Center. For the purpose of determining an optimal (dose and schedule) pair, ‘toxicity’ is defined as any of the following adverse events (AEs): (1) severe (grade 3 or 4) toxicity of the kidney, liver, heart or lung or neural toxicity, as defined by standard NCI grading criteria; (2) severe graft versus host disease; (3) systemic infection that cannot be resolved by antibiotics within two weeks; (4) severe hematologic toxicity, with thrombocytopenia and or neutropenia or (5) an AE of any of these types that leads to subsequent delay or termination of therapy, or a dose reduction. Each patient may receive up to four courses of therapy, and the dose may be reduced up to two times for reasons other than the toxicities listed above. Thus, a patient’s treatment may consist of an initial dose and the times at which it was administered, a second, possibly lower dose, along with its administration times, and so on, up to four courses. In practice, a patient’s administration times may deviate from the planned schedule due to practical difficulties in adhering to the schedule over several months of therapy, or intentional delay of a planned course by the physician to allow a patient to recover from a low-grade toxicity. Additionally, a patient may receive the wrong dose due to human error. Thus, an important feature of our model is that it accommodates each patient’s actual treatment sequence by accounting for the contribution of each dose and its time of administration to the patient’s overall risk of toxicity.

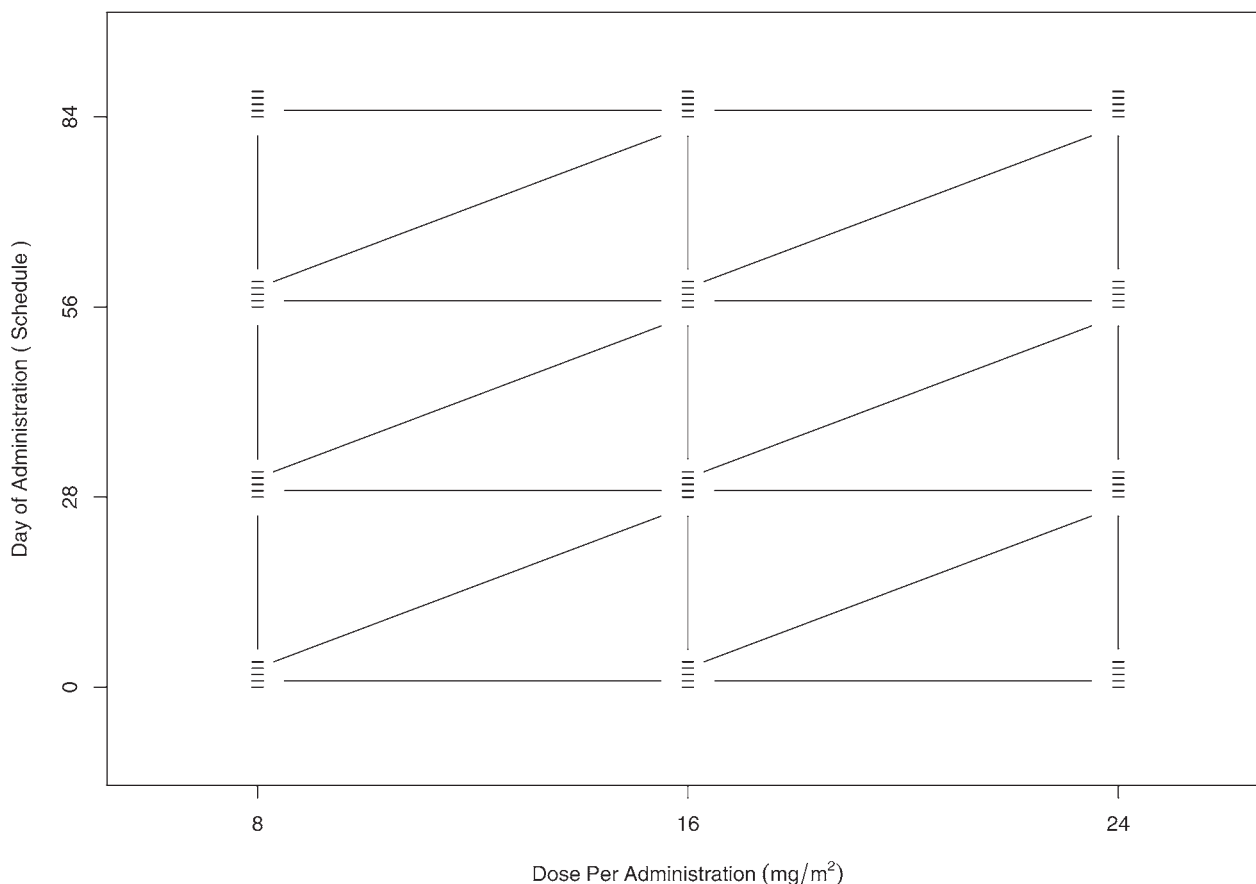
## Probability model

### General form of the hazard and likelihood

Suppose one wishes to evaluate  $J$  doses,  $d_1 < d_2 < \dots < d_j$ , and  $K$  nested schedules,  $s^{(1)}, \dots, s^{(K)}$ . The  $k$ th schedule is a sequence of administration times,  $s^{(k)} = (s_1, s_2, \dots, s_m^{(k)})$ , with  $s^{(k)}$  a subsequence of  $s^{(k+1)}$  for each  $k = 1, \dots, K - 1$ , and  $m^{(1)} < m^{(2)} \dots < m^{(K)}$ . Here, ‘dose’ is the amount of the agent given at each administration. For example, a patient given  $d_2$  under schedule  $s^{(3)} = (s_1, s_2, \dots, s_m^{(3)})$  receives the cumulative amount  $d_2 m^{(3)}$  of the agent in  $m^{(3)}$  successive administrations, unless therapy is terminated early due to toxicity. Thus, a patient’s assigned treatment is indexed by the pair  $(j, k)$ , representing  $(d_j, s^{(k)})$ , there are  $M = JK$  such pairs under consideration, and the total amount of the agent given to the patient increases with both dose and schedule.

