Supplementary Materials for "Accuracy and Safety of Novel Designs for Phase I Drug-Combination Oncology Trials"

A. Details of the designs for one maximum tolerated dose (MTD)

A1. Notations

In a drug-combination trial, J dose levels ($d_1^A < \cdots < d_K^A$) of drug A combined with K dose levels ($d_1^B < \cdots < d_K^B$) of drug B are investigated. Let (j,k) denote the dose level of a combination with dose d_j^A of drug A and dose d_k^B of drug B. Let $p_1 < \cdots < p_K$ and $q_1 < \cdots < q_J$ be the marginal toxicity probabilities of drug A and drug B, respectively. The joint toxicity probability at dose combination (j,k) is denoted by π_{jk}, and the target toxicity probability is denoted by ϕ. A common assumption imposed in existing phase I drug-combination trials is the partial ordering constraint, which says that we only know that the toxicity rates increase with the dose level of one drug when the dose level of the other drug is fixed, i.e., $\pi_{1k} < \cdots < \pi_{Jk}$ for $k = 1, \ldots, K$ and $\pi_{j1} < \cdots < \pi_{jK}$ for $j = 1, \ldots, J$.

A2. 3+3 design

The 2D 3+3 design first selects a subset of dose combinations $\{(1,1), (j,k), \ldots, (J,K)\}$ that satisfy $\pi_{11} < \pi_{jk} < \cdots < \pi_{JK}$ from the whole drug-combination space. In other words, the selected subset constitutes a one-dimensional searching line such that the toxicity rate increases monotonically with the dose level. Then the 2D 3+3 design applies the conventional 3+3 method to the selected dose combination levels.

1. The first three patients are treated at the lowest dose combination $(1,1)$.
2. Suppose that three patients have been treated at the current dose combination.
    a. If there are no patients with DLT, escalate to the next higher dose combination in the selected subset.
    b. If there is one patient with DLT, treat three more patients at the current dose combination.

c. If there is more than one patient with DLT, de-escalate to the next lower dose combination in the selected subset. If the next lower dose combination has already treated six patients, then claim it as the MTD.

3. Suppose that six patients have been treated at the current dose combination,
   a. If there are one or no patients with DLT, escalate to the next higher dose combination in the selected subset. If the number of patients treated at the next higher dose combination is not zero, then claim the current dose combination as the MTD.
   b. If there is more than one patient with DLT, de-escalate to the next lower dose combination in the selected subset. If the next lower dose combination has already treated six patients, then claim it as the MTD.

In the simulation study with fixed scenarios, the subset of selected dose combinations is provided in Figure 2 from the main manuscript; in the study with random scenarios, the subset is randomly selected for each simulated trial. To match the sample size with other designs, after the dose-escalation stage of the 3+3 design, the remaining patients will be treated at the selected MTD in a subsequent cohort expansion stage.

A3. Partial ordering continual reassessment method (POCRM)

Suppose that the toxicity order of the dose levels in the drug-combination space is completely known, then the two-dimensional searching space can be reduced on a one-dimensional searching line based on the complete ordering. As a result, the standard CRM can be applied to the reduced, one-dimensional searching line. According to the CRM, the joint toxicity probability can be modeled using the following empiric function,

$$\pi_{jk} = a_l^{exp(\beta)},$$

where l is the rank of dose combination (j, k) in the completely known ordering, β is the unknown parameter, and $\alpha_1 < \cdots < \alpha_{JK}$ is the prespecified toxicity probabilities of a set of $J \times K$ dose levels, i.e., the skeleton of the CRM.

In real applications, the true toxicity order is typically unknown. The POCRM[1] adopts the idea of Bayesian model selection and prespecifies a set of several ordering relationships, according to the

partial order information. For example, suppose M orderings are prespecified, $O_1, \ldots, O_M$, and the prior probability of ordering O_m is denoted by $\Pr(O_m), m = 1, \ldots, M$. Let $L(\beta \mid O_m, D)$ denotes the likelihood based on the order O_m and the observed data D. Then the posterior probability of order O_m is given by

$$\Pr(O_m \mid D) \propto \Pr(O_m) \int L(\beta \mid O_m, D) f(\beta) d\beta,$$

where $f(\beta)$ is the prior distribution of the unknown parameter β.

The next dose assignment of POCRM is guided by the following steps.

- Based on the accumulated data D, select the ordering O_m that has the largest posterior model probability $\Pr(O_m \mid D)$.
- The estimated toxicity probabilities $\hat{\pi}_{jk}$ are obtained based on the selected ordering O_m.
- The next cohort of patients are then allocated to the dose combination that has the estimated toxicity probability closest to the target toxicity rate.
- At the end of the trial, the MTD is selected as the suggested next dose combination.

We obtained the simulation results of the POCRM based on the R package "pocrm" available from CRAN. To implement POCRM in our simulation study, we took five orderings for the 2×3 trial:

$$O_1: 1 \to 2 \to 3 \to 4 \to 5 \to 6;$$
$$O_2: 1 \to 2 \to 4 \to 3 \to 5 \to 6;$$
$$O_3: 1 \to 2 \to 4 \to 5 \to 3 \to 6;$$
$$O_4: 1 \to 4 \to 2 \to 3 \to 5 \to 6;$$
$$O_5: 1 \to 4 \to 2 \to 5 \to 3 \to 6;$$

and used the model calibration approach[2] to specify the skeleton by setting the halfwidth at 0.05 and the prior guess of the MTD at dose 3. We took eight orderings for the 2×4 trial:

$$O_1: 1 \to 2 \to 3 \to 4 \to 5 \to 6 \to 7 \to 8;$$
$$O_2: 1 \to 3 \to 2 \to 4 \to 5 \to 6 \to 7 \to 8;$$
$$O_3: 1 \to 2 \to 3 \to 5 \to 4 \to 6 \to 7 \to 8;$$
$$O_4: 1 \to 2 \to 3 \to 4 \to 5 \to 7 \to 6 \to 8;$$
$$O_5: 1 \to 3 \to 2 \to 5 \to 4 \to 6 \to 7 \to 8;$$

$$O_6: 1 \to 3 \to 2 \to 4 \to 5 \to 7 \to 6 \to 8;$$
$$O_7: 1 \to 2 \to 3 \to 5 \to 4 \to 7 \to 6 \to 8;$$
$$O_8: 1 \to 3 \to 2 \to 5 \to 4 \to 7 \to 6 \to 8,$$

and used the model calibration approach[2] to specify the skeleton by setting the halfwidth at 0.05 and the prior guess of the MTD at dose 4; We took six orderings for the 3×5 trial:

$$O_1: 1 \to 2 \to 3 \to 4 \to 5 \to 6 \to 7 \to 8 \to 9 \to 10 \to 11 \to 12 \to 13 \to 14 \to 15;$$
$$O_2: 1 \to 2 \to 6 \to 3 \to 7 \to 11 \to 4 \to 8 \to 12 \to 5 \to 9 \to 13 \to 10 \to 14 \to 15;$$
$$O_3: 1 \to 6 \to 11 \to 2 \to 7 \to 12 \to 3 \to 8 \to 13 \to 4 \to 9 \to 14 \to 5 \to 10 \to 15;$$
$$O_4: 1 \to 6 \to 2 \to 11 \to 7 \to 3 \to 12 \to 8 \to 4 \to 13 \to 9 \to 5 \to 14 \to 10 \to 15;$$
$$O_5: 1 \to 2 \to 6 \to 11 \to 7 \to 3 \to 4 \to 8 \to 12 \to 13 \to 9 \to 5 \to 10 \to 14 \to 15;$$
$$O_6: 1 \to 6 \to 2 \to 3 \to 7 \to 11 \to 12 \to 8 \to 4 \to 5 \to 9 \to 13 \to 14 \to 10 \to 15,$$

and used the model calibration approach[2] to specify the skeleton by setting the halfwidth at 0.05 and the prior guess of the MTD at dose 8. Similarly, we took six orderings for the 4×4 trial:

$$O_1: 1 \to 2 \to 3 \to 4 \to 5 \to 6 \to 7 \to 8 \to 9 \to 10 \to 11 \to 12 \to 13 \to 14 \to 15 \to 16;$$
$$O_2: 1 \to 2 \to 5 \to 3 \to 6 \to 9 \to 4 \to 7 \to 10 \to 13 \to 8 \to 11 \to 14 \to 12 \to 15 \to 16;$$
$$O_3: 1 \to 5 \to 2 \to 3 \to 6 \to 9 \to 13 \to 10 \to 7 \to 4 \to 8 \to 11 \to 14 \to 15 \to 12 \to 16;$$
$$O_4: 1 \to 5 \to 2 \to 9 \to 6 \to 3 \to 13 \to 10 \to 7 \to 4 \to 14 \to 11 \to 8 \to 15 \to 12 \to 16;$$
$$O_5: 1 \to 5 \to 9 \to 13 \to 2 \to 6 \to 10 \to 14 \to 3 \to 7 \to 11 \to 15 \to 4 \to 8 \to 12 \to 16;$$
$$O_6: 1 \to 2 \to 5 \to 9 \to 6 \to 3 \to 4 \to 7 \to 10 \to 13 \to 14 \to 11 \to 8 \to 12 \to 15 \to 16,$$

and used the model calibration approach[2] to specify the skeleton by setting the halfwidth at 0.05 and the prior guess of the MTD at dose 10.

The reason why we used more orderings in 2×3 and 2×4 trials is all (or most) possible orderings can be enumerated in these cases where the numbers of dose levels for the combined drugs are small. Using as many as possible orderings can ensure the completeness of the parameter space. However, for 3×5 and 4×4 trials, it is infeasible to list all possible ordering. According to the guidance on POCRM, the setting with six orderings is capable of yielding good performances[3]. The discrete uniform distribution was taken as the prior order probability.

