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Practical designs for phase I combination studies in oncology

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Abstract

Phase I trials evaluating the safety of multi-drug combinations are becoming more common in oncology. Despite the emergence of novel methodology in the area, it is rare that innovative approaches are used in practice. In this article, we review three methods for Phase I combination studies that are easy to understand and straightforward to implement. We demonstrate the operating characteristics of the designs through illustration in a single trial, as well as through extensive simulation studies, with the aim of increasing the use of novel approaches in phase I combination studies. Design specifications and software capabilities are also discussed.

Keywords

dose finding; phase I trials; partial ordering; drug combination; continual reassessment method

1 Introduction

In oncology drug development, there has been an increasing interest in investigating the potential of drug combinations for patient treatment. The motivation to treat with drug combinations stems from the desire to improve the response of the patient, especially those who have been resistant to traditional treatment. Multi-agent dose-finding trials present the significant challenge of finding a MTD combination (MTDC), or combinations, of the agents being tested with the typically small sample sizes involved in phase I studies. Many authors have developed dose-finding methods for drug combinations, a thorough review of which is given in Harrington et al. (2013). Despite the developments of new methods in the area, a recent literature review revealed that the use of novel methods in practice is quite limited (Riviere et al., 2015). A recent editorial in *Journal of Clinical Oncology* by Mandrekar (2014) described the use of the method of Ivanova and Wang (2004) in a Phase I study of neratinib in combination with temsirolimus in patients with human epidermal

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growth factor receptor 2-dependent and other solid tumors (Gandhi et al., 2014), and called for more frequent use of novel designs. Wages et al. (2015) added to the discussion of Riviere et al. (2015) by describing the current implementation of novel methods in several ongoing early-phase combination studies, two of which are described below as motivating examples.

The limited use of innovative approaches in practice has lead to a recent push to introduce simpler methods centered on toxicity probability intervals, with the aim of greater feasibility and likelihood of being implemented. In the single-agent setting, Ivanova et al (2007) proposed the cumulative cohort design, which was extended to ordinal and continuous outcomes by Ivanova and Kim (2009). Ji et al.(2010) developed the modified toxicity probability interval (mTPI) design and, more recently, Liu and Yuan (2015) introduced the Bayesian optimal interval (BOIN) method. In the multi-agent setting, Mander and Sweeting (2015) proposed a curve-free method that relies on the product of independent beta probabilities, similar to the mTPI. This method aims to identify several combinations that form a maximum tolerated contour. The BOIN method has recently been extended to the combination setting by Lin and Yin (2015). In this paper, our objective is to shed some light on BOIN for combinations and compare it to some existing approaches that have been recently implemented in practice, within the context of real trial examples. Clinical trial design specifications, such as cohort size, skipping restrictions, stopping rules, etc., can be application (i.e. protocol/design) specific, and can therefore be difficult to generalize to all practical situations. In this paper, two of the designs discussed have been implemented in published/ongoing studies, so we illustrate them using the specifications utilized in practice. In the next section, we discuss some of the challenges associated with designing phase I combination studies. In Sections 3 – 5, we review three practical multi-agent dose-finding methods. In Section 6, we conduct simulations in order to illustrate the methods in a single trial, as well as to assess their performance over many trials. Finally, we conclude with some discussion.

2 General considerations in combination dose-finding

In general, we consider two-agent combination trials to be testing agents A and B with dose levels $i = 1, \ldots, I$ for A and $j = 1, \ldots, J$ for B, resulting in a $I \times J$ dose combination matrix. Let d_{ij} denote the combination consisting of dose level i of agent A and dose level j of agent B. Denote the probability of dose-limiting toxicity (DLT) at d_{ij} with π_{ij} and the target toxicity rate specified by physicians by φ. A key assumption to phase I methods for single-agent trials is the monotonicity of the dose-toxicity curve. In this case, the curve is said to follow a “simple order” because the ordering of DLT probabilities for any pair of doses is known and administration of greater doses of the agent can be expected to produce DLT's in increasing proportions of patients. In studies testing combinations, the probabilities of DLT often follow a “partial order” (Barlow et al, 1972) in that there are pairs of combinations for which the ordering of the probabilities is not known.

The monotonicity assumption lends itself to escalation along a single line of doses. Given the toxicity response (DLT; yes/no) for a particular patient, we either recommend the same dose for the next patient or move to one of two adjacent doses (i.e. either escalate one dose

higher or de-escalate to one dose lower). In a multi-agent trial, there will most likely be more than one possible treatment on which to enroll the next patient cohort in a decision of escalation, which implies a set, $\mathscr{E}$, of "possible escalation combinations." As an illustration, consider the 3 × 3 matrix in Figure 1. Suppose the first cohort receives combination d_{11} and no DLT's are observed. If d_{11} is well-tolerated, it is not clear which dose pair should be assigned to the next cohort of patients. The set of possible escalation combinations for d_{11} would then consist of two combinations $\mathscr{E}=\{d_{12}, d_{21}\}$. As demonstrated in Figure 1, there are several directions in which the trial could move in deciding which combination the next entered cohort should receive. Because we make the assumption that each drug has been carefully investigated before being combined, we assume that the probability of DLT for each drug increases monotonically when the dose of the other drug is being held fixed (i.e. across rows and up columns of the matrix of drug combinations). It may be clear that dose d_{12} is more toxic than d_{11}, but, in the off-diagonal direction, we may not know the ordering between d_{12} and d_{21} because we increased the dose of *A* and decreased the dose of *B*. In terms of DLT probability, the conditions $\pi_{11} < \pi_{12}$ and $\pi_{11} < \pi_{21}$ may hold without it being possible to order π_{21} and π_{12} with respect to one another. It could be that $\pi_{12} < \pi_{21}$ or $\pi_{12} > \pi_{21}$.

2.1 Assumption of a single ordering

A traditional approach to this problem is to pre-select combinations with a known toxicity order, and apply a single-agent design by escalating and de-escalating along a chosen path. This could be done by, a priori, pre-specifying a subset of combinations for which we know the toxicity ordering. For instance, in the 3 × 3 grid in Figure 1, a selected subset of combinations that satisfies the monotonicity assumption is given by

$$d_{11} \rightarrow d_{21} \rightarrow d_{22} \rightarrow d_{32} \rightarrow d_{33}.$$

This approach transforms the two-dimensional dose-finding space into a one-dimensional space, and was the approach taken in much of the early early work in combinations. Korn and Simon (1993) present a graphical method, called the "tolerable dose diagram," based on single agent toxicity profiles, for guiding the escalation strategy in combination. Kramar, Lebecq and Candahl (1999) also lay out an a priori ordering for the combinations, and estimate the MTDC using a parametric model for the probability of a DLT as a function of the doses of the two agents in combination. The disadvantage of this approach is that it limits the number of combinations that can be considered and it can potentially miss promising dose combinations located outside of the path.