In the motivating study, there are three doses of interest: 8, 16 and 24 mg/m<sup>2</sup>, and four schedules, for a total of  $M = 12$  combinations. One course consists of five consecutive daily administrations. Ideally, the first course begins 40 days post-transplant, although this may vary since the physician may decide to delay administration due to early complications, such as infection. We thus define the time to toxicity from the time when the first course is actually begun, the patient’s enrollment time. The first schedule,  $s^{(1)} = (0, 1, 2, 3, 4)$ , consists of one course. The second schedule includes one additional course starting 28 days after the beginning of  $s^{(1)}$ , so that  $s^{(2)} = (0, 1, 2, 3, 4, 28, 29, 30, 31, 32) = (s^{(1)}, s^{(1)} + 28)$ . The third and fourth schedules are defined similarly, with  $s^{(3)} = (s^{(1)}, s^{(1)} + 28, s^{(1)} + 56)$  and  $s^{(4)} = (s^{(1)}, s^{(1)} + 28, s^{(1)} + 56, s^{(1)} + 84)$ . Figure 1 provides a schematic representation of the 12 (dose schedule) combinations evaluated in the trial. We denote the maximum length of follow-up for each patient specified by the investigators by  $\tau$ , which should be large enough to include toxicities arising from the longest schedule,  $s^{(K)}$ . In the motivating trial,  $\tau = 116$  days, which is 28 days after the start of the fourth course.

Our model generalizes that used by Braun *et al.* [4] by extending it to allow the dose per administration to vary and also using a new parameterization to facilitate computation. While other models are possible, we use this model here because it is robust (Robustness Section, Table 4, below) and because our primary focus is the new algorithm for optimizing (dose, schedule). Let  $t^*$  denote a time, from the start of the trial, when one evaluates the data and either assigns a particular pair  $(j, k)$  to the next patient or terminates the trial early if no pair is acceptable. Denote by  $e$  the study time when the patient’s therapy begins. We denote the time to toxicity by  $Y$  and let  $Y^o$  be the patient’s observed time from  $e$  to either toxicity or last follow-up at study time  $t^*$ . Thus,  $Y^o = Y$  if  $e + Y \leq t^*$  or  $Y^o = t^* - e$  if  $e + Y > t^*$ . Let  $\delta = I(Y^o = Y)$  indicate that the patient has toxicity by study time  $t^*$ . Let  $h(u|\theta, d)$  denote the hazard of toxicity associated with a single administration of dose  $d$  of the agent given  $u$  days previously, where  $\theta$  is a vector of model parameters; we define  $h(u|\theta, d) = 0$  for  $u < 0$ . Let  $s = (s_1, \dots, s_k)$  denote the patient’s sequence of administration times and  $\mathbf{d}_s = (d_{j(s_1)}, \dots, d_{j(s_k)})$  the corresponding doses up to study time  $t^*$ . Thus,  $j(s_\ell)$  indexes the dose given to the patient at time  $s_\ell$  after entry, at study time  $e + s_\ell$ . The overall hazard of toxicity at study time  $t^*$  for a patient treated with schedule  $s$  and doses  $\mathbf{d}_s$  is  $\lambda(t^*|\theta, s, \mathbf{d}_s) = \sum_{\ell=1}^k h(t^* - e - s_\ell|\theta, d_{j(s_\ell)})$ . Consequently, the cumulative hazard function at  $t^*$  is  $\Lambda(t^*|\theta, s, \mathbf{d}_s) = \sum_{\ell=1}^k H(t^* - e - s_\ell|\theta, d_{j(s_\ell)})$ , where  $H(x|\theta, d) = \int_0^x \int_0^x h(u|\theta, d) du$ , with survivor function  $\Pr(Y > t^*|\theta, s, \mathbf{d}_s) = \bar{F}(t^*|\theta, s, \mathbf{d}_s) = \exp\{-\Lambda(t^*|\theta, s, \mathbf{d}_s)\}$  and density  $f(t^*|\theta, s, \mathbf{d}_s) = \lambda(t^*|\theta, s, \mathbf{d}_s)\bar{F}(t^*|\theta, s, \mathbf{d}_s)$ . Let  $n^*$  denotes



**Figure 1** Schematic representation of study

the number of patients enrolled up to  $t^*$ . For the  $i$ th patient,  $e_i$  is the entry time, the sequence of administration times up to  $t^*$  is  $e_i + \mathbf{s}_i = (e_i + s_{i,1}, \dots, e_i + s_{i,k_i})$ , and  $\mathbf{d}_{s_i} = (d_{j(s_i,1)}, \dots, d_{j(s_i, k_i)})$  is the corresponding sequence of doses,  $i = 1, \dots, n^*$ . For treatment sequences  $(s_i, \mathbf{d}_{s_i})$  and outcome data  $(Y_i^o, \delta_i)$ , patient  $i$  has likelihood  $L_i(\boldsymbol{\theta} | Y_i^o, \delta_i, s_i, \mathbf{d}_{s_i}) = \lambda(Y_i^o | \boldsymbol{\theta}, s_i, \mathbf{d}_{s_i})^{\delta_i} \bar{F}(Y_i^o | \boldsymbol{\theta}, s_i, \mathbf{d}_{s_i})$ , and the overall likelihood at  $t^*$  is  $\mathcal{L}(\boldsymbol{\theta} | \text{data}_n^*) = \prod_{i=1}^{n^*} L_i(\boldsymbol{\theta} | Y_i^o, \delta_i, s_i, \mathbf{d}_{s_i})$ .

This model accommodates each patient's *actual* sequence of administration times and doses, which often deviate from his/her planned treatment. For example, suppose a patient's planned treatment was two courses with 24 mg/m<sup>2</sup> at each of the 10 administrations, but the patient began the first course two days late, was reduced to 8 mg/m<sup>2</sup> in the second course due to a grade 2 infection, and was given 16 mg/m<sup>2</sup> by mistake at the 10th administration. Then, the patient's actual treatment would be  $s = (2, 3, 4, 5, 6, 30, 31, 32, 33, 34)$  and  $\mathbf{d}_s = (24, 24, 24, 24, 24, 8, 8, 8, 8, 16)$ . While this is not any of the 12 (dose, schedule) combinations being studied in the Vidaza<sup>®</sup> trial (Figure 1), the model allows this patient's data to be included in the likelihood.

It may be unclear how to score  $Y$  for some patients. The definition of toxicity in the Vidaza<sup>®</sup> trial includes grade 2 toxicities that cannot be resolved therapeutically within two weeks from onset or that necessitate a dose reduction. We chose to score such toxicities as occurring at the time of initial onset. For example, if a patient has a grade 2 thrombocytopenia starting at day 10 of therapy that persists beyond day 24 and requires a dose reduction, we define  $Y^o = 10$  and  $\delta = 1$ . However, if the thrombocytopenia is resolved by day 24, then it is not scored as a toxicity, and at day 24 we define  $Y^o = 24$  and  $\delta = 0$ , provided that no other toxicity has occurred. This approach is conservative in that toxicity is assumed to have occurred as soon as possible.