A4. Copula method

Usually, prior to the combination trial, each drug has been thoroughly studied when administered alone. This means that we have plenty of prior information on the marginal toxicity rate p_j and q_k. The copula dose-finding method adopts a copula function to model the joint toxicity rate π_{jk} by linking the marginal rates p_j and q_k. For example, by borrowing the structure of the Clayton copula, Yin and Yuan[4] proposed that π_{jk} can be modeled as

$$\pi_{jk} = 1 - \left\{\left(1 - p_j^{\alpha}\right)^{-\gamma} + \left(1 - q_k^{\beta}\right)^{-\gamma} - 1\right\}^{-1/\gamma},$$

where α, β, and γ are unknown parameters, and the drug-drug interactions are characterized by the parameter γ. The copula dose-finding method is not specific to the Clayton copula, and any copula function from the Archimedean copula family can be employed to model π_{jk}. Under the Bayesian framework, the dose escalation/de-escalation rule of the copula method is guided by the posterior probabilities $\Pr(\pi_{jk} < \phi \mid D)$ and the posterior mean estimate $\hat{\pi}_{jk}$. Suppose the current dose combination is (j, k), then the following rules apply.

- If $\Pr(\pi_{jk} < \phi \mid D) > c_e$, then assign the next cohort of patients to the adjacent dose combination whose estimated toxicity probability is higher than $\hat{\pi}_{jk}$ and closest to the target toxicity rate ϕ.
- If $\Pr(\pi_{jk} > \phi \mid D) > c_d$, then assign the next cohort of patients to the adjacent dose combination whose estimated toxicity probability is lower than $\hat{\pi}_{jk}$ and closest to the target toxicity rate ϕ.
- Otherwise, treat the next cohort of patients at the current dose combination.

Here, c_e and c_d are prespecified probability cutoffs. At the end of the trial, the MTD is selected as the dose combination (j, k) that has the estimated toxicity rate $\hat{\pi}_{jk}$ closest to the target toxicity rate ϕ.

In the simulation study, we consider $c_e = 0.8$ and $c_d = 0.45$. The prior distributions for α, β, and γ are specified as follows: $\alpha \sim Gamma(1.2,0.6)$, $\beta \sim Gamma(1.2,0.6)$, and $\gamma \sim Gamma(0.1,0.1)$. In 2×3 drug-combination trials, we took $(p_1, p_2) = (0.15, 0.3)$ and $(q_1, q_2, q_3) = (0.10, 0.20, 0.30)$. In 2×4 drug-combination studies, we choose $(p_1, p_2) = (0.15,0.3)$ and $(q_1, \ldots, q_4) = (0.08,0.15,0.23,0.30)$. In 3×5 combination studies, we choose

$(p_1, p_2, p_3) = (0.10, 0.20, 0.30)$, and $(q_1, \dots, q_5) = (0.06,0.12,0.18,0.24,0.30)$. In 4×4 drug-combination studies, we choose $(p_1, \dots, p_4) = (q_1, \dots, q_4) = (0.08,0.15,0.23,0.30)$.

A5. Bayesian logistic regression method (BLRM)

The BLRM[5] first quantifies the marginal toxicity rates for each drug using the logistic regression model

$$log\left(odds(p_j)\right) = log\,\alpha_1 + \beta_1\, log\left(d_j^A/\tilde{d}^A\right),$$
$$log\left(odds(q_k)\right) = log\,\alpha_2 + \beta_2\, log\left(d_k^B/\tilde{d}^B\right),$$

where $\tilde{d}^A$ and $\tilde{d}^B$ are reference doses for drugs A and B, respectively. When there is no interaction between the two drugs, the toxicity rate of the combined dose (j, k) is given by

$$\pi_{jk}^0 = p_j + q_j - p_j q_k.$$

By adding interaction, the joint toxicity probability can be modeled as

$$odds(\pi_{jk}) = odds(\pi_{jk}^0)\, exp(\frac{\eta d_j^A d_k^B}{\tilde{d}^A \tilde{d}^B}).$$

As a result, the joint toxicity rate model of 2D BLRM has five unknown parameters $(\alpha_1, \beta_1, \alpha_2, \beta_2, \eta)$, where the parameter η characterizes the drug-drug interactive effects.

The BLRM categorizes the probability of DLT into three intervals. For example, if the target toxicity rate $\phi = 0.25$, according to Neuenschwander et al.,[5] the three intervals can be defined as

- Underdosing interval: $\pi_{jk} \in (0,0.16)$;
- Targeted dosing interval: $\pi_{jk} \in (0.16,0.33)$;
- Overdosing interval: $\pi_{jk} \in (0.33,1)$.

For the next cohort of patients, BLRM selects the adjacent dose combination that has the highest posterior probability of target dosing, i.e., $\Pr(\pi_{jk} \in (0.16,0.33) \mid D)$ as well as has the posterior probability of overdosing less than 25%.

The trial based on the BLRM will be terminated and selects the dose combination (j,k) as the MTD if one of the following conditions is satisfied:

(a) At least 15 patients have been enrolled;

(b) The posterior probability of target dosing at (j,k) exceeds 50%, i.e., $\Pr(\pi_{jk} \in (0.16,0.33) \mid D) \geq 0.5$; or at least 6 patients have been treated at dose combination (j,k).

If the maximum sample size is exhausted while neither of the above conditions is met, the MTD is selected as the suggested next dose combination.

Following the original article of the BLRM,[5] we assume independent normal priors, $N(logit(0.1), 2.5^2)$, for $\log \alpha_1$ and $\log \alpha_2$; independent standard normal priors, $N(0,1)$, for $\log \beta_1$ and $\log \beta_2$; and a normal prior, $N(0,1^2)$, for η. For 2×4 drug-combination studies, we take $(d_1^A, d_2^A) = (0.5,1)$, $(d_1^B, \ldots, d_4^B) = (0.25,0.5,0.75,1)$, $\tilde{d}^A = 1$, and $\tilde{d}^B = 1$. For 3×5 combination studies, we take $(d_1^A, d_2^A, d_3^A) = (0.33, 0.67, 1)$, $(d_1^B, \ldots, d_5^B) = (0.125,0.25,0.5,0.75,1)$, and $\tilde{d}^A = \tilde{d}^B = 1$. For 4×4 drug-combination studies, we take $(d_1^A, d_2^A, d_3^A, d_4^A) = (d_1^B, d_2^B, d_3^B, d_4^B) = (0.25,0.5,0.75,1)$, and $\tilde{d}^A = \tilde{d}^B = 1$.

To avoid confounding issues due to early stopping and ensure a fair comparison with other designs, we do not include the aforementioned stopping rule of BLRM in the main study. Instead, we conduct an additional study of the BLRM and make comparisons with other designs using similar stopping rules. Details of this additional study can be found in Section E of Supplementary Materials.

A6. BOIN combination design

The dose assignment rules of the BOIN combination design are guided by comparing the observed toxicity rate $\hat{\pi}_{jk} = y_{jk}/n_{jk}$ with some prespecified lower and upper cutoff values, denoted by λ_e and λ_u. Liu and Yuan[6] optimized λ_e and λ_d by minimizing the probability of incorrect assignments,

$$\lambda_e = log\left(\frac{1-\phi_1}{1-\phi}\right) / log\left(\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right), \lambda_d = log\left(\frac{1-\phi}{1-\phi_2}\right) / log\left(\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right),$$

where ϕ_1 denotes a prespecified DLT rate that is regarded as subtherapeutic and ϕ_2 denotes a DLT rate that is considered too toxic. Suppose the current dose level is (j,k), define an admissible dose

escalation set as $A_E = \{(j+1,k),(j,k+1)\}$ and an admissible dose de-escalation set as $A_D = \{(j-1,k),(j,k-1)\}$. The BOIN combination design treats the patients according to the following rules[7]:

- If $\hat{\pi}_{jk} \leq \lambda_e$, then escalate to the dose combination in A_E that has the maximum value of $\Pr(\pi_{j'k'} \in (\lambda_e, \lambda_d) \mid D_{j'k'})$.
- If $\hat{\pi}_{jk} \geq \lambda_u$, then de-escalate to the dose combination in A_D that has the maximum value of $\Pr(\pi_{j'k'} \in (\lambda_e, \lambda_d) \mid D_{j'k'})$.
- Otherwise, if $\lambda_e < \hat{\pi}_{jk} < \lambda_u$, stay at the current dose level (j,k).

Here $D_{jk} = (y_{jk}, n_{jk})$ denotes the observed data at dose combination (j,k). At the end of the trial, the bivariate isotonic regression procedure is applied to the observed toxicity rates $\{\hat{\pi}_{jk}\}$ to obtain the isotonic estimates $\{\tilde{\pi}_{jk}\}$. The MTD is selected as the dose combination that has been tested as well as has $\tilde{\pi}_{jk}$ closest to the target toxicity rate ϕ. In the simulation study, we take the default values of ϕ_1 and ϕ_2, i.e., $\phi_1 = 0.6\phi$ and $\phi_2 = 1.4\phi$.

The BOIN combination design only uses the local data collected at the current dose combination, and it does not look "ahead" when making dose escalation decisions. To prevent escalating to overly toxic dose levels, a dose-elimination rule is imposed: if the current dose combination (j,k) is too toxic, as noted by $\Pr(\pi_{jk} > \phi \mid D_{jk}) > \eta$ with η being a cutoff probability, then the current dose combination and its higher combinations $\{(j',k'): j' \geq j, k' \geq k\}$ are eliminated from the trial. In the simulation study, a uniform $Unif(0,1)$ prior distribution is assigned to π_{jk} and η is chosen to be 0.95.

A7. Additional rules

Start-up rule

For model-based methods including POCRM, Copula, and BLRM, a start-up phase is needed to prevent aggressive dose escalation at the beginning of the trial when the data are too sparse. To make the methods comparable, we initiate the same start-up rule for all the model-based methods. Specifically, the first cohort of patients are treated at the lowest dose combination $(1,1)$. If no DLT

is observed, then we randomly increase one dose level of drug A or one dose level of drug B, while fixing the dose level of the other drug for the next cohorts. As long as one DLT is observed, the start-up phase is terminated, and the trial is kicked into the main phase.

Early stopping rule

We impose an early stopping rule for all considered designs for fair comparisons: if the lowest dose combination is too toxic, as noted by $\Pr(\pi_{11} > \phi \mid D_{11}) > \eta$, then the trial is early terminated for safety. The posterior probability is modeled by the Beta-Binomial model and calculated based on the local data of the lowest dose combination only. Using such an approach can avoid an excessively high/low incorrect early termination probability under model misspecification. In the simulation study, a uniform $\text{Unif}(0,1)$ prior distribution is assigned to π_{11} and η is chosen to be 0.95.