2.2 Specifying a small set of possible orderings

Rather than work with a single ordering, another approach to dealing with added complexity is to specify multiple possible orderings and appeal to established model selection techniques. Taking into account known and unknown relationships between combinations using the assumption of monotonicity up columns and across rows of the matrix, this approach proceeds by laying out multiple possible simple orders of the dose-toxicity relationship. For instance, for the 3 × 3 grid in Figure 1, two possible orderings of the DLT probabilities, π_{ij}, are

$$\pi_{11}<\pi_{12}<\pi_{21}<\pi_{13}<\pi_{22}<\pi_{31}<\pi_{32}<\pi_{23}<\pi_{33}$$

$$\pi_{11}<\pi_{21}<\pi_{12}<\pi_{31}<\pi_{22}<\pi_{13}<\pi_{23}<\pi_{32}<\pi_{33}.$$

Two methods making use of this approach are the Conaway, Dunbar, and Peddada (CDP) design (Conaway et al., 2004) and Wages, Conaway and O'Quigley (POCRM, 2011a,b), which are described in detail in subsequent sections.

2.3 Use of more fully parameterized models

The CDP design and POCRM both take an “underparameterized” approach, and, in the case of POCRM, rely upon several single parameter models from a CRM class of models (O'Quigley et al., 1990). Additional parameters can be utilized to further increase flexibility and account for possible interactive effects the two agents may have on the DLT probabilities. Thall et al. (2003) proposed a six-parameter model for the DLT probabilities of the dose combinations in order to identify a toxicity equivalence contour. Wang and Ivanova (2005) proposed a logistic-type regression for combinations that used the doses of the two agents as the covariates. Yin and Yuan (2009a,b) developed a Bayesian adaptive design based on latent 2 × 2 tables (2009a) and a copula-type model (2009b) for two agents. Braun and Wang (2010) proposed a hierarchical Bayesian model for the probability of toxicity at each combination. Hirakawa et al. (2013) proposed a dose-finding method based on the shrunken predictive probability of toxicity for the two agents. Baily et al. (2009) and Riviere et al. (2014) outlined Bayesian dose-finding procedures employing a logistic model. Jin et al. (2015) described using Bayesian model averaging over several candidate models, including a logistic model, a log-linear model, a Clayton-type copula (Clayton, 1978) model, and the six-parameter model of Thall et al. (2003). The added mathematical complexity in using more flexible models may hinder the implementation of these methods in practice. Estimation of the model parameters can be unstable due to the limited sample sizes observed in early-phase studies.

The review of Riviere et al. (2015) concluded that these approaches are not being employed in practice, with very few of the trials described by the authors implementing a novel approach. Most used some form of the one-dimensional approach described above in Section 2.1. This argues for the development of more simple approaches, provided they perform as well, or nearly as well, as methods that attempt to fully model the drug combination surface. Simulation results in recent publications (Wages, 2015; Hirakawa et al., 2015; Yin and Lin, 2015) demonstrate the strong performance of under-parameterized approaches, relative to more fully-parameterized approaches. In this article, we compare performance of three methods - (1) the CDP design, (2) POCRM, and (3) the BOIN method for combinations - based on 6 evaluation indices under 12 true combination-toxicity scenarios. In general, our goal is to evaluate (1) how well each method identifies MTDC's at and around the target rate, and (2) how well each method allocates patients to combinations at and around the target rate. We also provide a brief discussion of how feasible it is to implement each method given its respective design specifications and software capabilities.

3 Conaway, Dunbar, Peddada (CDP) design

3.1 Phase I trial example using CDP method

A phase I, single-institution, investigator-initiated trial was designed and conducted to study induction therapy with VELCADE and Vorinostat in patients with surgically resectable non-small cell lung cancer (NSCLC) (Jones et al., 2012). The primary objective of the study was to determine the MTDC of 3 doses (1.0, 1.3, 1.6 mg/m^2) of VELCADE and 4 doses (100, 200, 400, 600 mg) of Vorinostat in patients with NSCLC. The two-staged design of Conaway et al. (CDP; 2004) was used to estimate the MTDC of the 12 (3 × 4) drug combinations. The target toxicity rate for determining the MTD combination was 33%.

3.2 CDP estimation procedure

The CDP design is based on the estimation procedure of Hwang and Peddada (1994), which discusses parameter estimation subject to order restrictions. The procedure uses different estimation procedures for “nodal” and “non-nodal” parameters. A nodal parameter is one whose ordering is known with respect to all other parameters. For example, in a $I \times J$ matrix of drug combinations, the probability of DLT, π_{11}, at combination d_{11} is a nodal parameter because it is known that $\pi_{11} < \pi_{i+1,j}$ and $\pi_{11} < \pi_{i,j+1}$ for $i, j \geq 1$. For nodal parameters, estimation proceeds by establishing a simple order that is consistent with the partial order. This is done by *guessing* the unknown inequalities, and obtaining isotonic regression estimates of the nodal parameters π_{ij} based on the Pool Adjacent Violators Algorithm (PAVA; Barlow et al., 1972). In order to estimate the non-nodal parameters, Hwang and Peddada (1994) eliminate the smallest number of parameters that make a non-nodal parameter into a nodal parameter. For instance, π_{12} is a non-nodal parameter because it is unknown whether $\pi_{12} < \pi_{21}$ or vice versa. Estimates of the non-nodal parameters can be obtained using a version of PAVA for simple orders that fixes the nodal parameters at their previously estimated values. Hwang and Peddada (1994) show that the resulting estimates satisfy the partial order. The CDP design computed estimates of the parameters under all possible guesses and averaged them in order to eliminate the dependence of the estimates on a single guess at the ordering between non-nodal parameters.

The CDP method is a two-stage design. The initial stage is designed to quickly escalate through treatment combinations that are non-toxic (in single patient cohorts until first DLT is observed) and the second stage implements the Hwang and Peddada (1994) estimates. Throughout the second stage, the toxic response data for combination d_{ij} is of the form $Y = \{y_{ij}; i = 1, \ldots, I; j = 1, \ldots, J\}$ with y_{ij} equal to the number of observed toxicities from patients treated with combination d_{ij}. Let $\mathscr{A}$ denote the set of treatments that have been administered thus far in the trial such that $\mathscr{A} = \{d_{ij} : n_{ij} > 0\}$, where n_{ij} denotes the number of patients treated on each combination. Using a Beta(α_{ij}, β_{ij}) prior for the π_{ij}, the updated DLT probabilities, only for $d_{ij} \in \mathscr{A}$, are given by

$$\hat{\pi}_{ij} = \frac{y_{ij} + \alpha_{ij}}{n_{ij} + \alpha_{ij} + \beta_{ij}}.$$

The estimation procedure of Hwang and Peddada (1994) is applied to the updated posterior means $\hat{\pi}_{ij}$ for $d_{ij} \in \mathscr{A}$.