### Single administration hazard function

The probability model is determined by the particular form of  $h$ , for which we employ a reparameterized version of the triangular hazard function used by Braun [4]. In this model, for each per-administration dose  $j = 1, \dots, J$ , denote  $\boldsymbol{\theta}_j = (a_j, b_j, c_j)$ , with  $\boldsymbol{\theta} = \{\boldsymbol{\theta}_1, \dots, \boldsymbol{\theta}_J\}$  and each entry of  $\boldsymbol{\theta}$  positive-valued.

The hazard of toxicity associated with a single administration of dose  $d_j$  is

$$h(u|\theta_j) = \begin{cases} \frac{2a_j}{b_j+c_j} \frac{u}{b_j}, & 0 \leq u \leq b_j \\ \frac{2a_j}{b_j+c_j} \frac{b_j+c_j-u}{c_j}, & b_j < u \leq b_j+c_j \\ 0, & u > b_j+c_j \text{ or } u < 0 \end{cases} \quad (1)$$

This is a triangle having base of length  $b_j + c_j$  and area equal to  $a_j$ , with the height of the triangle,  $2a_j/(b_j + c_j)$ , occurring at  $u = b_j$ . The area of this triangle is the cumulative single-administration hazard  $H_j = a_j$  for dose  $d_j$ . The constraint that the per-administration cumulative hazard of toxicity increases with dose says that  $a_1 < a_2 < \dots < a_J$ . In some applications, however, the risk of toxicity may reach a plateau or may even decrease with a higher dose or longer schedule, such as in studies of anti-infection agents that have adverse effects, and such an ordering constraint is inappropriate.

**Establishing priors**

To enforce the constraint  $a_1 < a_2 < \dots < a_J$  so that  $F(\tau|\theta, d_j, s^{(k)})$ , the probability of toxicity by  $\tau$ , increases with dose, we let  $a_j^* = a_j - a_{j-1}$  for  $j \geq 2$ , with  $a_1^* = a_1$ . We assume that  $(a_1^*, \dots, a_J^*)$  follows a  $J$ -variate lognormal prior with all correlations equal to zero, although *a posteriori*, the  $a_j^*$ 's may be correlated. Denoting the marginals by  $a_j^* \sim \text{LN}(\mu_{a_j^*}, \sigma_a^2)$ , this implies that  $E(a_j^*) = \exp(\mu_{a_j^*} + \sigma_a^2/2)$  and  $\text{var}(a_j^*) = \exp(2\mu_{a_j^*} + \sigma_a^2) \{ \exp(\sigma_a^2) - 1 \}$ . Similarly,  $(b_1, \dots, b_J)$  and  $(c_1, \dots, c_J)$  each follow  $J$ -variate lognormal priors, with marginals  $b_j \sim \text{LN}(\mu_{b_j}, \sigma_b^2)$  and  $c_j \sim \text{LN}(\mu_{c_j}, \sigma_c^2)$  for each  $j$ . We chose the multivariate lognormal for its generality and tractability. Denoting  $\mu_j = (\mu_{a_j^*}, \mu_{b_j}, \mu_{c_j})$  and  $\sigma^2 = (\sigma_a^2, \sigma_b^2, \sigma_c^2)$ , the model has three  $J$  location hyperparameters,  $\mu = (\mu_1, \dots, \mu_J)$  and three scale hyperparameters,  $\sigma^2 = (\sigma_a^2, \sigma_b^2, \sigma_c^2)$ ; we denote  $\theta = (\mu, \sigma^2)$ . In Application Section, we will illustrate how to determine  $\theta$  in the context of the application.

Appropriate values for the prior mean and variance parameters may be elicited from the investigators in many ways [6], although in general, it is easiest to elicit values on domains with which the investigator is familiar [7]. Thus, we elicit the *expected* values of the following three quantities for each dose  $j = 1, \dots, J$ :

1.  $\xi_{j,1} = \log\{1 - F_j(\tau|s^{(1)}, \theta)\} = m^{(1)}a_j$ , the transformed probability of toxicity by time  $\tau$  under the shortest schedule  $s^{(1)}$ ,

2.  $\xi_{j,2}$ , the time until the maximum hazard is reached for one administration of dose  $j$ , and
3.  $\xi_{j,3}$ , the time from the peak of the hazard until the hazard vanishes completely or becomes negligible for a single administration of dose  $j$ .

In practice, one elicits the mean probability  $E\{F_j(\tau|s^{(1)}, \theta)|\tilde{\theta}\}$  and then derives  $E\{\xi_{j,1}|\tilde{\theta}\} \approx -\log\{1 - E\{F_j(\tau|s^{(1)}, \theta)|\tilde{\theta}\}\}$ . We will use the superscript  $(e)$  to denote elicited values, with  $\xi_{j,\ell}^{(e)}$  the elicited mean of  $\xi_{j,\ell}$ ,  $\ell = 1, 3$ .

We derive additional functions of the hyperparameter vector  $\theta$  by assuming that  $\xi_{j,1}$  has an inverse Gamma (IG) distribution with variance  $(\xi_{j,1}^{(e)})^2 / (\nu_1 - 1)$ , and that  $\xi_{j,2}$  and  $\xi_{j,3}$  have IG distributions with respective variances  $(\xi_{j,2}^{(e)})^2 / (\nu_2 - 1)$  and  $(\xi_{j,3}^{(e)})^2 / (\nu_2 - 1)$ . We use the same value  $\nu_2$  in the distributions of  $\xi_{j,2}$  and  $\xi_{j,3}$  as they both describe time durations and differ in nature from  $\xi_{j,1}$ . Since  $\xi_{j,1}$ ,  $\xi_{j,2}$  and  $\xi_{j,3}$  correspond, respectively, to  $m^{(1)}a_j$ ,  $b_j$  and  $c_j$ , we use the following method-of-moments approach to solve for  $\theta$  by equating the *elicited* moments of  $\xi_{j,1}$ ,  $\xi_{j,2}$  and  $\xi_{j,3}$  to their corresponding *theoretical* moments. Denoting  $\xi_{0,1}^{(e)} = 0$ , we solve the following set of equations for  $\theta$ :

$$\exp\left(\frac{\mu_{a_j^*} + \sigma_a^2}{2}\right) = \frac{(\xi_{j,2}^{(e)} - \xi_{j-1,1}^{(e)})}{m^{(1)}} \quad (2)$$

$$\exp(2\mu_{a_j^*} + \sigma_a^2) \{ \exp(\sigma_a^2) - 1 \} = \left[ \frac{(\xi_{j,1}^{(e)} - \xi_{j-1,1}^{(e)}) / m^{(1)}}{(\nu_1 - 1)} \right]^2 \quad (3)$$

$$\exp\left(\frac{\mu_{a_j^*} + \sigma_a^2}{2}\right) = \xi_{j,2}^{(e)} \quad (4)$$

$$\exp(2\mu_{b_j} + \sigma_b^2) \{ \exp(\sigma_b^2) - 1 \} = \frac{(\xi_{j,2}^{(e)})^2}{(\nu_2 - 1)} \quad (5)$$

$$\exp\left(\mu_{c_j} + \frac{\sigma_c^2}{2}\right) = \xi_{j,3}^{(e)} \quad (6)$$

$$\exp(2\mu_{c_j} + \sigma_c^2) \{ \exp(\sigma_c^2) - 1 \} = \frac{(\xi_{j,3}^{(e)})^2}{(\nu_2 - 1)} \quad (7)$$