B. Details of the designs for multiple MTDs

B1. PIPE design

The dose escalation of the product of independent beta probabilities escalation (PIPE)[8] is guided by finding the most likely MTD contour, which is a contour partitioning the dose combination space into the regions with the target toxicity rate above ϕ and less than or equal to ϕ, respecitvley. We impose a toxicity monotonicity constraint, such that the MTD contour does not violate the assumption that the toxicity probability increases as the dose increases.

Given n_{jk} patients at the dose combination (j,k), the number of DLT(s) y_{jk} follows a binomial distribution $Bin(n_{jk}, \pi_{jk})$, where π_{jk} is the probability of DLT at the dose combination (j,k). Assume an independent beta prior $Beta(a,b)$ for π_{jk}. Then the posterior probability of DLT $\pi_{jk}|D_{jk}$ is also a beta distribution $Beta(y_{jk}+a, n_{jk}-y_{jk}+b)$.

Denote the MTD contour as a binary matrix where 1 represents the toxicity risk $> \phi$ and 0 represents the toxicity risk $\leq \phi$. Then the posterior probability that an MTD contour binary matrix C_s is the true MTD contour MTD_θ is as follows:

$$P\left(MTC_{\phi} = C_s \middle| Y\right) \propto \prod_{j,k}\left\{1 - p_{jk}\left(\phi \middle| D_{jk}\right)\right\}^{C_s[j,k]} p_{jk}\left(\phi \middle| D_{jk}\right)^{1-C_s[j,k]},$$

where $p_{jk}(\phi|Y)$ is the posterior probability that the DLT rate is less than or equal to ϕ, i.e., $p_{jk}\left(\phi \middle| D_{jk}\right) = P\left(\pi_{jk} \leq \phi \middle| D_{jk}\right)$, in which $P(.)$ is the cumulative distribution function of $\pi_{jk}|D_{jk}$, and $C_s[j,k]$ is the (j,k)th element of the binary matrix C_s.

For each monotonic MTD contour indexed by the matrix C_s, its posterior probability of being the true contour MTD_{ϕ} , $P\left(MTC_{\phi} = C_s \middle| Y\right)$, is computed, and the contour with the largest $P\left(MTC_{\phi} = C_s \middle| Y\right)$ is selected as the most likely MTD contour and denoted as C^*. The next cohort is assigned to the least experimented dose among the admissible doses, which are the dose combinations that are adjacent (i.e., differ by one dose level of only one drug) to the most likely MTD contour C^*. After each cohort of patients has been recruited, the most likely MTD contour C^* is estimated (updated). The MTDs are selected as the already tested lower dose combinations that are closest to C^* and that meet the safety constraint.

The simulation results of PIPE were obtained based on the R package "pipe.design" available from CRAN. The prior median probability for each dose combination was set to be equal to the target toxicity rate ϕ, and the prior sample size was chosen to be $1/JK$. According to the reference manual, we took strategy="ss", constraint="neighbouring", epsilon=0.8, admis="closest", and alternate=FALSE as the specification for the other design parameters.

B2. Waterfall design

Built upon the single-agent BOIN design, the waterfall design uses a divide-and-conquer strategy to find multiple MTDs. To illustrate the general dose-finding rule of the waterfall design, we consider a 3× 4 drug-combination trial as an example. As illustrated in Figure S4, the waterfall design partitions the $J \times K$ dose-combination matrix into J subtrials (or blocks), within which the toxicity rates of the doses are fully ordered. As a result, the single-agent BOIN design can be applied to each subtrial for finding a candidate MTD. These subtrials are conducted sequentially from the top of the matrix to the bottom, which is why we refer to the design as the waterfall design.

As shown in panel (a) of Figure S4, the waterfall design conducts the first subtrial with the starting dose$(1,1)$ using the BOIN design. After the first subtrial identified $(3,2)$as the candidate MTD, we then conduct the second subtrial with the starting dose $(2,3)$(see panel (b)). After the second subtrial identified $(2,3)$ as the candidate MTD, we conduct the third subtrial with the starting dose $(1,4)$ (see panel (c)). After all subtrials complete, we select the MTD contour based on the data from all subtrials using a statistical method known as matrix isotonic regression, as shown in panel (d). Using the results of each subtrial to inform the design (e.g., the dose range and the starting dose) of subsequent subtrials is a key feature of the waterfall design. Such information borrowing allows the design to explore the two-dimensional dose space efficiently using limited sample size, and decreases the chance of overdosing or underdosing patients.

The waterfall design requires the users to specify a stopping rule for the subtrials. As a rule of thumb, Zhang and Yuan[9] recommend the jth subtrial, $j = 1, \dots, J$, terminates, if the number of patients allocated to this subtrial reaches $N_j^{max} = 4 \times$ the number of doses in the jth subtrial. This means that given a $J \times K$ dose combination, the maximum total sample size for the trial is $4 \times J \times K$.

To simulate the waterfall design, we implement the "get.oc.comb" function in the R package "BOIN" available from CRAN. For a 2×4 combination trial with 27 patients, we allocate 18 patients to subtrial 1, and the remaining 9 patients to subtrial 2; For a 2×4 combination trial with 36 patients, we allocate 24 patients to subtrial 1, and the remaining 12 patients to subtrial 2; For a 3×5 combination trial with 48 patients, we allocate 24 patients to subtrial 1, and allocate 12 patients to each of the remaining two subtrials; For a 4×4 combination trial with 48, we allocate 21 patients to subtrial 1, and allocate 9 patients to each of the remaining three subtrials. Default values are used for the other design parameters of the waterfall design.

C. A random scenario generator

Let ϕ denote the target toxicity rate, and $\epsilon > 0$ be a small positive number that defines the indifference interval of the target, i.e., any dose with a DLT rate inside $(\phi - \epsilon, \phi + \epsilon)$ can be treated as an MTD. Given a $J \times K$ drug-combination space and n_m, the number of MTDs that exist in the dose-combination space, and p_u, the upper limit of the toxicity probability, and let (j_i, k_i)

denote the dose combination of the ith MTD, we generate two-dimensional dose-toxicity scenarios via the following steps:

1. Determine the locations of the n_m MTDs in the $J \times K$ space. For the ith MTD, $i = 1, \dots, n_m$,

   a. Randomly sample j_i from the set $\{j_{i-1} + 1, \dots, J - n_m + 1\}$, where $j_0 = 0$.

   b. Randomly sample k_i from the set $\{n_m - i + 1, n_m - i + 2, \dots, k_{i-1} - 1\}$, where $k_0 = K + 1$.

2. Generate a random variable u from Unif(0,1).

3. If $u < 0.5$, then the dose-toxicity space is generated by row as follows:

   a. Initiate $m_0 = 0$ and $m_1 = min\{k_i\}$. For the jth row, starting from the highest row J to the lowest row 1, i.e., $j = J, \dots, 1$.

   b. If the jth row does not contain the MTD, then let $m_2 = m_1 - m_0 - 1$. Generate m_0 samples from Unif$(0, \phi - \epsilon)$, m_2 samples from $0.5\text{Unif}(0, \phi - \epsilon) + 0.5\text{Unif}(\phi + \epsilon, p_u)$, and $K - m_1 + 1$ samples from Unif$(\phi + \epsilon, p_u)$. Then sort these samples.

   c. If the jth row contains the MTD and supposing that the MTD is dose combination (j, k), then generate $k - 1$ samples from Unif$(0, \phi - \epsilon)$, one sample from Unif$(\phi - \epsilon, \phi + \epsilon)$, and $K - k$ samples from Unif$(\phi + \epsilon, p_u)$. Then sort these samples. In the meantime, update $m_0 = k$ and m_1 to be the lowest dose level of drug B in the remaining MTD set. If there is no MTD remaining, $m_1 = K + 1$.

   d. In the end, sort the column vectors to satisfy the partial ordering.

4. If $u \geq 0.5$, the dose-toxicity space is symmetrically generated by column, and thus is omitted.

In the simulation study, we fix $\epsilon = 0.05$ and $p_u = 0.75$, which can generate various reasonable dose-toxicity spaces. We have provided the R code to generate random drug-combination scenarios in Table S3.

D. Simulation results

The results of all designs were computed using R. In particular, the POCRM, BOIN, PIPE, and waterfall designs were simulated based on their respective R packages (as listed in Table 1), which are available from the R CRAN network. The BLRM and Copula designs involve Bayesian posterior samplings, which were conducted using the JAGS software through the "R2jags" package available from CRAN.

The simulation results using random scenarios, stratified by the number of MTDs presenting in the dose space, are reported in Figures S5-S6 (for designs aimed at finding one MTD) and Figures S7-S8 (for designs aimed at findings multiple MTDs), respectively. It shows that when the number of MTDs presenting in the dose space is one or two, the BOIN design on average has a good and robust selection percentage of the MTD, and the BLRM design generally is safer compared to other designs. Among designs for finding multiple MTDs, the Waterfall design's performance on average is better than PIPE, regardless of how many MTDs exist in the dose space.

E. Additional study

We conducted additional simulation studies, for the designs aimed at one MTD, by including a stopping rule. Suppose the current dose combination is (j,k), we implemented the following stopping rules for the BLRM design:

(a) At least 15 patients have been enrolled;
(b) The posterior probability of target dosing at (j,k) exceeds 50%, i.e., $\Pr(\pi_{jk} \in (0.16,0.33) \mid D) \geq 0.5$; or at least 6 patients have been treated at dose combination (j,k).

For the other designs, we adopted the following stopping criteria:

(a) At least 15 patients have been enrolled;
(b) The posterior probability of target dosing at (j,k) exceeds 50%, i.e., $\Pr(\pi_{jk} \in (0.16,0.33) \mid D) \geq 0.5$; or at least 6 patients have been treated at dose combination (j,k).

In this study, we only considered the 2×4 combination trial and took the maximum sample size of 36. According to Figure S9 of Supplementary Materials, the designs except Copula generally yield similar average sample sizes. In terms of accuracy, BOIN achieves the highest correct selection percentage with comparably small sample size. The trial efficiency index, defined as the

ratio of the correct MTD selection percentage divided by the average sample size, shows that both the BLRM and BOIN are more efficient than the other designs in MTD identification.