3.3 CDP design specifications

If appropriate prior information is available to investigators, it is described through a prior distribution of the form $\pi_{ij} \sim \text{Beta}(\alpha_{ij}, \beta_{ij})$. The investigators specify the expected value of π_{ij} and an upper limit u_{ij} such that they are 95% certain that the toxicity probability will not exceed u_{ij}. The equations,

$$\mathbb{E}[\pi_{ij}] = \frac{\alpha_{ij}}{\alpha_{ij}+\beta_{ij}} \text{and} \;\; \Pr[\pi_{ij} \leq u_{ij}] = 0.95,$$

are solved in order to obtain prior specifications for α_{ij} and β_{ij}. Another prior specification for the CDP method is to choose a subset of possible dose-toxicity orders based on ordering the combinations by rows, columns, and diagonals of the drug combination matrix. Using the guidance of Wages and Conaway (2013), we choose a subset of approximately 6–9 orderings. This provides an appropriate balance between choosing enough orderings so that we include adequate information to account for the uncertainty surrounding partially ordered dose-toxicity curves, without increasing the dimension of the problem so much so that we diminish performance. Arrange the orderings according to movements across rows, up columns and along diagonals. Since, in a large matrix, there could many ways to arrange combinations along a diagonal, we restrict movements to only *moving across rows*, *up columns*, and *up or down any diagonal*. For instance, in the 3 × 3 grid in Figure 1, six orderings arranged in this manner are given by:

1. across rows:

$$\pi_{11} < \pi_{12} < \pi_{13} < \pi_{21} < \pi_{22} < \pi_{23} < \pi_{31} < \pi_{32} < \pi_{33}$$

2. up columns:

$$\pi_{11} < \pi_{21} < \pi_{31} < \pi_{12} < \pi_{22} < \pi_{32} < \pi_{13} < \pi_{23} < \pi_{33}$$

3. up diagonals:

$$\pi_{11} < \pi_{12} < \pi_{21} < \pi_{13} < \pi_{22} < \pi_{31} < \pi_{23} < \pi_{32} < \pi_{33}$$

4. down diagonals:

$$\pi_{11} < \pi_{21} < \pi_{12} < \pi_{31} < \pi_{22} < \pi_{13} < \pi_{32} < \pi_{23} < \pi_{33}$$

5. down-up diagonals:

$$\pi_{11} < \pi_{12} < \pi_{21} < \pi_{31} < \pi_{22} < \pi_{13} < \pi_{23} < \pi_{32} < \pi_{33}$$

6. up-down diagonals:

$$\pi_{11}<\pi_{21}<\pi_{12}<\pi_{13}<\pi_{22}<\pi_{31}<\pi_{32}<\pi_{23}<\pi_{33}.$$

3.4 CDP dose-finding algorithm

Stage 1—The first patient is entered at the lowest combination d_{11}. In the CDP method, the possible escalation combinations are defined as

$$\mathscr{E}=\{(i+1,j),(i,j+1)\},$$

so that $\mathscr{E}$ = {neighboring combinations for which we know we are escalating}. For instance, if combination d_{11} is deemed safe, then the next cohort is treated with a combination chosen from among $\mathscr{E} = \{d_{21}, d_{12}\}$. If $\mathscr{E}$ contains multiple combinations, the next cohort is randomized to a combination in the set. Once a DLT is observed, Stage 2 begins.

Stage 2—For all $d_{ij} \in \mathscr{A}$, we compute the loss, $L(\hat{\pi}_{ij}, \varphi)$, associated with each combination. In this paper, as in the CDP design, we implement a symmetric loss function so that $L(\hat{\pi}_{ij}, \varphi) = |\hat{\pi}_{ij} - \varphi|$.

1. Let $l_{min}=\min_{d_{ij}\in\mathscr{A}} L_{ij}(\hat{\pi}_{ij},\phi)$, and let $\mathscr{C}$ be the set of combinations with losses equal to the minimum observed loss, $\mathscr{C} = \{d_{ij} : L_{ij}(\hat{\pi}_{ij}, \varphi) = l_{min}\}$.
2. If there is a single combination, $d_{ij} \in \mathscr{C}$, then the suggested combination is d_{ij}, with an estimated DLT probability of $\hat{\pi}_{ij}$
3. If $\mathscr{C}$ contains more than one combination, then we randomly choose from among them according to the rules:
   a. If $\hat{\pi}_{ij} > \varphi \; \forall \; d_{ij} \in \mathscr{C}$, we randomly choose from among the set $\mathscr{C}$ of candidate combinations.
   b. If $\hat{\pi}_{ij} \leq \varphi$ for at least one $d_{ij} \in \mathscr{C}$, we choose randomly among the combinations in $\mathscr{C}$ that are candidate for having the "largest" DLT probability.
4. If the suggested combination has an estimated DLT probability that is less than the target, a combination is chosen at random from $\mathscr{E}$ that have not yet been tested in the trial.
5. The MTDC is defined as $d_{i^*j^*}$ such that

$$d_{i^*j^*}=\arg\min_{d_{ij}\in\mathscr{N}}|\hat{\pi}_{ij}-\phi|,$$

where $\mathscr{N}$ = {($d_{ij} : n_{ij} > 0$} is the set of tried combinations.

4 Partial order continual reassessment method (POCRM)

4.1 Phase I trial example 1 using POCRM

A dose escalation study was designed to determine the MTD / appropriate phase II dose combination of two small molecule inhibitors for refractory solid tumors and untreated metastatic disease. Agent *A* contained three doses (1.0, 1.5, 2.0 mg/day) and Agent *B* contained three doses (1000, 1250, 1500 mg/day), for a total of 9 (3 ×3) drug combinations. This FDA/IRB approved trial was designed using the two-stage POCRM (Wages et al., 2011b). Each stage treated patients in single patient cohorts, and the target toxicity rate for determining the MTD combination was 30%.

4.2 Phase I trial example 2 using POCRM

A phase I trial was designed to determine the MTD of a combination of long peptides plus a toll-like receptor (TLR) agonists with or without a form of incomplete Freund's adjuvant (IFA) for the treatment of melanoma (NCT01585350). In this FDA/IRB approved trial, TLR agonists had 4 dose levels (25, 100, 400, 1600 EU) and IFA had three subgroups: 0 - IFA is not administered with any vaccine, V1 - IFA is administered with just the first vaccine, and V6 - IFA is administered in all vaccines. This trial was also designed using the two-stage POCRM (Wages et al., 2011b) There are a total of 12 combinations under consideration, and the target rate for determining the MTD combination was 33%.