Comparing Equations (2) and (3) shows that  $\exp(\sigma_a^2) - 1 = (\nu_1 - 1)^{-1}$ , hence  $\sigma_a^2 = \log\{\nu_1 / (\nu_1 - 1)\}$ , which is a function solely of  $\nu_1$ . Comparing Equations (4) and (5) and Equations (6) and (7), shows that  $\sigma_b^2 = \sigma_c^2 = \log\{\nu_2 / (\nu_2 - 1)\}$ . Thus,  $\nu_1$  and  $\nu_2$  are tuning parameters that determine the informativeness of the prior. Solving for the prior

location parameters gives  $\mu_{aj}^* = \log([\xi_{j,1}^{(e)} - \xi_{j-1,1}^{(e)}] / m^{(1)} - \sigma_a^2/2)$ ,  $\mu_{bj} = \log(\xi_{j,2}^{(e)} - \sigma_b^2/2)$  and  $\mu_{cj} = \log(\xi_{j,3}^{(e)} - \sigma_c^2/2)$ . Thus,  $\sigma^2$  is determined by the tuning parameters  $\nu_1$  and  $\nu_2$ , and given  $\sigma^2$ , the elicited quantities are used to determine the prior location parameters  $\mu$ .

### Choosing (dose schedule) combinations

Because trial conduct uses decision criteria based on the most recent posterior computed when a new patient is accrued, the data must be monitored continuously, making the design computationally intensive. We compute the posterior of  $\theta$  using Markov Chain Monte Carlo (MCMC) methods as described in Appendix. For each  $(j, k)$ , we base decisions on  $F_{jk}(\theta) = F(\tau|\theta, d_j, s^{(k)})$ , the cumulative probability of toxicity within  $\tau$  days after enrollment for a patient treated with dose  $j$  and schedule  $k$ . We will say that the pair  $(j, k)$  is *acceptable* if:

$$\Pr\{F_{jk}(\theta) > F_{\max} \mid \text{data}_n\} < p_u \tag{8}$$

where  $F_{\max}$  is a fixed upper bound on the probability of toxicity by  $\tau$  specified by the physician and  $p_u$  is a fixed decision cut-off, typically, set to 0.80 or larger. This is similar to the criterion used for defining acceptable toxicity used by Thall and Cook [8], in the context of dose-finding based on efficacy and toxicity. We denote the set of acceptable (dose schedule) combinations by  $\mathcal{O}^*$ . If  $\mathcal{O}^*$  is the empty set, then all  $(j, k)$  combinations are unacceptable and the trial is terminated. If  $\mathcal{O}^*$  has two or more elements, then we compute the distance measure

$$d_{jk}^* = |E\{F_{jk}(\theta) \mid \text{data}_n\} - \pi^0| \tag{9}$$

for each  $(j, k) \in \mathcal{O}^*$ , where  $\pi^0$  is a desired target for  $\Pr(Y < \tau)$  specified by the physician. We assign patient  $n^* + 1$  to the element of  $\mathcal{O}^*$  having smallest  $d_{jk}^*$ .

To protect patient safety, we constrain  $\mathcal{O}^*$  to include only  $(j, k)$  pairs with doses that are at most one dose above and/or one schedule longer than those combinations already assigned to previous patients. If  $(j^*, k^*)$  is the pair that was assigned to the previous subject, and no pair with higher dose or longer schedule has previously been tried, then the next patient may be assigned any pair  $(j, k)$  for which  $j \leq j^* + 1$  and  $k \leq k^* + 1$ ; we call this the ‘do not skip’ rule. Thus, one may de-escalate, stay at  $(j^*, k^*)$ , increase either dose or schedule by one

level, or increase both dose and schedule by one level, as shown by Figure 1. These restrictions only apply to untried  $(j, k)$  pairs when escalating, and we place no restriction on de-escalation of either dose or schedule. Combining all of the above criteria and rules, our algorithm for trial conduct is as follows:

### Trial Conduct

- 1) Treat the first patient at the lowest (dose, schedule) pair,  $(j, k) = (1, 1)$ .
- 2) For each patient after the first, based on the current posterior of  $\theta$ , determine the set,  $\mathcal{O}^*$ , of acceptable  $(j, k)$  combinations.
- 3) If  $\mathcal{O}^*$  is empty, then stop the trial and conclude that no  $(j, k)$  combination is acceptable.
- 4) If  $\mathcal{O}^*$  is not empty, then assign the next patient to the element of  $\mathcal{O}^*$  with smallest  $d_{jk}^*$ , that is, the combination whose posterior mean cumulative probability of toxicity by  $\tau$  is closest to  $\pi^0$ .
- 5) If the study is not terminated before  $N$  patients have been enrolled and fully evaluated with follow-up to  $\tau$ , select the pair  $(j^*, k^*)$  that minimizes  $d_{jk}^*$  as the optimal (dose and schedule) combination.

For example, suppose that the first patient has been assigned to combination (1, 1) and has not experienced toxicity. Due to the ‘do not skip’ rule, there are four possible (dose, schedule) combinations for the next patient:  $\mathcal{O}^* = \{(1, 1), (1, 2), (2, 1), (2, 2)\}$ . If we assign the second patient to combination (2, 1), and both enrolled patients have not experienced toxicity when the third patient is enrolled, then there are now six possible (dose, schedule) combinations for the third patient:  $\mathcal{O}^* = \{(1, 1), (1, 2), (2, 1), (2, 2), (3, 1), (3, 2)\}$ . This process is repeated with all successively enrolled patients. Note that if  $(j, k)$  is determined to be unsafe by Equation (8), then all pairs  $(j', k')$  with  $j' \geq j$  and  $k' \geq k$  must be unsafe.