F. Matching prior distributions

To ensure fair comparisons, it is desirable to make sure that the prior distributions of the model-based designs (including POCRM, Copula and BLRM) are comparable with each other. We do so by matching approximately the prior distributions of the joint toxicity probability of each dose combination among the three designs. However, because different parametric models of different designs have different numbers of parameters, equivalently different degrees of freedom, it is impossible to obtain a perfect match for all dose combinations, especially for higher-dimensional dose combination spaces. The final prior distributions used in this simulation study were carefully selected such that 1) the prior distributions of the joint toxicity probabilities of the majority dose combinations are comparable between the three model-based designs, and 2) each design on average has desirable or best performance among the prespecified set of prior distributions. For example, Figure S12 displays prior density distributions of the joint toxicity probabilities in the 2×3 combination trial for the POCRM, Copula and BLRM methods. Since there are only 6 dose combinations under consideration, it is easier to obtain a good match for the 6 combinations. In contrast, Figure S13 shows the boxplots of the prior joint toxicity probabilities in the 4×4 combination trial for the three methods. Since POCRM only has two degrees of freedom, it is less flexible in controlling the prior joint toxicity probabilities.

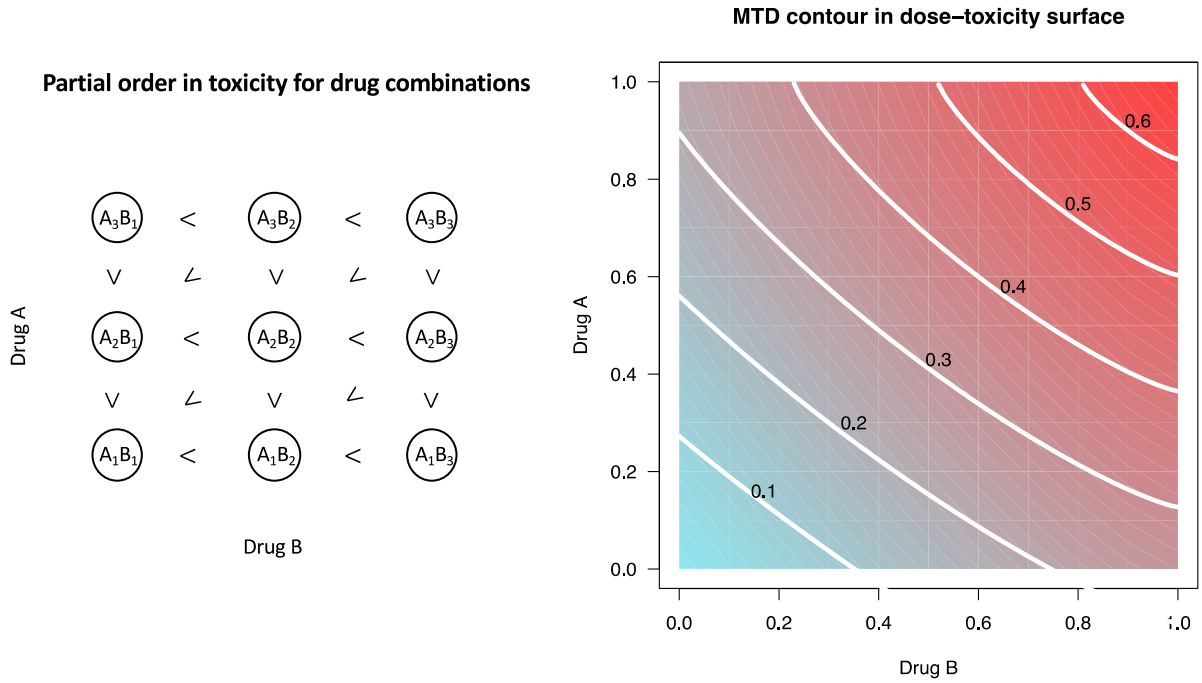


Figure S1. Challenges in drug-combination dose-finding trials. In the left panel, partial order in toxicity is present, where $A_1B_1 < A_1B_2$ indicates that the toxicity probability of combination A_1B_2 is greater than that of A_1B_1. In the drug-combination trial, the toxicity order among all dose combinations is not fully known. In the right panel, MTD contour is present in the dose--toxicity surface.

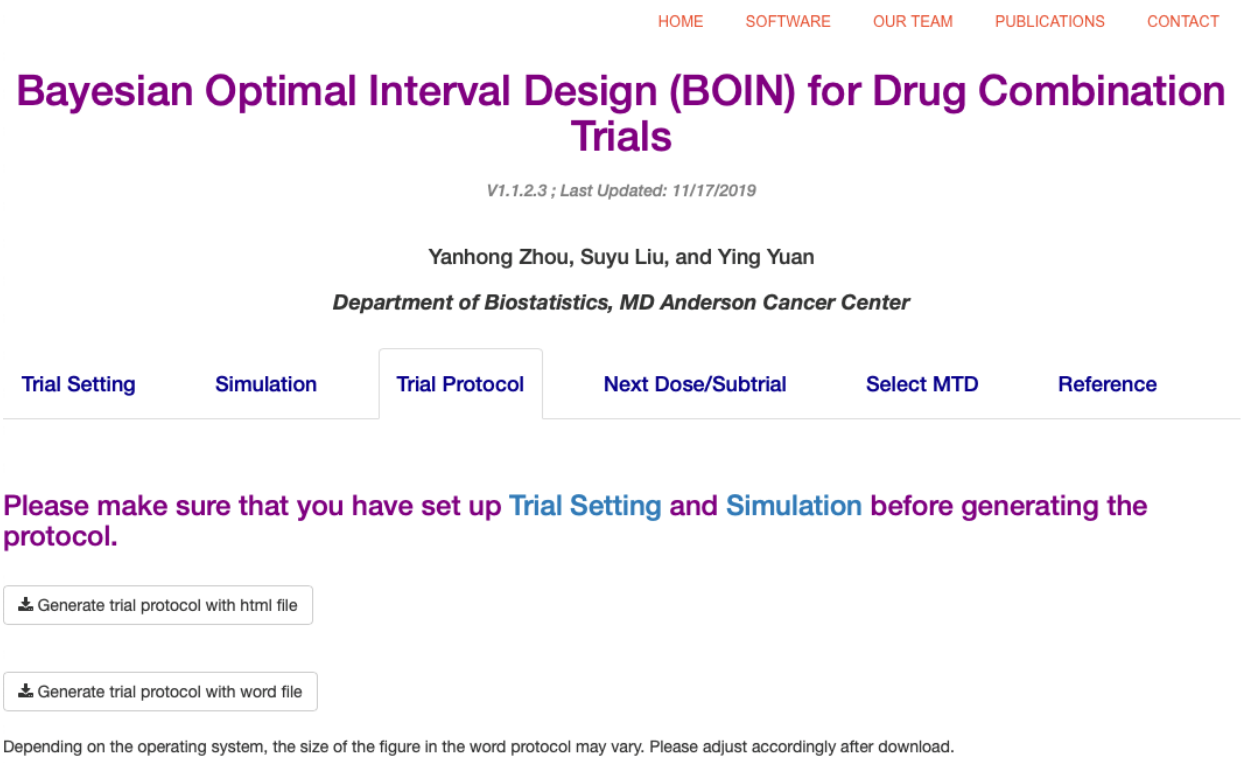


Figure S2. The "Trial Protocol" tab included in the BOIN combination design web app, freely available from https://trialdesign.org, to generate the trial protocol template.

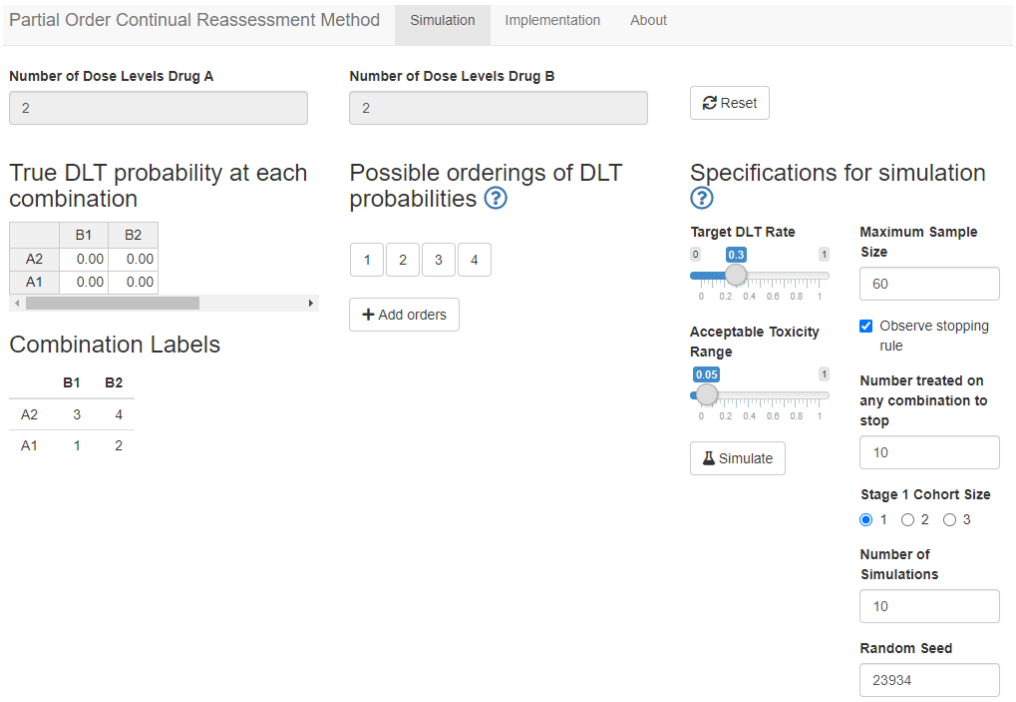


Figure S3. The interface window of the POCRM web app, freely available from http://uvatrapps.uvadcos.io/pocrm/.