4.3 POCRM estimation procedure

The CRM for partial orders is based on utilizing a class of working models that correspond to possible orderings of the toxicity probabilities for the combinations. Specifically, suppose there are *M* possible orderings being considered which are indexed by *m*. For a particular ordering, we model the true probability of toxicity, π_{ij}, corresponding to combination d_{ij}, via a power model

$$\pi_{ij} \approx \psi_m(d_{ij}, a_m) = [\alpha_{ij}(m)]^{a_m}; m = 1, \ldots, M,$$

where the $\alpha_{ij}(m)$ represent the skeleton of the model under ordering *m*. In work done by Wages, the use of other single-parameter working models common to the CRM class, such as a hyperbolic tangent function or a one-parameter logistic model, was explored and found that there is little difference in the operating characteristics among the various model choices. We let the plausibility of each ordering under consideration be described by a set of prior weights $\tau = \{\tau(1), \ldots, \tau(M)\}$, where $\tau(m) \geq 0$ and $\sum\tau(m) = 1; m = 1, \ldots, M$. Using the accumulated data, Ω_i, from *i* patients, the MLE $\hat{a}_m$ of the parameter a_m can be computed for each of the *m* orderings, along with the value of the log-likelihood, $\mathscr{L}_m(\hat{a}_m \mid \Omega_i)$, at $\hat{a}_m$. Wages et al. (2011b) proposes an escalation method that first chooses the ordering that maximizes the updated model weight

$$\omega(m) = \frac{\exp\{\mathscr{L}_m(\hat{a}_m|\Omega_i)\}\tau(m)}{\sum_{m=1}^{M} \exp\{\mathscr{L}_m(\hat{a}_m|\Omega_i)\}\tau(m)}$$

before each patient inclusion. If we denote this ordering by m^*, the authors use the estimate $\hat{a}_{m^*}$ to estimate the toxicity probabilities for each combination under ordering m^* so that $\hat{\pi}_{ij} \approx \psi_{m^*}(d_{ij}, \hat{a}_{m^*})$.

4.4 POCRM design specifications

As in the CDP design, a prior specification for POCRM is to choose a subset of possible dose-toxicity orders. We again rely on the guidance of Wages and Conaway (2013) and choose approximately 6–9 orderings based on ordering the combinations by rows, columns, and diagonals of the drug combination matrix. Another specification that needs to be made prior to beginning the study is a set of skeleton values $\alpha_{ij}(m)$. We utilize the algorithm of Lee and Cheung (2009) to generate reasonable skeleton values using the function **getprior** in **R** package **dfcrm**. We simply need to specify skeleton values at each combination that are adequately spaced (O'Quigley and Zohar, 2010), and adjust them to correspond to each of the possible orderings, in order for POCRM to have good performance in terms of identifying an MTDC. The location of these skeleton values can be adjusted to correspond to each of the possible orderings using the **getwm** function in **R** package **pocrm** (Wages and Varhegyi, 2013).

4.5 POCRM dose-finding algorithm

Within the framework of sequential likelihood estimation, an initial escalation scheme is needed, since the likelihood fails to have a solution on the interior of the parameter space unless some heterogeneity (i.e. at least one DLT and one non-DLT) in the responses has been observed.

Stage 1—In our comparative study, in attempt to make the methods as comparable as possible, the initial escalation stage utilized in POCRM simulations is the same as that of the CDP design, where allocation is guided according to $\mathscr{E} = \{(i + 1, j), (i, j + 1)\}$.

Stage 2—Subsequent to a DLT being observed, the second stage of the trial begins.

1. Based on the accumulated data from i patients Ω_i, the estimated toxicity probabilities $\hat{\pi}_{ij}$ are obtained for all combinations being tested, based on the procedure described above.
2. The next entered patient is then allocated to the dose combination with estimated toxicity probability closest to the target rate so that $|\hat{\pi}_{ij} - \varphi|$ is minimized.
3. There is no formal skipping restriction placed on model-based allocation in the POCRM method. That is, movement within the matrix is not restricted to a neighbor of the currently occupied combination in Stage 2. This is meant to allow for adequate exploration of the drug combination space. For instance, movement from d_{13} to d_{31} "skips" over d_{22}, yet it is unknown whether this move is actually an escalation or a de-escalation due to the partial order, so we allow such a move to encourage experimentation throughout the matrix and to avoid getting "stuck" in certain regions of the space.
4. The MTDC is defined as $d_{i^*j^*}$ such that

$$d_{i^*j^*}=\underset{d_{ij}}{\operatorname{argmin}}|\hat{\pi}_{ij}-\phi|$$

after a total sample size of n patients.

5 Bayesian optimal interval (BOIN) design

5.1 BOIN estimation procedure

The BOIN method allocates patients to combinations based on lower and upper cut-off values, denoted $\Delta_L > 0$ and $\Delta_U > 0$, such that $0 < \varphi - \Delta_L < \varphi + \Delta_U < 1$. Optimal values of Δ_L and Δ_U are given by

$$\Delta_L=\phi-\frac{\log\left(\frac{1-\phi_1}{1-\phi}\right)}{\log\left\{\frac{\phi(1-\phi_1)}{\phi_1(1-\phi)}\right\}},\Delta_U=\frac{\log\left(\frac{1-\phi}{1-\phi_2}\right)}{\log\left\{\frac{\phi_2(1-\phi)}{\phi(1-\phi_2)}\right\}}-\phi,$$

where φ_1 is the highest DLT probability that is regarded as sub-therapeutic indicating escalation should be considered and φ_2 ($> \varphi_1$) is the lowest DLT probability that is regarded as too toxic indicating that de-escalation should be considered. Detailed derivations of Δ_L and Δ_U are provided in Lin and Yin (2015). Suppose the current cohort of patients is treated at d_{ij}, and let $\hat{\pi}_{ij} = y_{ij}/n_{ij}$ be the estimated DLT rate, where y_{ij} is the number of observed DLT's and n_{ij} is the number of patients treated at d_{ij}. Based on the data from the current cohort, possible sets, $\mathscr{E}$ and $\mathscr{D}$, for escalation and de-escalation, respectively, consist of row and column neighbors to the current combination.

$$\mathscr{E}=\{(i+1,j),(i,j+1)\}\text{and}\mathscr{D}=\{(i-1,j),(i,j-1)\}.$$

5.2 BOIN design specifications

In practical situations, given a target rate of φ, the specifications of $\varphi_1 \in [0.5\varphi, 0.7\varphi]$ and $\varphi_2 \in [1.3\varphi, 1.5\varphi]$ are appropriate and yield good operating characteristics. The default values recommended by the authors of the BOIN method, both in single- (Liu and Yuan, 2015) and multiple-agents (Lin and Yin, 2015), are $\varphi_1 = 0.6\varphi$ and $\varphi_2 = 1.4\varphi$. The prior distribution on each π_{ij} is Beta(0.5, 0.5).

5.3 BOIN allocation algorithm

The BOIN method for combinations allocates patient cohorts according to the following dose-finding algorithm.