### Application

#### Design and priors

The Vidaza<sup>®</sup> trial has three doses,  $d_1 = 8$ ,  $d_2 = 16$  and  $d_3 = 24$  mg/m<sup>2</sup> and four schedules with  $m^{(1)} = 5$ ,  $m^{(2)} = 10$ ,  $m^{(3)} = 15$  or  $m^{(4)} = 20$  administrations. The trial will enroll a maximum of  $N = 60$  patients, with each patient followed for up to  $\tau = 116$  days. Using the trial conduct algorithm given above, a (dose, schedule) combination is assigned to each

new patient at the time of his/her enrollment. The goal is to find a (dose, schedule) combination with mean probability of toxicity by  $\tau$  closest to  $\pi^0 = 0.30$ . The investigators believed that the single-administration hazards for the three doses have expected peaks at  $\xi_{1,2}^{(e)} = 18$ ,  $\xi_{2,2}^{(e)} = 14$  and  $\xi_{3,2}^{(e)} = 10$  days, respectively, with expected remaining durations of  $\xi_{1,3}^{(e)} = 10$ ,  $\xi_{2,3}^{(e)} = 14$  and  $\xi_{3,3}^{(e)} = 18$  days. They also believed that the expected probabilities of toxicity by 116 days for the three doses under the shortest schedule are 0.20, 0.25 and 0.30, so that  $\xi_{1,1}^{(e)} = -\log(1 - 0.20)$ ,  $\xi_{2,1}^{(e)} = -\log(1 - 0.25)$  and  $\xi_{3,1}^{(e)} = -\log(1 - 0.30)$ . We derived  $\hat{\theta}$  using this elicited information as described in Establishing priors. The prior is characterized by  $\sigma_a^2 = \sigma_b^2 = \sigma_c^2 = 1.1$ ,  $\mu_1 = (-3.66, 2.34, 1.75)$ ,  $\mu_2 = (-4.90, 2.09, 2.09)$  and  $\mu_3 = (-4.83, 1.75, 2.34)$ . The safety criterion parameters for applying Equation (4) were defined to be  $F_{\max} = 0.30$  and  $p_u = 0.80$ , so that a pair  $(j, k)$  is deemed acceptable if  $<80\%$  of the posterior mass of  $F_{jk}(\theta)$  is above 0.30.

**Simulation design**

For the simulation study, we specified seven scenarios in terms of fixed true probabilities of toxicity by day  $\tau = 116$ ,  $F_{jk}^{\text{true}}$ , for each  $(j, k)$ . These scenarios are summarized in Table 1 and illustrated by Figure 2. In scenario 1, all 12 combinations are safe, with  $F_{jk}^{\text{true}} \leq 0.30$ , and the pairs (2, 4) and (3, 4) have  $F_{jk}^{\text{true}}$  closest to 0.30. Scenarios 2 and 3 have several combinations with  $F_{jk}^{\text{true}} > 0.30$ , and all 12 combinations are toxic in scenario 4. In each of scenarios 5–7, combination (2, 2) has  $F_{22}^{\text{true}} = 0.30$ , but the scenarios differ in terms of how the  $F_{jk}^{\text{true}}$  values of the other combinations vary around combination (2, 2).

Based on the input from the principal investigator, patient inter-arrival times were simulated from an exponential distribution with mean of two weeks, reflecting an accrual rate of about two patients per month, and we simulated 10% of all toxicities to be low-grade, which are classified as dose-limiting at their onset if they fail to resolve within two weeks. Thus, there is a two-week delay in the recording of toxicities that began as low-grade toxicities.

We determined the values  $\nu_1$ ,  $\nu_2$  and  $p_u$  used for the actual trial by first running an extensive series of preliminary simulations using candidate values  $1.1 \leq \nu_1 \leq 3$ ,  $1.1 \leq \nu_2 \leq 14$  and  $p_u \in \{0.70, 0.75, 0.80, 0.85, 0.90\}$ . Initially, we examined multiple combinations of the three parameters under scenario 4, our ‘worst-case’ scenario, and we selected a set of  $(\nu_1, \nu_2, p_u)$  combinations to ensure a high probability ( $\geq 90\%$ ) of stopping early, to ensure a safe design. Once we found a subset of safe  $(\nu_1, \nu_2, p_u)$  combinations, we ran additional simulations using those combinations under each of the other scenarios to identify final values giving a design

**Table 1** The fixed toxicity probabilities of each (dose, schedule) pair under each of scenario in the simulation study

Scenario	Schedule	Dose (mg/m <sup>2</sup> )		
		8	16	24
1	4	0.22	0.26	0.30
	3	0.16	0.18	0.23
	2	0.09	0.12	0.18
	1	0.05	0.07	0.11
2	4	0.31	0.45	0.62
	3	0.18	0.32	0.54
	2	0.09	0.21	0.40
	1	0.03	0.14	0.28
3	4	0.55	0.62	0.72
	3	0.45	0.50	0.62
	2	0.30	0.32	0.50
	1	0.10	0.26	0.35
4	4	0.57	0.73	0.78
	3	0.55	0.65	0.75
	2	0.53	0.60	0.65
	1	0.50	0.54	0.58
5	4	0.30	0.48	0.70
	3	0.14	0.32	0.55
	2	0.12	0.30	0.48
	1	0.10	0.28	0.45
6	4	0.50	0.60	0.75
	3	0.30	0.50	0.60
	2	0.12	0.30	0.50
	1	0.03	0.15	0.30
7	4	0.10	0.60	0.70
	3	0.05	0.50	0.60
	2	0.03	0.30	0.55
	1	0.01	0.10	0.50