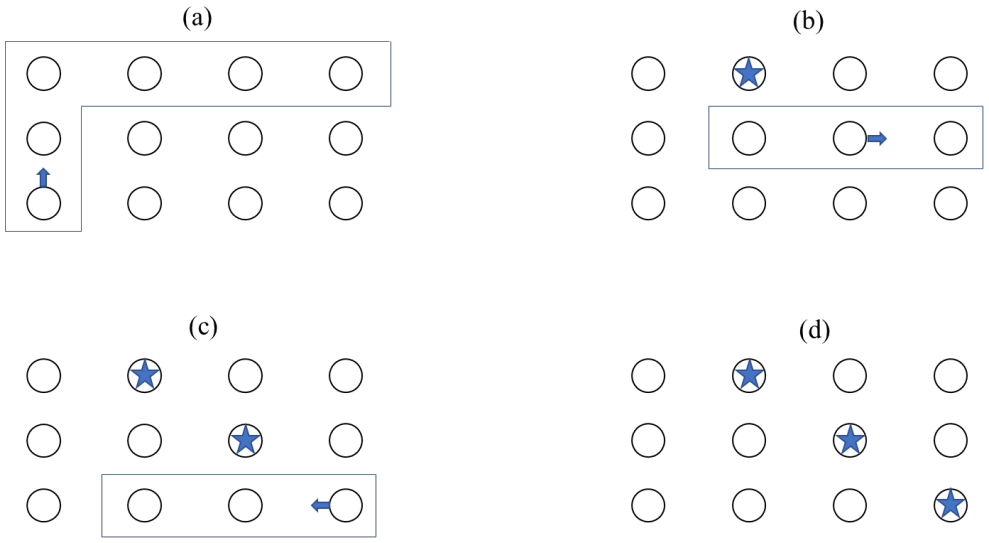


Figure S4. Illustration of the waterfall design for a 3×4 combination trial. The doses in the rectangle form a subtrial, and the star denotes the candidate MTD.

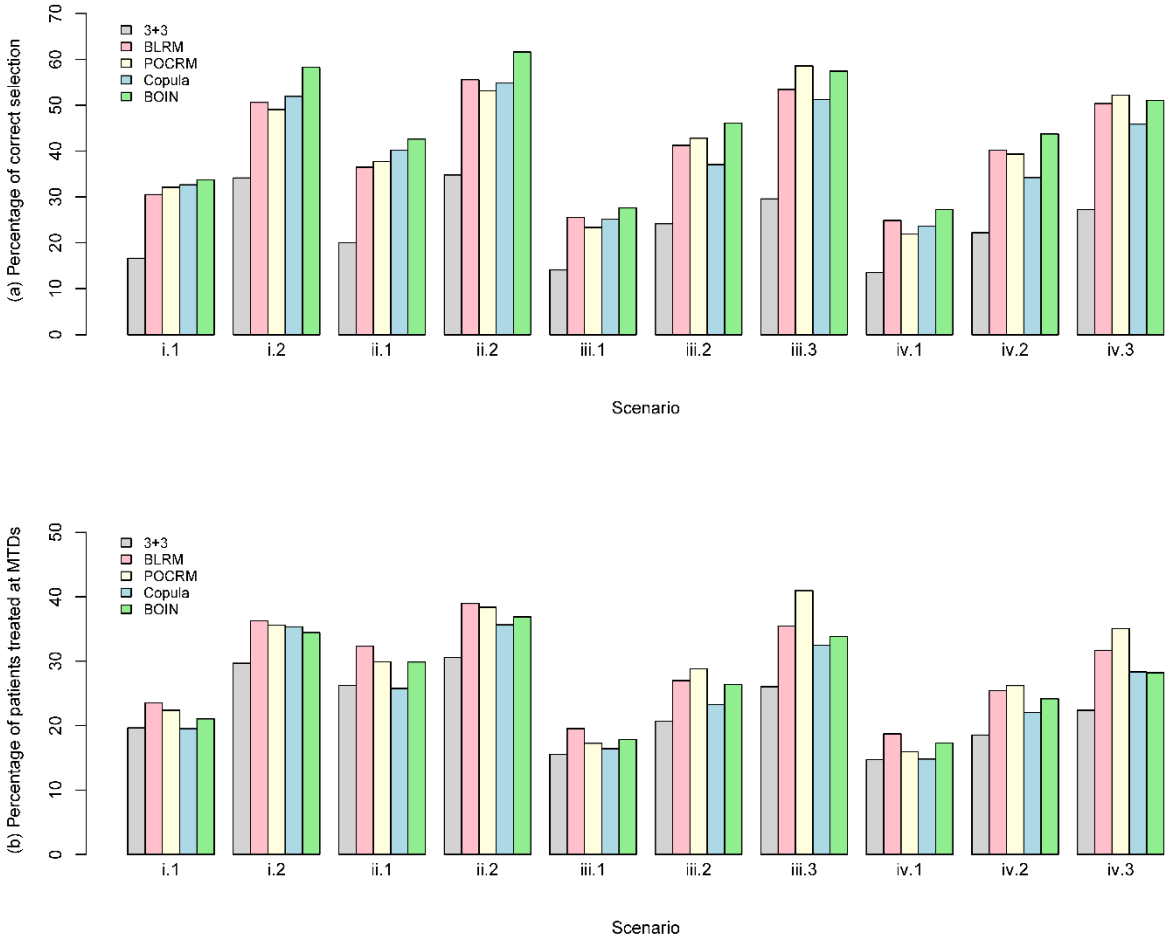
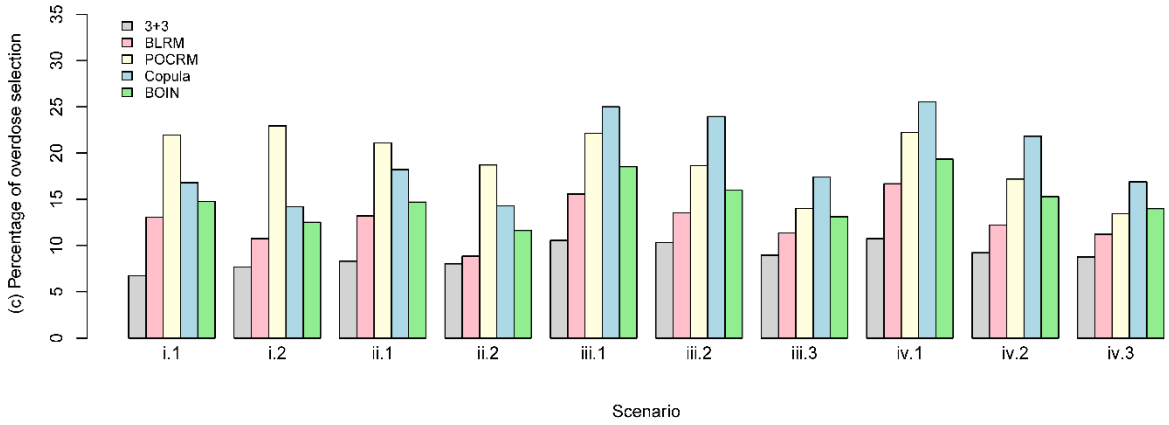


Figure S5. Average percentage of correct selection (panel (a)) and average percentage of patients treated at MTDs (panel (b)) based on 3000 random scenarios, stratified by number of MTDs presenting in the dose space, for each of the 3+3, BLRM, POCRM, Copula, and BOIN designs. Scenario "a.x" indicates that "a" = (i) 2 × 4 dose space with 27 patients; (ii) 2 × 4 dose space with 36 patients; (iii) 3 × 5 dose space with 48 patients; and (iv) 4 × 4 dose space with 48 patients. The number "x" indicates the number of MTDs presenting in the dose space.



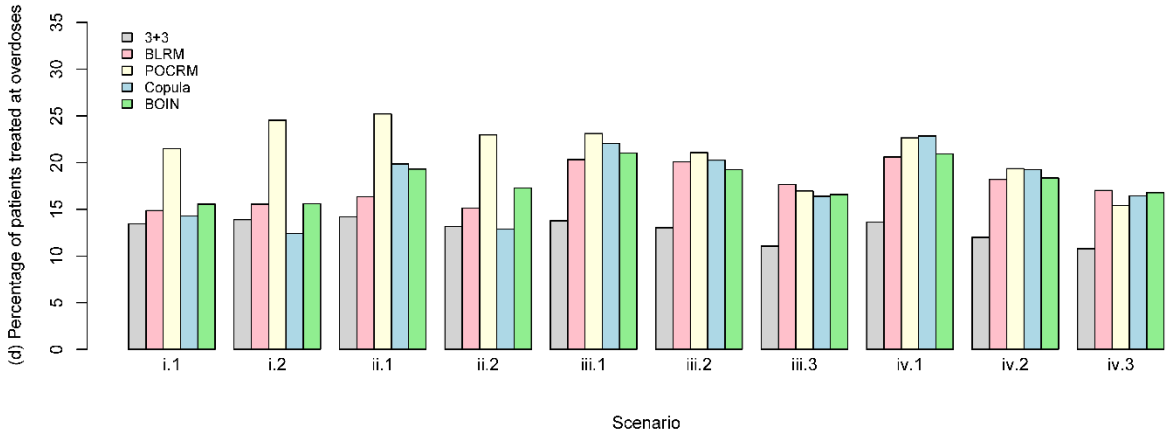


Figure S6. Average percentage of overdose selection (panel (a)) and average percentage of patients treated at overdoses (panel (b)) based on 3000 random scenarios, stratified by number of MTDs presenting in the dose space, for each of the 3+3, BLRM, POCRM, Copula, and BOIN designs. Scenario "a.x" indicates that "a" = (i) 2 × 4 dose space with 27 patients; (ii) 2 × 4 dose space with 36 patients; (iii) 3 × 5 dose space with 48 patients; and (iv) 4 × 4 dose space with 48 patients. The number "x" indicates the number of MTDs presenting in the dose space. The overdoses were defined as the dose combinations with DLT rates greater than 0.33.