1. Allocate the first cohort of patients to the lowest dose of each drug, i.e. combination d_{11}
2. Based on the treatment of the current cohort at combination d_{ij}
   a. If $\hat{\pi}_{ij} \le \varphi - \Delta_L$, escalate to the combination in $\mathscr{E}$ that maximizes $\Pr\{\pi_{i'j'} \in (\varphi - \Delta_L, \varphi + \Delta_U)|\, y_{i'j'}\}$

b. If $\hat{\pi}_{ij} \geq \varphi + \Delta_U$, de-escalate to the combination in $\mathscr{D}$ that maximizes $\Pr\{\pi_{i'j'} \in (\varphi - \Delta_L, \varphi + \Delta_U) | y_{i'j'}\}$

c. Otherwise, if $\varphi - \Delta_L < \hat{\pi}_{ij} < \varphi + \Delta_U$, stay at the current combination d_{ij}

3. Continue this allocation procedure until the maximum sample size is reached.

During the allocation algorithm, if more than one combination is contained in $\mathscr{E}$ or $\mathscr{D}$, the method randomly chooses one with equal probability. If no combinations are contained in $\mathscr{E}$ and $\mathscr{D}$, the current combination is retained. On the boundary of the combination space, if $i = 1$ and $\hat{\pi}_{ij} \geq \varphi + \Delta_U$, the next combination is $d_{i,j-1}$, unless $d_{ij} = d_{11}$ in which case the combination would remain d_{11}. If $i = I$ and $\pi_{ij} \leq \varphi - \Delta_L$, the next combination is $d_{i,j+1}$, unless $d_{ij} = d_{IJ}$ in which case the combination would remain d_{IJ}. Similar allocations can be made with respect to the boundaries of j. After accrual of the maximum sample size into the study, estimates of the DLT rates, $\tilde{\pi}_{ij}$, at each combinations are generated using bivariate isotonic regression (Barlow et al., 1972). The MTD combination d_{i^*,j^*} that is selected at the conclusion of the trial is that with the estimated DLT rate closest to the target rate so that

$$d_{i^*j^*} = \arg\min_{d_{ij} \in \mathscr{N}} |\tilde{\pi}_{ij} - \phi|,$$

where $\mathscr{N} = \{(d_{ij} : n_{ij} > 0\}$ is the set of tried combinations.

6 Numerical studies

6.1 Simulation settings

We compared the operating characteristics among the three methods by simulating 2000 trials under 12 scenarios with 3 × 3, 3 × 4, and 4 × 3 dose combination matrices with varying positions and number of true MTDCs, as shown in Table 1. These matrices, as well the simulation specifications (target rate φ, sample size n, etc.), correspond to the trial examples described in the previous sections. The target rate is set to $\varphi = 0.30$ in Scenarios 1–4, $\varphi = 0.33$ in Scenarios 5–8, and $\varphi = 0.20$ in Scenarios 9–12. The sample size is $n = 27$ in Scenarios 1–4, $n = 36$ in Scenarios 5–8, and $n = 36$ in Scenarios 9–12. Throughout the simulations studies, for each method, a cohort of size 1 is used. In practice, patients can sometimes be treated in larger cohort sizes (i.e. 3), but since the POCRM and CDP methods were implemented in practical situations using smaller cohorts, we decided to illustrate performance using this specification. This was also aided by the fact that the **R** code for the BOIN method allowed the cohort size to be specified by the user, so we thought the most justifiable comparison would involve making it the same as the other methods. The true scenarios were used in designing the trial and obtaining approval of scientific review committees; IRBs and the FDA. In each scenario, an **acceptable MTDC** is defined as any combination with a true DLT probability within 5% of the target rate; (i.e. $\varphi \pm 0.05$). An **overdose combination** is defined as any combination with true DLT probability larger than 5% above the target rate; (i.e. $> \varphi + 0.05$).

For the CDP design, we present results for a prior that sets the prior mean equal to the target rate. We take the prior mean to equal φ, and a prior upper 95% limit of 0.70 for all

combinations. We utilized six possible orderings in all scenarios, arranging the combinations across rows, up columns, and up or down any diagonal. For POCRM, we utilized the same set of possible orderings as the CDP design. A uniform prior, τ, was placed on the orderings. The skeleton values, $\alpha_{ij}(m)$, were generated according to the algorithm of Lee and Cheung (2009) using the **getprior** function in R package **dfcrm**. Specifically, for 3 × 3 combinations, we used **getprior(0.05,0.30,4,9)**; for 3 × 4 combinations, we used **getprior(0.05,0.33,6,12)**; and for 4 × 3 combinations, we used **getprior(0.04,0.20,6,12)**. All simulation results were carried out using the functions of **pocrm**. For the BOIN method, we used the default values $\varphi_1 = 0.6\varphi$ and $\varphi_2 = 1.4\varphi$ and Beta(0.5, 0.5) prior for the DLT probability at each combination. The boundaries for the BOIN method are $\varphi - \Delta_L \approx 0.236$, $\varphi + \Delta_U \approx 0.359$ for Scenarios 1–4, $\varphi - \Delta_L \approx 0.263$, $\varphi + \Delta_U \approx 0.398$ for Scenarios 5–8, and $\varphi - \Delta_L \approx 0.157$, $\varphi + \Delta_U \approx 0.238$ for Scenarios 9–12.

6.2 Single trial illustration

In the simulation of DLT outcomes in a trial, the tolerance of each patient can be considered a uniformly distributed random variable on the interval [0, 1], which we term a patient's latent toxicity tolerance and denote u_k for the kth entered patient (O'Quigley, Paoletti, Maccario, 2002). At the combination (d_{ij}) assigned to patient k, if the tolerance is less than or equal to its true DLT probability (i.e. $u_k \leq \pi_{ij}$), then patient k has a DLT; otherwise the patient has a non-DLT outcome. Of course, in a real trial, it is impossible to observe a patient's latent tolerance, but it is a useful tool in simulation and can be used to compare the operating characteristics of different designs within a single trial. Based on the same latent tolerance sequence, the allocation algorithms of the BOIN method, the CDP method, and POCRM can be evaluated using the same patients, although each patient will not be necessarily treated at the same combination with each method.

In conducting this exercise to compare the three methods discussed in this paper, we generated the latent tolerance sequence in Table 2 for $n = 27$ patients using the function **runif(27)** in **R**. The allocation algorithm is illustrated using the true DLT probabilities in Scenario 3 from Table 1, with target rate $\varphi = 0.30$. Each method begins on the lowest combination so that patient 1 receives d_{11}. Because the tolerance $u_1 = 0.9776$, he/she does not have a DLT, since $u_1 > 0.02$. Escalating in cohorts of size 1, each method then recommends that the second patient receive one of two combinations in the set $\mathscr{C} = \{d_{12}, d_{21}\}$. The BOIN method and the CDP method randomize the second patient to d_{12}, whereas POCRM randomizes to d_{21}. The latent tolerance $u_2 = 0.5949$ is larger than both $\pi_{12} = 0.20$ and $\pi_{21} = 0.06$, resulting in a non-DLT outcome for each method. The first DLT occurs for each method at the 4th entered patient, based on a latent tolerance of $u_4 = 0.055$, which is less than the true DLT probability for the combination recommended to this patient by each method. Notice at this point, both the CDP method and POCRM would terminate Stage 1 of their designs due to heterogeneity in the DLT outcomes, and proceed with their respective Stage 2. The BOIN method is a single stage design and thus proceeds in the same manner throughout the trial.