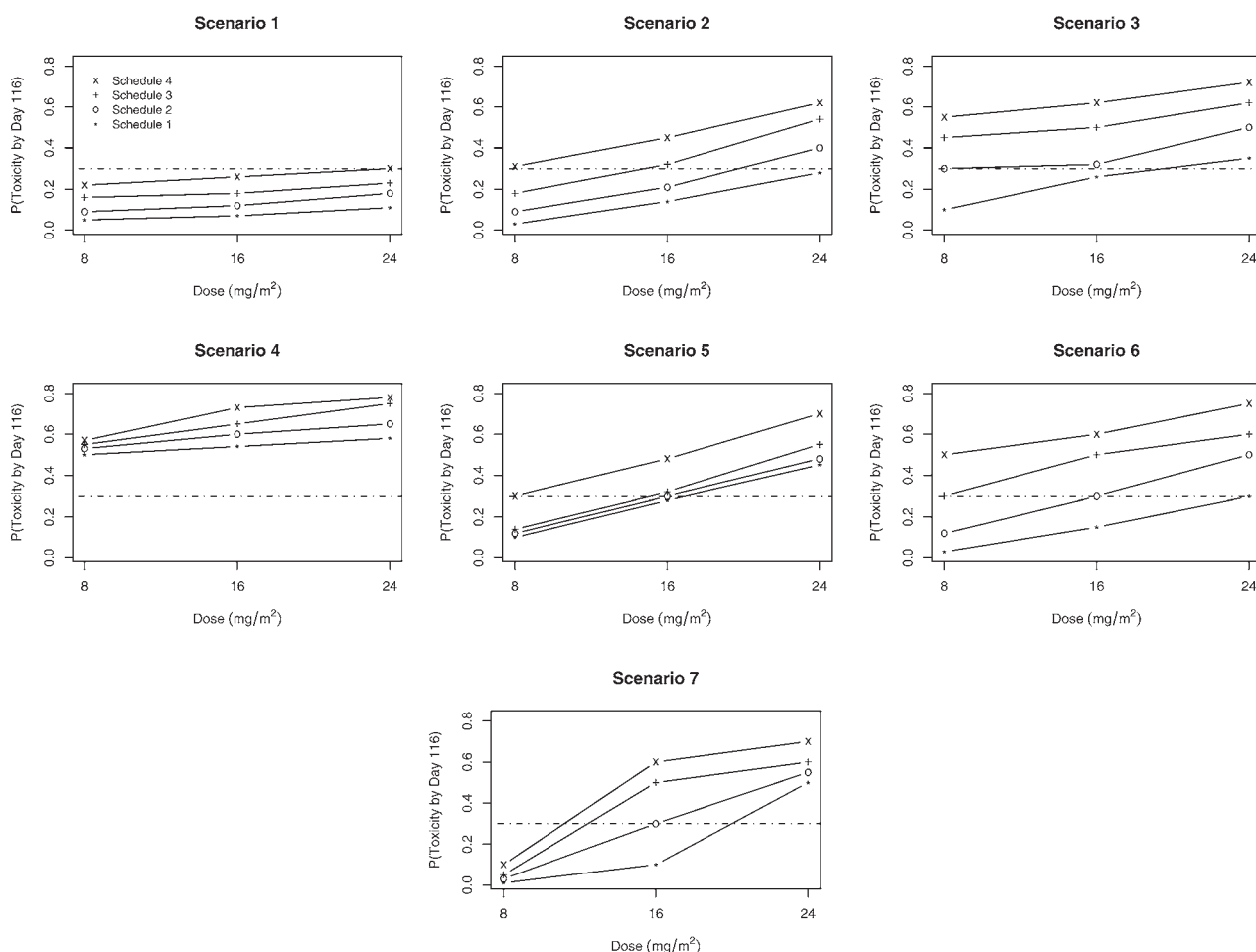
with good properties under all scenarios. We found that  $\nu_1 = 1.5$ ,  $\nu_2 = 1.5$  and  $p_u = 0.80$  reliably chooses  $(j, k)$  pairs with  $F_{jk}^{\text{true}}$  close to the targeted  $\pi^0 = 0.30$  in each of the non-worst case scenarios, while forcing early termination of the study with at least 90% probability under scenario 4.

To examine the design’s robustness, we generated the  $Y_i$ ’s from each of the several different parameterizations of Weibull, exponential and lognormal distributions under each scenario. In Tables 2 and 3, we report simulation results for an exponential distribution with scale parameter chosen so that each  $F_{jk}^{\text{true}}$  equalled the value specified in Table 1. Table 4 summarizes results under scenario 5 when the  $Y_i$ ’s are generated from a Weibull distribution with shape parameter 0.4 and a lognormal distribution with variance equal to that of the exponential. The scale parameters of the Weibull and lognormal distributions were chosen so that  $F_{jk}^{\text{true}}$  equalled the value specified in Table 1.

**Simulation results**

Table 2 gives the selection frequency and the mean number of patients assigned to each (dose, schedule)





**Figure 2** The fixed toxicity probabilities of each (dose, schedule) pair under each of scenario in the simulation study. The dashed horizontal line represents the target toxicity probability 0.30

pair under each of the scenarios using the proposed design, referred to as 'MTDS.' As a basis for comparison, we also include results for a conventional phase I dose-finding design using the continual reassessment method (CRM) [9] with the schedule fixed at schedule 4, assuming  $\Pr(Y_i \leq 116|d_j, \text{schedule } 4) = p_j^{\exp(\alpha)}$  for  $j = 1-3$ , with  $(p_1, p_2, p_3) = (0.10, 0.30, 0.50)$  and  $\alpha$  following a normal prior with mean 0 and variance 2. Table 3 displays summary statistics for both the MTDS and CRM designs under all seven scenarios. We consider (dose, schedule) combinations with  $0.20 \leq F_{jk}^{\text{true}} \leq 0.40$  to be acceptable choices, with boldfaced values in Table 2 corresponding to such combinations.

In scenario 1, the MTDS design identifies one of the four acceptable combinations as optimal 87% of the time, with an average of about 38 patients assigned to one of these four combinations. The CRM assigns all 60 patients to an acceptable combination, because in this case, the CRM design fortuitously only examines schedule 4. In scenario 2, one of the five acceptable combinations is identified as

optimal by the MTDS design in 81% of the simulations, with an average of nearly 42 patients assigned to one of these five combinations and around seven patients assigned to combinations with  $F_{jk}^{\text{true}} > 0.40$ . Because the CRM design is limited to doses with schedule 4, it can possibly find only the one acceptable combination (1, 4) in scenario 2, which it identifies as the MTD 66% of the time, with 41 patients assigned to that combination. The CRM terminates early with no dose selected 16% of the time, in contrast to 0% for the MTDS design, because the other two doses are extremely toxic under schedule 4. That is, there is a probability 0.16 that a truly safe agent, when appropriately administered, will be abandoned based on a conventional phase I trial using the CRM. The limitations of fixing schedule and only varying dose are further illustrated by Table 3. In particular, the CRM has probability 0 of selecting an acceptable dose under each of scenarios 3, 6 and 7, where all of the acceptable doses are at schedules below schedule 4.