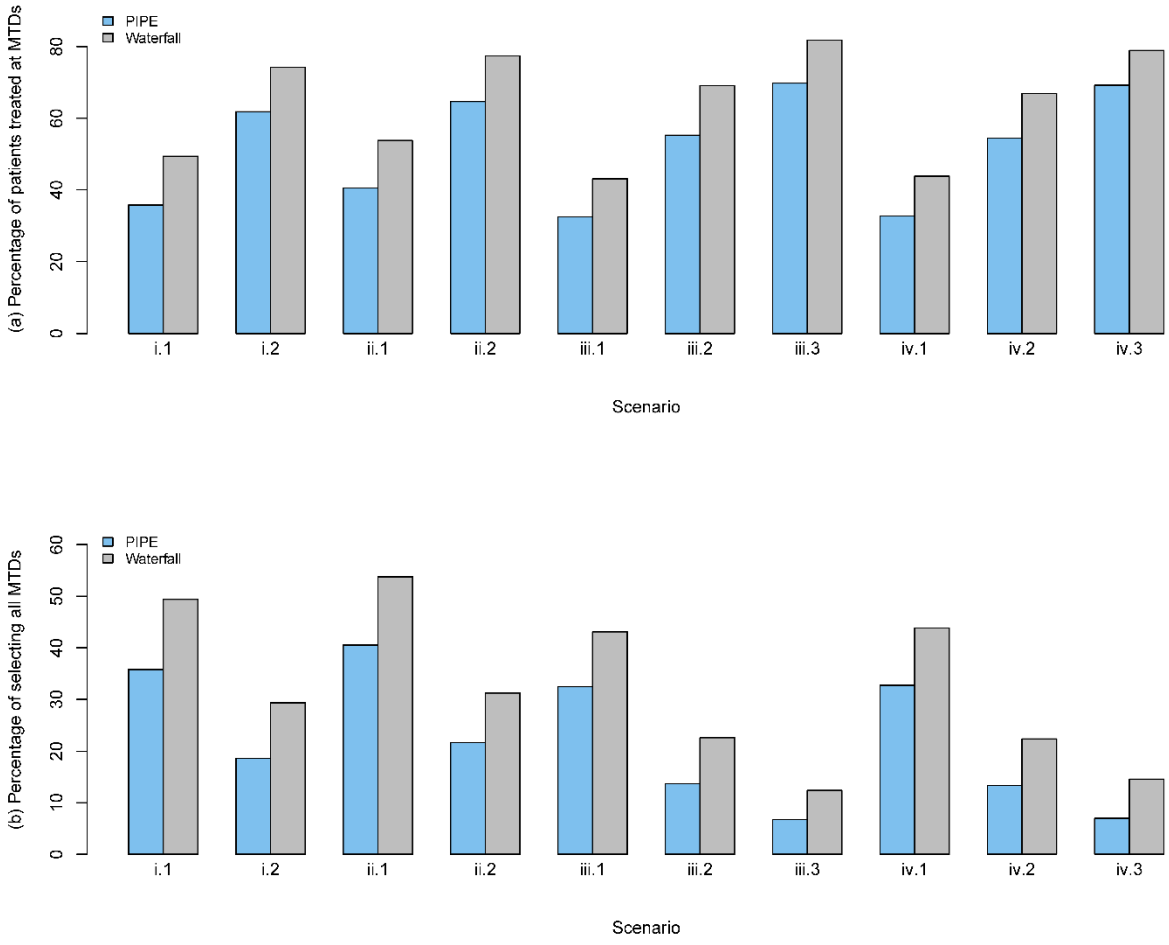


Figure S7. Average percentage of patients treated at MTDs (panel (a)) and percentage of selecting all MTDs (panel (b)) based on 3000 random scenarios, stratified by number of MTDs presenting in the dose space, for each of the PIPE and Waterfall designs. Scenario "a.x" indicates that "a" = (i) 2 × 4 dose space with 27 patients; (ii) 2 × 4 dose space with 36 patients; (iii) 3 × 5 dose space with 48 patients; and (iv) 4 × 4 dose space with 48 patients. The number "x" indicates the number of MTDs presenting in the dose space.

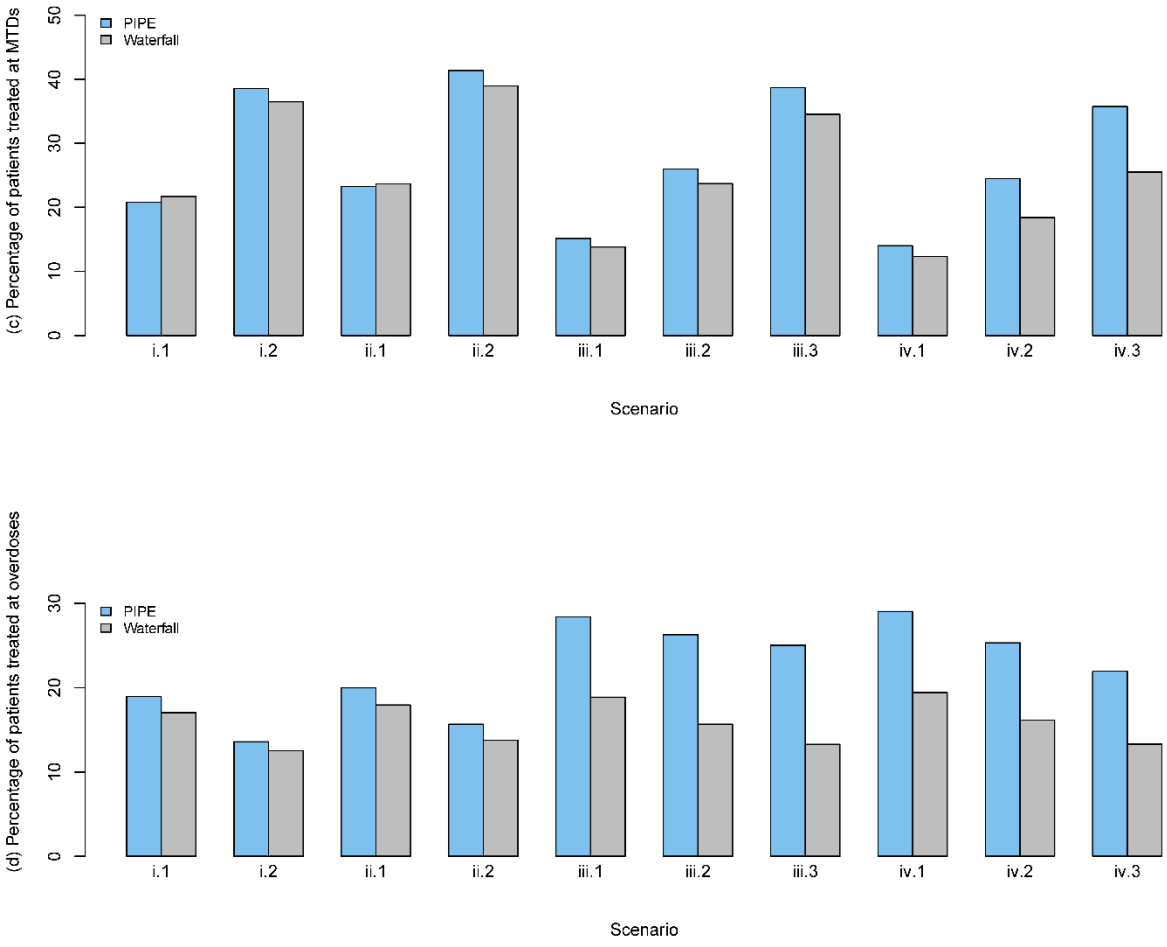


Figure S8. Average percentage of overdose selection (panel (c)) and average percentage of patients treated at overdoses (panel (d)) based on 3000 random scenarios, stratified by number of MTDs presenting in the dose space, for each of the PIPE and Waterfall designs. Scenario "a.x" indicates that "a" = (i) 2 × 4 dose space with 27 patients; (ii) 2 × 4 dose space with 36 patients; (iii) 3 × 5 dose space with 48 patients; and (iv) 4 × 4 dose space with 48 patients. The number "x" indicates the number of MTDs presenting in the dose space. The overdoses were defined as the dose combinations with DLT rates greater than 0.33.