There are some interesting features to each design as it sequentially allocates. For this particular latent tolerance sequence, the algorithm of the CDP method appears to settle on

d_{22} very quickly (i.e. after patient 5), while POCRM and the BOIN method move around the drug combination space more. For this tolerance sequence, given this scenario, this is a very attractive feature for the CDP design, because it treats 23 of 27 patients, and ultimately recommends as the MTDC, d_{22}, which has a true DLT probability of $\pi_{22} = 0.33$. However, this is only one simulated trial for a single latent sequence. Quickly settling on a combination can be a very good thing if that combination is an acceptable MTDC, but can be a poor design feature if the settled on combination is not an acceptable MTDC. Related to movement around the drug combination space, it is of interest to note that POCRM allows movement at both ends of a diagonal of the matrix. In other words, after patient 13 receives d_{13}, the next combination recommended is d_{31}. This represents a two dose level change in both agents, although it is unknown in practice whether this is actually an escalation or a de-escalation. After $n = 27$ patients, POCRM recommends d_{13} as the MTDC, which has a true DLT probability of $\pi_{13} = 0.33$.

For the BOIN method, it is worth paying close attention to patients 22–24. Patient 22 receives d_{22} and experiences DLT. At this point in the trial, $\hat{\pi}_{22} = y_{22}/n_{22} = 2/9 \approx 0.22$. Since $\hat{\pi}_{22} < 0.236(\varphi - \Delta_L)$, the method recommends escalation to d_{32} after this DLT. Patient 23 receives d_{32} and does not experience DLT. At this point in the trial, $\hat{\pi}_{32} = y_{32}/n_{32} = 3/8 \approx 0.38$. Since $\hat{\pi}_{32} > 0.358(\varphi + \Delta_U)$, the method recommends de-escalation to d_{23} after this non-DLT. Thus, in this simulated trial, there are instances in which the BOIN method allows a de-escalation after non-DLT, as well as an escalation after a DLT. These recommendations appear to violate the principle of coherence, as defined by Cheung (2005). However, Liu and Yuan (2015) extended the coherence definition to include both *short-term memory coherence* and *long-term memory coherence*, and discussed the notion that long-term memory coherence is more practically relevant. Although the recommendations of patients 23 and 24 violate short-term memory coherence, they obey long-term memory coherence, and, by this definition, can be considered justifiable allocations. At the conclusion of the trial, the BOIN method recommends d_{22} as the MTDC, which has a true DLT probability of $\pi_{22} = 0.33$. Each method recommends an acceptable MTDC in this simulated trial given the same latent toxicity sequence.

6.3 Evaluating performance over many situations

We assessed performance of the three methods based on 6 evaluation indices under 12 toxicity scenarios. In general, our goal is to evaluate (1) how well each method locates MTDC's at and around the target rate (i.e. acceptable MTDC's), and (2) how well each method allocates patients to acceptable MTDC's. Of course, there will always be certain scenarios in which some methods perform better than others. Therefore, a useful tool in comparing dose-finding designs can be average performance over a broad range of scenarios. While traditional evaluation measures, such as the percentage of recommendation and allocation for true MTDC's are useful in assessing performance, it is also beneficial to consider the entire distribution of selected dose combination, as it provides more detailed information as to what combinations are being recommended if a true acceptable MTDC is missed. Cheung (2011) proposes to use the accuracy index, after n patients, defined as

$$A_n = 1 - I \times J \times \frac{\sum_{i=1}^{I}\sum_{j=1}^{J} |\pi_{ij} - \phi| \times \rho_{ij}}{\sum_{i=1}^{I}\sum_{j=1}^{J} |\pi_{ij} - \phi|},$$

where π_{ij} is the true toxicity probability of dose combination d_{ij} and ρ_{ij} is the probability of selecting dose combination d_{ij} as the MTDC. The maximum value of A_n is 1 with larger values (close to 1) indicating that the method possesses high accuracy.

6.4 Results

Figures 2 and 3 show the operating characteristics of the 3 methods under 12 scenarios. Across the 12 scenarios, the BOIN method, the CDP design and POCRM methods demonstrated averages of 47.4%, 43.0%, and 48.3% recommendation rates for true acceptable MTDCs, respectively. The BOIN design, the CDP design, and POCRM demonstrated averages of 26.7%, 23.7%, and 25.7% recommendation rates for overdose combinations, respectively. The average number of patients allocated to true acceptable MTDCs of the the BOIN method, the CDP design, and POCRM methods were averages of 11.8, 11.3, and 12.7, respectively. The overall percentage of observed toxicities of the BOIN method, the CDP design, and POCRM methods were averages of 27.3%, 26.3%, and 25.7%, respectively. Although this percentage is lowest for POCRM, it is desirable for the value to be as close as possible to the target rate φ, which varies over the scenarios considered. Therefore, this overall percentage as a benchmark for performance is difficult to judge. In Scenarios 1–8, the BOIN method yields the average overall toxicity percentage closest to φ, whereas POCRM does so in Scenarios 9–12. Average number of patients allocated to a dose combination above the true MTDCs of the BOIN method, the CDP design, and POCRM methods were averages of 12.7, 11.23, and 9.92, respectively. Based on the accuracy index, the POCRM yielded a value of 0.583, the BOIN method produced a value of 0.576, and the CDP design resulted in a value of 0.564.

One of the most notable operating characteristics that should be taken away from these results occurs in Scenarios 2, 5, and 9 in which the only acceptable MTDC is the highest dose level of each agent, and thus is located at the top right corner of the drug combination matrix. In these cases, the CDP design struggles to select the highest combination relative to the other methods, and its performance in terms of recommending and allocating patients to acceptable MTDC's diminishes in these scenarios. For instance, in Scenario 2, the recommendation percentage of true acceptable MTDC's is 56.2% and 53.9% for the BOIN method and POCRM, respectively, where as this percentage is 34.1% for the CDP method. Scenarios 5 and 9 contain similar results, and these findings are also reflected in the accuracy index. In scenarios other than 2, 5, and 9, the CDP method performs very well, and is the best performing method, in terms of the evaluation metrics used, in five of the nine remaining scenarios (1, 3, 6, 8, and 11). This highlights the importance of average performance. The CDP method offers a higher risk-reward approach than the other two methods in terms of performance. If the true acceptable MTDC(s) are in the interior of the drug combination space, then the CDP method appears to be the best method, yielding the

highest performance in many scenarios. However, its drop-off in performance in the scenarios in which the true MTDC is at the top of the matrix makes the alternative methods more attractive options in these cases, and the overall average performance reflect the more consistent results of POCRM and the BOIN method. Overall, the results of these two methods are comparable, on average, across the scenarios considered.