**Table 2** Simulation results for the MTDS method and the CRM used within schedule 4. For each (dose, schedule) pair, column (a) gives the selection percentage and column (b) gives the mean number of patients assigned to the pair. Boldface values correspond to pairs with toxicity probability between 0.20 and 0.40

Scenario	Method	Schedule	Dose (mg/m <sup>2</sup> )					
			8		16		24	
			(a)	(b)	(a)	(b)	(a)	(b)
1	MTDS	4	<b>0.02</b>	<b>3.5</b>	<b>0.16</b>	<b>10.1</b>	<b>0.44</b>	<b>13.1</b>
		3	0.01	2.6	0.06	6.4	<b>0.25</b>	<b>11.4</b>
		2	0.00	1.6	0.00	3.5	0.05	6.5
	CRM	1	0.00	1.0	0.00	0.1	0.00	0.3
		4	<b>0.47</b>	<b>30.6</b>	<b>0.31</b>	<b>17.8</b>	<b>0.19</b>	<b>10.3</b>
		3	0.00	1.6	0.00	3.5	0.05	6.5
2	MTDS	4	<b>0.17</b>	<b>8.6</b>	0.08	5.7	0.00	0.2
		3	0.10	6.7	<b>0.29</b>	<b>11.7</b>	0.01	1.3
		2	0.00	2.8	<b>0.19</b>	<b>10.6</b>	<b>0.13</b>	<b>8.7</b>
	CRM	1	0.00	1.1	0.00	0.5	<b>0.03</b>	<b>2.2</b>
		4	<b>0.66</b>	<b>41.2</b>	0.18	12.1	0.00	0.4
		3	0.00	1.6	0.00	3.5	0.05	6.5
3	MTDS	4	0.01	2.9	0.00	0.5	0.00	0.0
		3	0.06	6.1	0.01	1.6	0.00	0.0
		2	<b>0.26</b>	<b>13.7</b>	<b>0.14</b>	<b>9.9</b>	0.01	1.7
	CRM	1	0.03	3.3	<b>0.19</b>	<b>7.3</b>	<b>0.29</b>	<b>12.4</b>
		4	0.03	15.6	0.00	1.1	0.00	0.0
		3	0.00	1.6	0.00	3.5	0.05	6.5
4	MTDS	4	0.00	0.8	0.00	0.0	0.00	0.0
		3	0.00	1.7	0.00	0.2	0.00	0.0
		2	0.00	3.7	0.00	2.0	0.00	0.2
	CRM	1	0.08	11.1	0.02	5.1	0.00	3.7
		4	0.01	13.8	0.00	0.5	0.00	0.0
		3	0.00	1.6	0.00	3.5	0.05	6.5
5	MTDS	4	<b>0.19</b>	<b>8.8</b>	0.04	3.7	0.00	0.1
		3	0.09	6.5	<b>0.19</b>	<b>9.7</b>	0.00	0.7
		2	0.01	3.4	<b>0.24</b>	<b>12.3</b>	0.06	5.8
	CRM	1	0.00	1.4	<b>0.09</b>	<b>3.1</b>	0.08	4.6
		4	<b>0.72</b>	<b>43.2</b>	0.15	11.0	0.00	0.2
		3	0.00	1.6	0.00	3.5	0.05	6.5
6	MTDS	4	0.09	6.9	0.00	0.9	0.00	0.0
		3	<b>0.32</b>	<b>12.9</b>	0.03	3.2	0.00	0.2
		2	0.13	9.3	<b>0.29</b>	<b>15.0</b>	0.01	3.0
	CRM	1	0.00	1.2	0.00	1.4	<b>0.11</b>	<b>6.1</b>
		4	0.08	20.6	0.00	1.7	0.00	0.0
		3	0.00	1.6	0.00	3.5	0.05	6.5
7	MTDS	4	0.03	6.1	0.01	2.2	0.00	0.0
		3	0.00	2.7	0.09	8.3	0.00	0.4
		2	0.00	1.5	<b>0.54</b>	<b>20.9</b>	0.01	5.3
	CRM	1	0.00	1.0	0.13	3.5	0.19	8.2
		4	0.77	40.1	0.23	19.6	0.00	0.2
		3	0.00	1.6	0.00	3.5	0.05	6.5

**Table 3** Summary statistics for the MTDS and CRM designs under each scenario

	Method	Scenario						
		1	2	3	4	5	6	7
Probability of selecting an acceptable dose	MTDS	0.87	0.81	0.88	n/a	0.71	0.72	0.54
	CRM	0.97	0.66	0.00	n/a	0.72	0.00	0.00
Probability of selecting no dose	MTDS	0.00	0.00	0.01	0.90	0.00	0.00	0.00
	CRM	0.03	0.16	0.97	0.99	0.13	0.92	0.00
Mean number of patients enrolled	MTDS	60.0	60.0	59.5	28.7	60.0	60.0	60.0
	CRM	58.7	53.6	16.7	14.3	54.5	22.4	59.9
Observed incidence of toxicity	MTDS	0.22	0.29	0.34	0.54	0.31	0.31	0.33
	CRM	0.25	0.34	0.55	0.58	0.34	0.51	0.27

In scenario 3, the MTDS design identifies one of the four acceptable combinations as optimal 88% of the time, with about 43 patients assigned to one of these four combinations and 13 patients assigned

to combinations with  $F_{jk}^{true} > 0.40$ . Because all three doses are unacceptably toxic under schedule 4 in scenario 3, the CRM is unable to find an acceptable dose simply because it never examines a lower

**Table 4** Simulation results for scenario 5 under different time to toxicity distributions. For each (dose, schedule) pair, column (a) gives the selection percentage, and column (b) gives the mean number of patients assigned to the pair. Boldface values correspond to pairs with cumulative toxicity probability between 0.20 and 0.40

Time-to-event distribution	Schedule	Dose (mg/m <sup>2</sup> )					
		8		16		24	
		(a)	(b)	(a)	(b)	(a)	(b)
Exponential	4	<b>0.19</b>	<b>8.8</b>	0.04	3.7	0.00	0.1
	3	0.09	6.5	<b>0.19</b>	<b>9.7</b>	0.00	0.7
	2	0.01	3.4	<b>0.24</b>	<b>12.3</b>	0.06	5.8
	1	0.00	1.4	<b>0.09</b>	<b>3.1</b>	0.08	4.6
Weibull	4	<b>0.25</b>	<b>9.4</b>	0.03	2.0	0.00	0.0
	3	0.11	8.4	<b>0.16</b>	<b>7.5</b>	0.00	0.2
	2	0.03	4.4	<b>0.20</b>	<b>11.7</b>	0.03	4.0
	1	0.00	2.2	<b>0.12</b>	<b>4.9</b>	0.08	4.9
Lognormal	4	<b>0.18</b>	<b>9.0</b>	0.07	5.5	0.00	0.1
	3	0.07	5.7	<b>0.17</b>	<b>9.3</b>	0.00	1.2
	2	0.01	2.9	<b>0.27</b>	<b>12.2</b>	0.04	6.6
	1	0.00	1.2	<b>0.07</b>	<b>1.9</b>	0.10	4.4

schedule. In scenario 3, the CRM exposes on average nearly 17 patients to toxic combinations with 55% of them experiencing toxicity, and nearly always terminates early with all combinations deemed unacceptable. In scenario 4, where no combination is acceptable, 29 patients on average are enrolled under the MTDS design before the study terminates, in contrast to only 14 patients under the CRM. However, in the scenario where all combinations are overly toxic the MTDS design assigns a majority of patients only to combination (1, 1) and its closest neighbors, with the overall incidence of toxicities similar between the MTDS and the CRM designs.