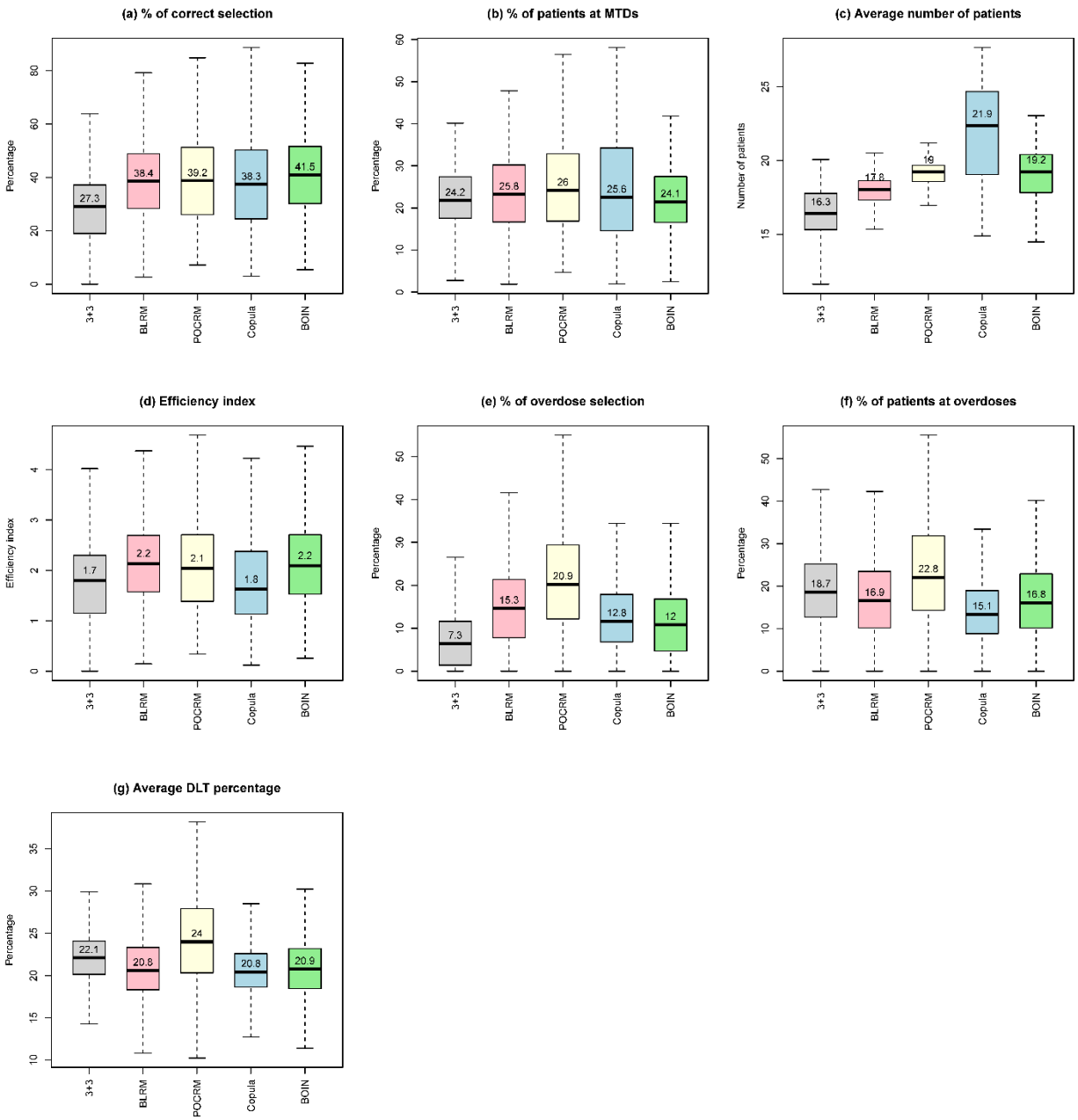


Figure S9. Simulation results of designs for finding one MTD, based on 3000 random scenarios of the 2 × 4 combination trial with a maximum of 36 patients with the stopping rule described in Section E included. The overdoses were defined as the dose combinations with DLT rates greater than 0.33. The trial efficiency index was defined as the percentage of correct MTD selection divided by the average sample size.

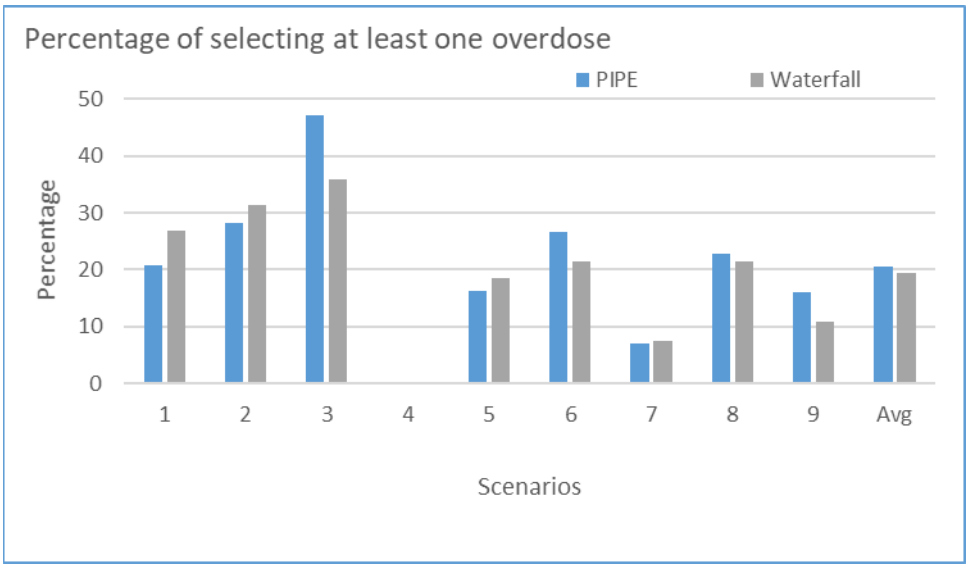


Figure S10. Average percentage of trials selecting at least one dose that is overly toxic as the MTD under 9 fixed scenarios for each combination design for finding multiple MTDs, including the product of independent beta probabilities escalation (PIPE) design and the waterfall design.

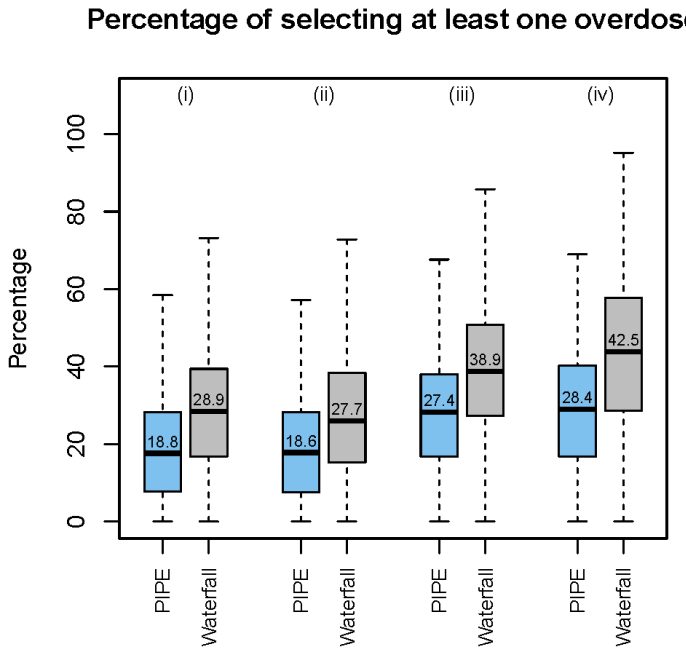


Figure S11. Average percentage of trials selecting at least one dose that is overly toxic as the MTD under 3000 random scenarios for each combination design for finding multiple MTDs, including the product of independent beta probabilities escalation (PIPE) design and the waterfall design. (i) 2×4 combination trial with 27 patients; (ii) 2×4 combination trial with 36 patients; (iii) 3×5 combination trial with 48 patients; and (iv) 4×4 combination trial with 48 patients.

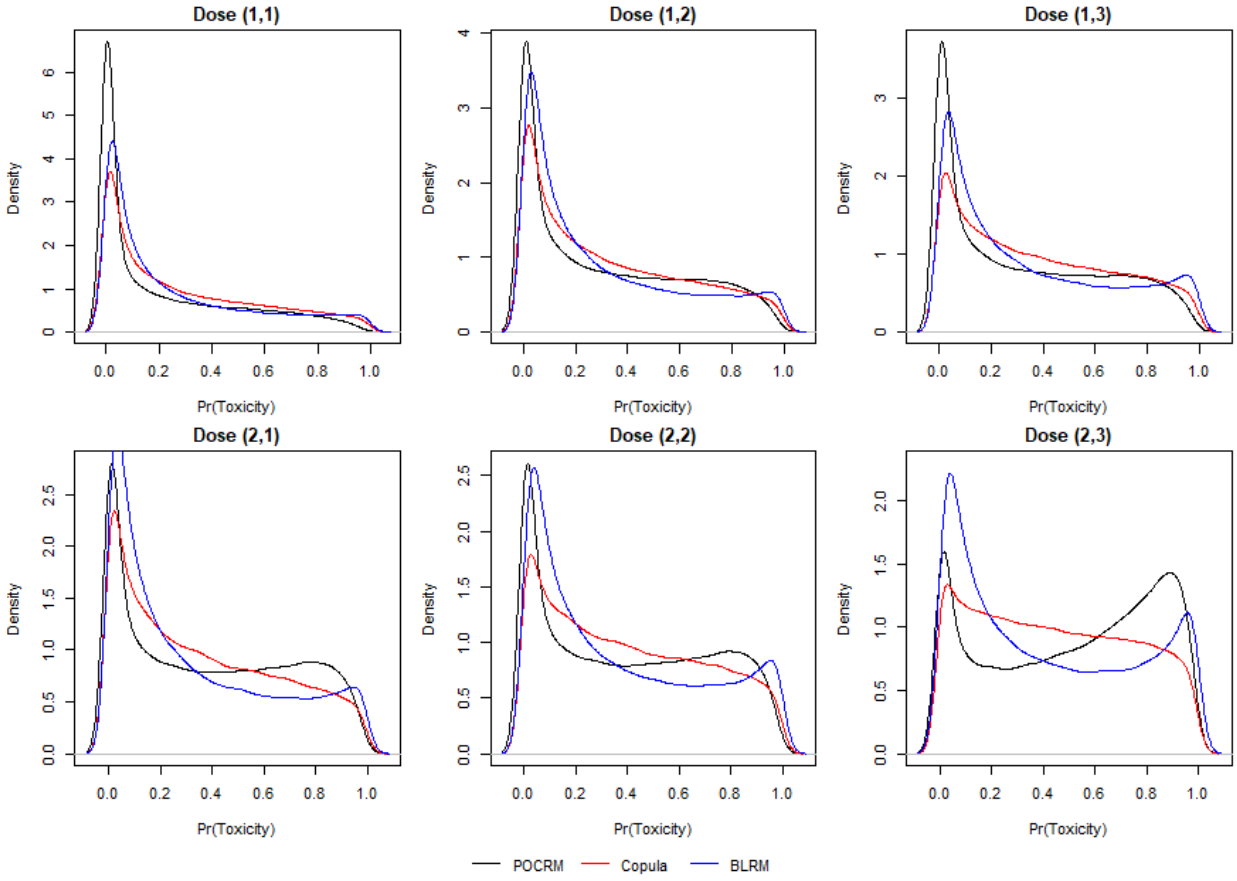


Figure S12. Prior density distributions of the joint toxicity probabilities in the 2×3 combination trial for the POCRM, Copula, and BLRM methods.