7 Concluding remarks

Motivated by real life examples in phase I trial settings, we studied the operating characteristics of three simple dose-finding methods for combinations under various practical scenarios. We considered several scenarios in which there was no “perfect” MTDC; i.e. there are no combinations with true DLT rate exactly equal to the target toxicity rate. All three methods would be useful in the practical setting of phase I combination trials over designs employing a more complex model, because the design specifications are considerably less in the approaches considered here. Additionally, simulation studies in Wages (2015), Hirakawa et al. (2015), and Lin and Yin (2015) indicate that the performance in terms of recommending true MTDCs may diminish as the mathematical complexity of the method increases, given the small sample size constraints of phase I studies. As for implementation in practice, there is no available software for the CDP method, and its escalation algorithm can be difficult and time-consuming to program. POCRM has the advantage of directly building off of the well-known CRM and is likely to be more easily understood by clinicians and review boards. The POCRM has recently been extended to handle time-to-event outcomes (Wages, Conaway, and O'Quigley, 2013). In addition to the trial examples described in this work, The POCRM was implemented as part of a multi-site, phase I/II trial of combination immunotherapies that is currently open to enrollment at UVA and M.D. Anderson Cancer Center (NCT02126579; Wages, Slingluff, and Petroni, 2015). The estimation procedure employed by POCRM is used in this trial to adaptively monitor safety and to identify an acceptable set of regimens in high-risk melanoma patients. After each patient inclusion, POCRM updates the acceptable set of safe regimens, and the next patient is allocated to the acceptable regimen exhibiting the highest immunogenicity. Most recently, a bivariate extension of POCRM (Wages and Conaway, 2014) was implemented in a phase I/II design for a trial combining two small molecule inhibitors in relapsed/refractory mantle cell lymphoma. This pharmaceutical industry-sponsored trial has FDA approval, and is slated to open in mid-2015. Currently, POCRM is the only method described in this work that has available software on the web that can be used for design implementation (i.e. obtaining a combination recommendation for the next entered cohort, given the data to that point in the trial), as well as simulating design operating characteristics. **R** code for simulating the BOIN method is available upon request from the first author of their paper. The **R** code for the BOIN method provided the fastest simulation time among the three methods, but results for each method were able to be generated in a reasonable amount of time, making them all feasible for practical use.

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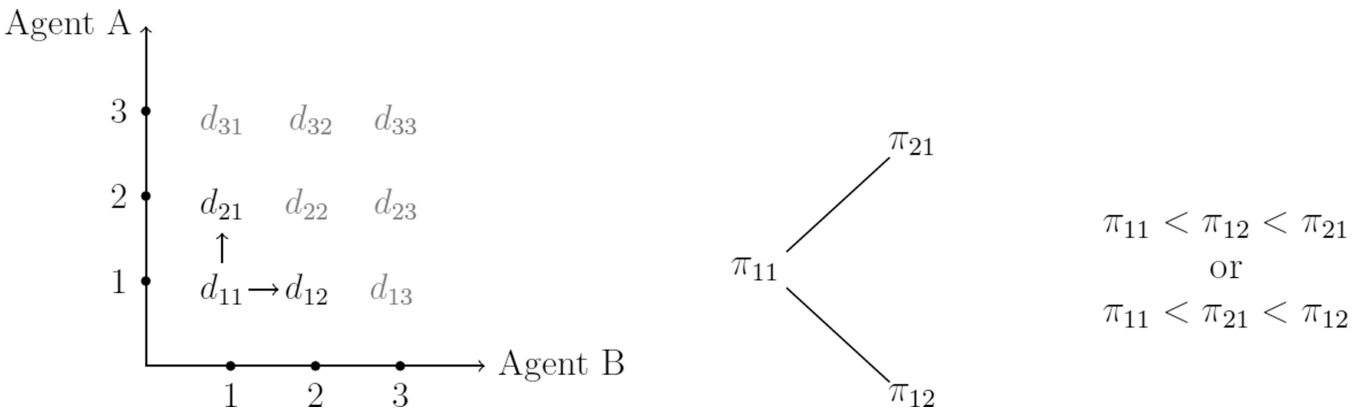

Figure 1.

Illustration of a partial order between π_{11}, π_{12} and π_{21} in a drug combination matrix. If d_{11} is well tolerated, the set of possible escalation combinations is $\mathcal{E}=\{d_{12}, d_{21}\}$. Two possible simple orders satisfy this partial order.