Scenarios 5–7 illustrate the MTDS method for different distributions of acceptable (dose, schedule) pairs over the matrix of 12 pairs studied. Tables 2 and 3 show that the MTDS reliably identifies acceptable pairs in all of these scenarios. The conclusions reached from scenarios 1–4 are re-emphasized: because it does not allow schedule to vary, a conventional CRM dose-finding design is likely to assign a majority of patients to suboptimal doses and is often unable to identify an optimal (dose, schedule) pair. In contrast, the MTDS design assigns more patients to acceptable combinations and often has a much greater likelihood of selecting a combination suitable for further study.

A critical issue illustrated by the simulations is that the MTDS method is superior to the CRM, or any method that searches for an optimal dose but does not allow the schedule to vary. The point is simply that, if the optimal (dose, schedule) combination occurs at a schedule different from the fixed schedule assumed by a method that only varies dose, such a method will have probability 0 of finding the optimal combination, as was the case with CRM under scenarios 3, 6 and 7. Similarly, the MTDS method also is superior to the MTS method of Braun

*et al.* [4], which fixes dose while only varying schedule. If the fixed dose is suboptimal for all schedules, the MTS method will have probability 0 of finding the optimal combination. We ran additional simulations (not shown) under each scenario in Table 2 using an MTS design that examined all four schedules but assigned all subjects to the same dose of 24 mg/m<sup>2</sup> (final column of Table 1). In scenario 3, in which 24 mg/m<sup>2</sup> is toxic with all four schedules, the MTS design identified the slightly toxic combination (3, 1) as optimal in 41% of simulations and treated an average of 29 subjects with that combination, compared with 29% of simulations and 12 subjects with the MTDS design (Table 2). More strikingly, in scenarios 5 and 7, where the MTS design is restricted to excessively toxic combinations, this design terminated the trial 83 and 96% of the time, respectively, with the false negative conclusion that no optimal combination existed and thus the agent should not be studied in further clinical trials.

### Robustness

Table 4 gives results for the MTDS design under scenario 5 with toxicity times generated from Weibull, exponential and lognormal distributions, described earlier. The first four rows replicate the values displayed in Table 2. Table 4 indicates that the performance of the MTDS method varies very little with the time-to-event distribution, in terms of selection of acceptable (dose, schedule) pairs and numbers of patients assigned. Results for other time-to-event distributions and other scenarios, not shown, were very similar to those presented in Table 4.

To study the effects of maximum sample size, we simulated the trial using the MTDS method with  $N = 40, 60$  or  $80$ . In scenario 1, the MTDS method

identified combination (3, 4) as optimal 32, 44 and 44% of the time with  $N = 40$ , 60 and 80, respectively. In scenario 4, where no combination is safe, the trial was terminated early 80, 90, and 96% of the time. In scenario 5, the four acceptable combinations were identified as optimal in 64, 71, and 79% of the time. Thus, although the design performs best with  $N = 80$ , our selected sample size of  $N = 60$  provides very desirable operating characteristics and improves substantively upon  $N = 40$ .

## Discussion

We have proposed a new paradigm for phase I clinical trials aiming to identify a best (dose, schedule) combination. The specific model and parameterization used here were selected for tractability and robustness, although other models certainly are possible. We also examined a version of our design that does not allow 'diagonal' escalation, that is, increasing both dose and schedule simultaneously, in order to protect patient safety when escalating. However, this restriction slowed escalation so severely that far too many patients were assigned to suboptimal combinations and too few were assigned to optimal combinations. One also may impose the safety constraint that escalation from the current combination ( $j^*$ ,  $k^*$ ) cannot occur until a cohort of at least  $M$  patients have been assigned to ( $j^*$ ,  $k^*$ ), analogous to the usual approach in conventional phase I designs. However, we found that  $M = 1$  yielded a safe design with good operating characteristics.

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## Appendix

We used MCMC with Gibbs sampling for integrating posterior quantities over the parameter space. For each integral, we generated a series of random vectors of model parameters distributed proportionally to the posterior integrand (likelihood times prior), with each series initialized by using the mode. At the start of the trial, we initialized the posterior integrand mode to be the same as the prior mode. When a new patient enrolled, the mode was updated by random sampling around the previous mode. We worked in terms of the log of the model parameters in order to generate all random values from normal distributions. We used two levels of sampling around the previous mode to ensure a good approximation. The first level generates 10000 normally distributed samples using a large variance for each parameter, roughly two orders of magnitude larger than that parameter's prior variance. In the rare case that this procedure failed to find a mode, we increased the variance and the number of samples and repeated. The second level takes 5000 more samples around the best mode approximation found at the first level, using the same variance. For the Gibbs sampling, the substep of drawing from the conditional distribution uses importance sampling with a symmetric normal proposal distribution. For each parameter  $\theta_i$ ,  $i = 1, 2, \dots, 9$ , we generated  $\tilde{\theta}_i \sim N(\theta_i, s_i)$ , in which  $s_i$  is approximately the prior standard deviation. Denoting  $\tilde{\theta} = (\theta_1, \dots, \theta_i - 1, \tilde{\theta}_i, \dots, \theta_9)$ , we computed  $A = \min\{1, q(\tilde{\theta}|\text{data})/q(\theta|\text{data})\}$ , in which  $q(\cdot)$  is the posterior integrand, and accepted  $\tilde{\theta}_i$  as the new  $\theta_i$  with probability  $A$ . The MCMC convergence was monitored by comparing the Monte Carlo standard error (MCSE) to the standard deviation of the decision variables (i.e. the posterior cumulative probabilities of toxicity.) We began with 4000 samples and gradually reduced this to a minimum of 1000 samples until the MCSE was  $\leq 3\%$  of the posterior standard deviation. Using the batch-means method to estimate the MCSE (with batch size 50), we observed that 1000 random samples were enough to keep the error ratio  $< 3\%$ . We also used these samples to construct the posterior marginal distribution of each model parameter and confirm that each was a proper distribution with a unimodal shape.

## Abbreviations

AML	acute myelogenous leukemia	MCSE	Monte Carlo standard error
CRM	continual reassessment method	MDS	myelodysplastic syndrome
DNA	deoxyribonucleic acid	MTD	maximum tolerated dose
GVL	graft versus leukemia	MTDS	maximum tolerated dose and schedule
IG	inverse Gamma		
MCMC	Markov Chain Monte Carlo	MTS	maximum tolerated schedule