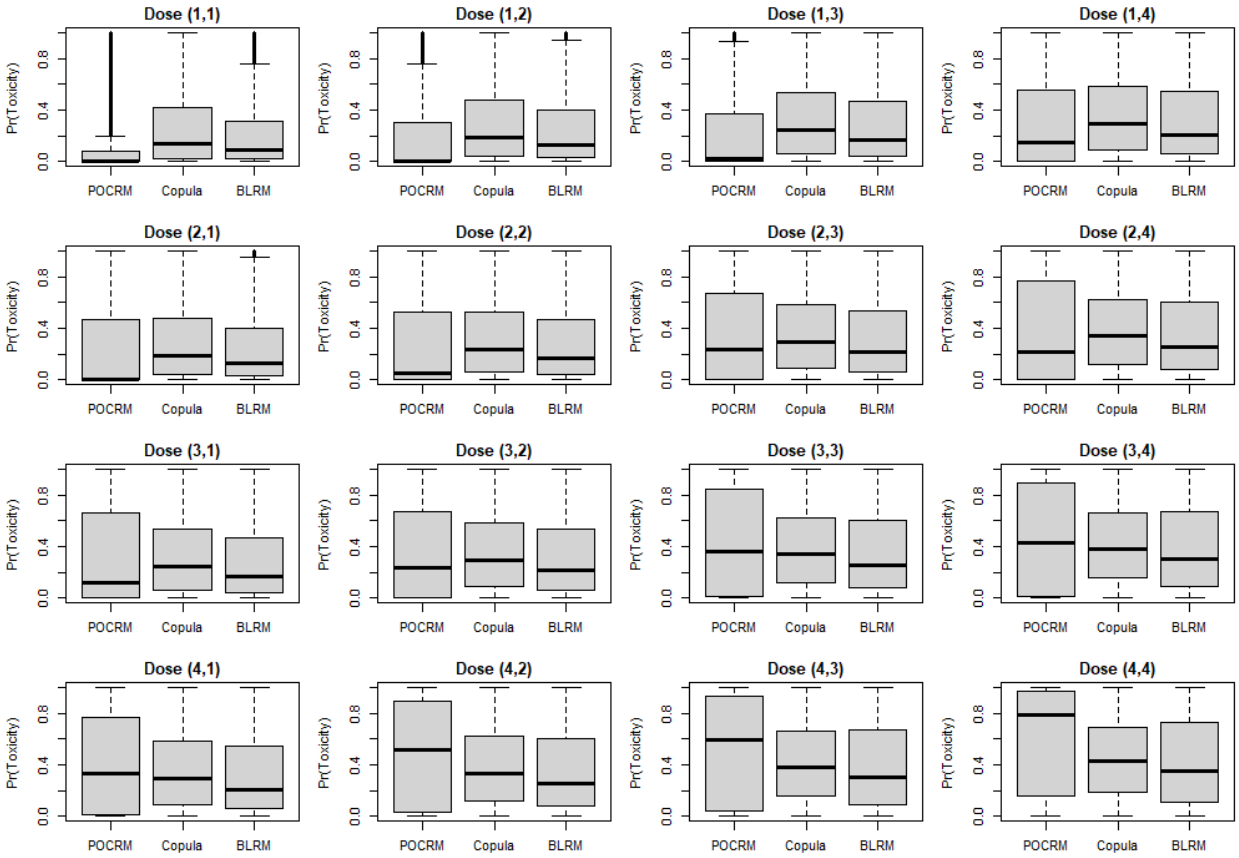


Figure S13. Boxplots of the prior joint toxicity probabilities in the 4×4 combination trial for the POCRM, Copula, and BLRM methods.

Table. Decision Tables for the BOIN design with the target rate of 0.25.

Dose escalation/De-escalation Table

Actions	The number of patients treated **at the current dose**											
	1	2	**3**	4	5	**6**	7	8	**9**	10	11	**12**
Escalate if # of DLT <=	0	0	**0**	0	0	**1**	1	1	**1**	1	2	**2**
De-escalate if # of DLT >=	1	1	**2**	2	2	**2**	3	3	**3**	3	4	**4**
Eliminate if # of DLT >=	NA	NA	**3**	3	3	**4**	4	4	**5**	5	6	**6**

Note: # of DLT is the number of patients with at least 1 DLT.

Desirability Score Table

# patients	# DLTs	Desirability score	# patients	# DLTs	Desirability score
0	0	**5**	9	2	**18**
3	0	**7**	9	3	**15**
3	1	**11**	9	4	**9**
3	2	**3**	9	≥ 5	**E**
3	≥ 3	**E**	12	0	**1**
6	0	**4**	12	1	**8**
6	1	**14**	12	2	**17**
6	2	**13**	12	3	**19**
6	3	**6**	12	4	**26**
6	≥ 4	**E**	12	5	**10**

9	0	**2**	12	≥ 6	**E**
9	1	**12**			

Table S2. Website URLs for the available software applications to implement the existing phase I drug-combination trial designs.

Designs	Software	Website URLs
3+3	No	
Copula	Executable app	https://odin.mdacc.tmc.edu/~yyuan/index_code.html
POCRM	R package	https://cran.r-project.org/web/packages/pocrm/index.html
	Web app	http://uvatrapps.uvadcos.io/pocrm/
BLRM	R package	https://cran.r-project.org/web/packages/OncoBayes2/index.html
	EAST app	https://www.cytel.com/software/east
BOIN	R package	https://cran.r-project.org/web/packages/BOIN/index.html
	Web app	https://trialdesign.org/
	Desktop app	https://biostatistics.mdanderson.org/SoftwareDownload/SingleSoftware/Index/99
Waterfall	R package	https://cran.r-project.org/web/packages/BOIN/index.html
	Web app	https://trialdesign.org/
	Desktop app	https://biostatistics.mdanderson.org/SoftwareDownload/SingleSoftware/Index/99
PIPE	R package	https://cran.r-project.org/web/packages/pipe.design/index.html
	EAST app	https://www.cytel.com/software/east

Table S3. R code to generate random drug-combination scenarios.

```
randcomb<-function(target,epi,ub,nmtd,J,K){

# target is the target toxicity rate

# epi is the epsilon in the algorithm

# ub is the upper bound

# nmtd is the number of MTDs in the dose space

if(nmtd==0){nmtd<-sample(seq(1,min(J,K)),1)}

mtdset<-c()

tempj<-0
```

```
 tempk<-K+1
 nmtd0<-nmtd
 for(i in 1:nmtd){
  candj<-seq(tempj+1,J-nmtd0+1)
  if(length(candj)==1){tempj<-candj} else {tempj<-sample(candj,1)}
  candk<-seq(nmtd0,tempk-1)
  if(length(candk)==1){tempk<-candk} else {tempk<-sample(candk,1)}
  nmtd0<-nmtd0-1
  mtdset<-rbind(mtdset,c(tempj,tempk))
 }

if(is.matrix(mtdset)==0){mtdset=rbind(mtdset,mtdset)}

for(i in 1:1){
p<-matrix(0,J,K)
u<-runif(1,0,1)
# generate row by row
if(u<0.5){
  ksaf<-0;ktox<-mtdset[ max(which(mtdset[,1]<(J+1))),2]
  for(j in J:1){
    if(sum(mtdset[,1]==j)==0){
      ktemp<-ktox-ksaf-1
      utemp<-rbinom(ktemp,1,0.5)
      p[j,]<-sort(c(runif(ksaf,0,target-epi),
                    runif(ktemp,0,target-epi)*utemp+runif(ktemp,target+epi,ub)*(1-utemp),
                    runif(K-ktox+1,target+epi,ub)))
    } else {
      ktemp<-mtdset[which(mtdset[,1]==j)[1],2]
      p[j,]<-sort(c(runif(ktemp-1,0,target-epi),
                    runif(1,target-epi,target+epi),
                    runif(K-ktemp,target+epi,ub)))
      ksaf<-mtdset[which(mtdset[,1]==j)[1],2]
```

```
    if(sum(mtdset[,1]<j)>0){
      ktox<-mtdset[max(which(mtdset[,1]<j)),2]
    } else {ktox<-K+1}
   }
  }
  for(k in 1:K){
   p[1:J,k]<-sort(p[1:J,k])
  }
 } else { # generate column by column
  jsaf<-0;jtox<-mtdset[ min(which(mtdset[,2]<(K+1))),1]
  for(k in K:1){
   if(sum(mtdset[,2]==k)==0){
    jtemp<-jtox-jsaf-1
    utemp<-rbinom(jtemp,1,0.5)
    p[,k]<-sort(c(runif(jsaf,0,target-epi),
                  runif(jtemp,0,target-epi)*utemp+runif(jtemp,target+epi,ub)*(1-utemp),
                  runif(J-jtox+1,target+epi,ub)))
   } else {
    jtemp<-mtdset[which(mtdset[,2]==k)[1],1]
    p[,k]<-sort(c(runif(jtemp-1,0,target-epi),
                  runif(1,target-epi,target+epi),
                  runif(J-jtemp,target+epi,ub)))
    jsaf<-mtdset[which(mtdset[,2]==k)[1],1]
    if(sum(mtdset[,2]<k)>0){
      jtox<-mtdset[min(which(mtdset[,2]<k)),1]
    } else {jtox<-J+1}
   }
  }
  for(j in 1:J){
   p[j,1:K]<-sort(p[j,1:K])
  }
 }
```

```
}

return(list(nmtd=nmtd,mtdset=mtdset,p=p))

}
```

References

1. Wages NA, Conaway MR, O'Quigley J: Dose-finding design for multi-drug combinations. Clin Trials 8:380-9, 2011
2. Lee SM, Ying Kuen C: Model calibration in the continual reassessment method. Clin Trials 6:227-38, 2009
3. Wages NA, Conaway MR: Specifications of a continual reassessment method design for phase I trials of combined drugs. Pharmaceutical Statistics 12:217-224, 2013
4. Yin GS, Yuan Y: Bayesian dose finding in oncology for drug combinations by copula regression. Journal of the Royal Statistical Society Series C-Applied Statistics 58:211-224, 2009
5. Neuenschwander B, Matano, A., Tang, Z., Roychoudhury, S., Wandel, S. Bailey, Stuart.: A Bayesian Industry Approach to Phase I Combination Trials in Oncology. Statistical Methods in Drug Combination Studies 69, 2014
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8. Mander AP, Sweeting MJ: A product of independent beta probabilities dose escalation design for dual-agent phase I trials. Statistics in Medicine 34:1261-1276, 2015
9. Zhang LC, Yuan Y: A practical Bayesian design to identify the maximum tolerated dose contour for drug combination trials. Statistics in Medicine 35:4924-4936, 2016