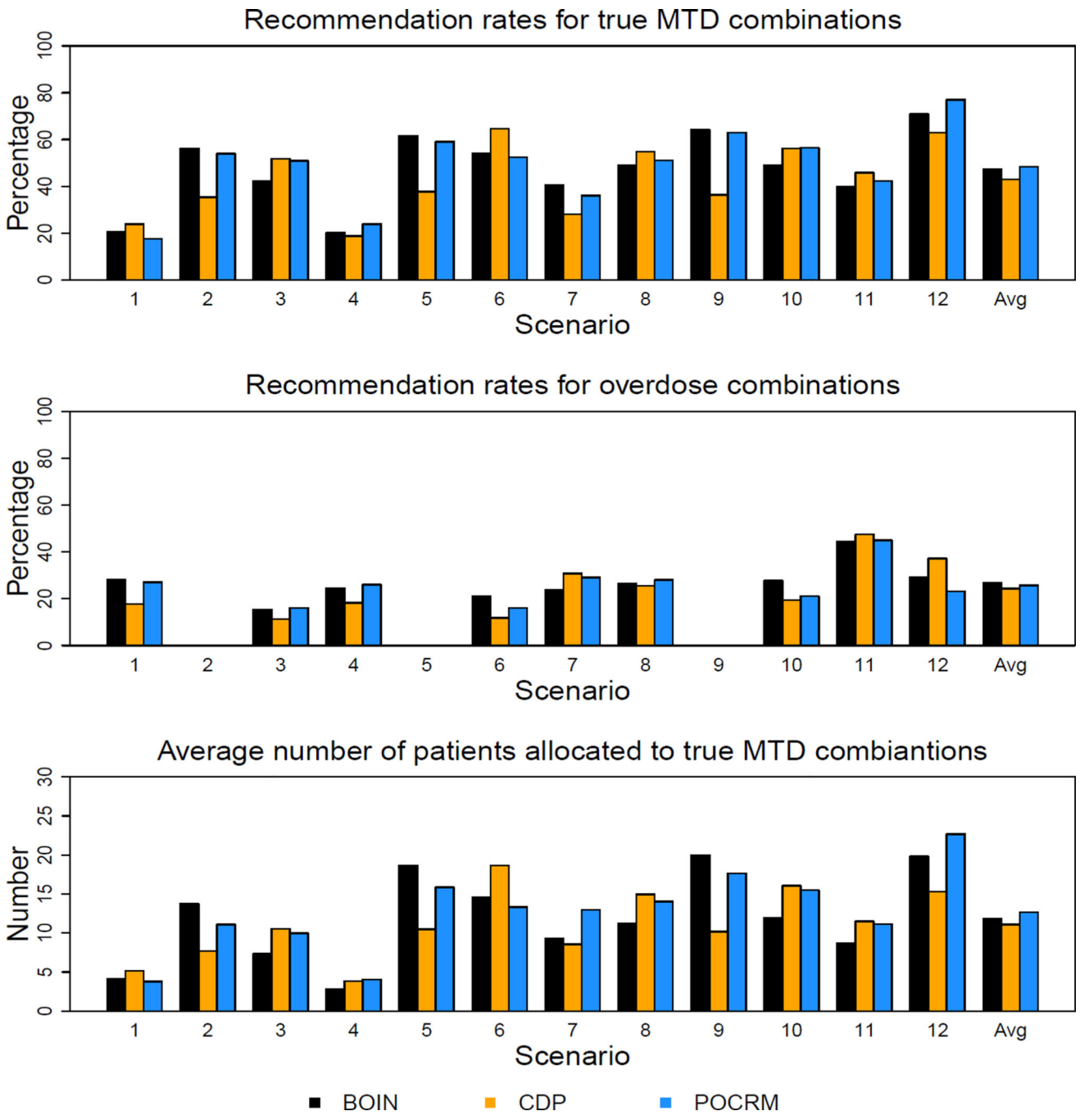

Figure 2.
Summary of the operating characteristics of the 3 methods in all scenarios.

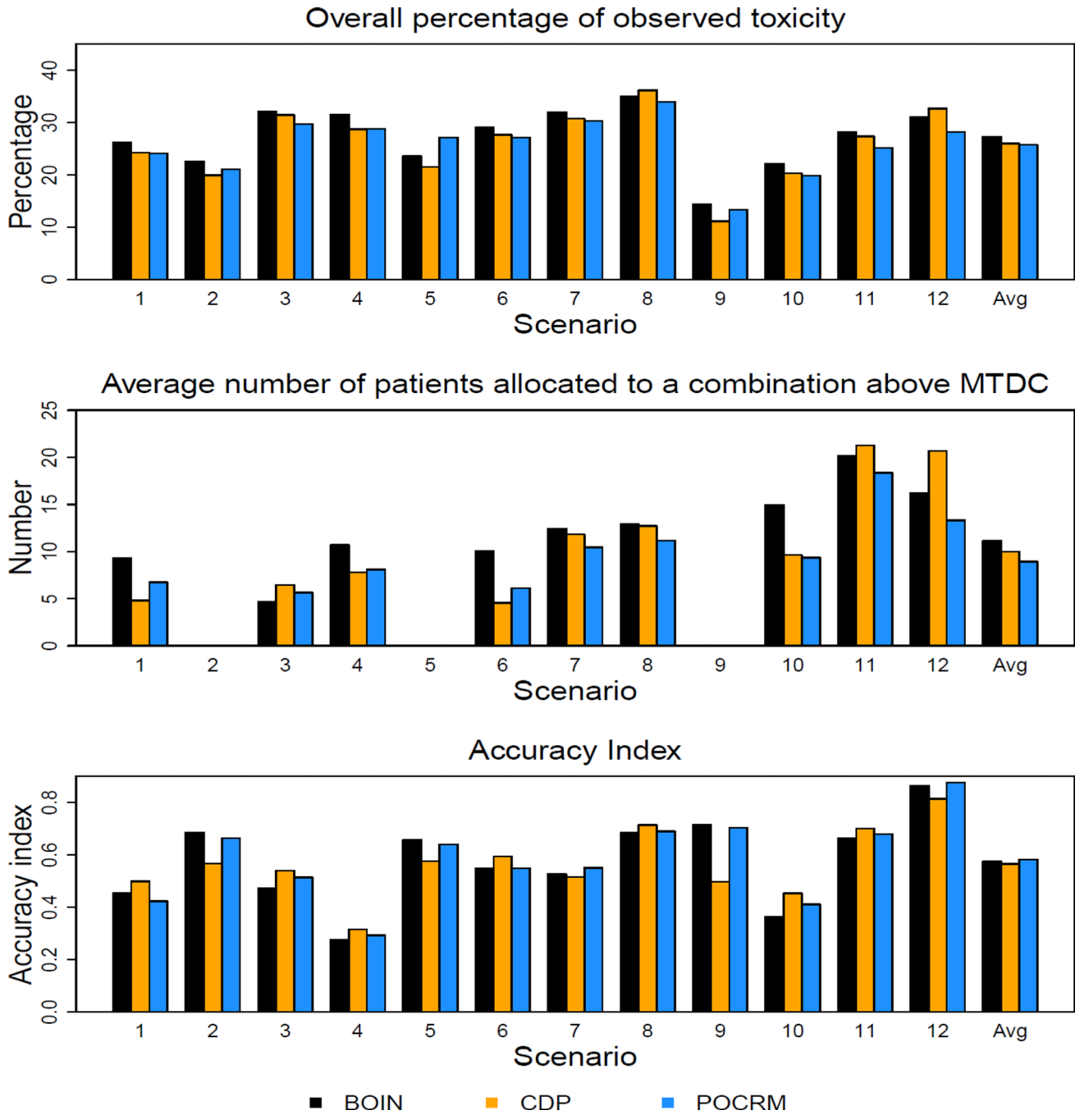

Figure 3.
Summary of the operating characteristics of the 3 methods in all scenarios.

Table 1

12 scenarios for a two-agent combination trial. “Acceptable” MTD combinations, defined by true DLT probabilities within 5% of the target rate φ, are in boldface. The total sample size is denoted by *n*.

		Agent A									
		1	**2**	**3**	**4**	**1**	**2**	**3**	**4**	***n***	**φ**
		Scenario 1				Scenario 2				27	0.30
Agent B	3	0.18	0.24	0.36		0.10	0.20	**0.30**			
	2	0.12	0.18	**0.30**		0.03	0.15	0.20			
	1	0.06	0.12	0.24		0.01	0.10	0.15			
		Scenario 3				Scenario 4					
	3	0.20	0.50	0.66		0.18	0.50	0.60			
	2	0.06	**0.33**	0.50		0.12	0.18	0.50			
	1	0.02	0.20	**0.33**		0.06	0.12	**0.33**			

										n	φ
		Scenario 5				Scenario 6				36	0.33
Agent B	3	0.20	0.21	0.23	**0.30**	0.25	**0.30**	**0.35**	0.40		
	2	0.07	0.10	0.12	0.20	0.10	0.15	0.20	**0.30**		
	1	0.01	0.02	0.05	0.07	0.02	0.10	0.15	0.20		
		Scenario 7				Scenario 8					
	3	**0.30**	0.40	0.50	0.60	0.40	0.68	0.80	0.99		
	2	0.05	0.15	0.25	**0.35**	0.20	**0.35**	0.50	0.70		
	1	0.01	0.10	0.15	0.20	0.01	0.10	0.20	**0.30**		

										n	φ
		Scenario 9				Scenario 10				36	0.20
Agent B	4	0.08	0.12	**0.20**		**0.24**	0.30	0.36			
	3	0.04	0.06	0.08		**0.16**	**0.22**	0.28			
	2	0.02	0.04	0.06		0.08	0.14	**0.20**			
	1	0.01	0.02	0.04		0.03	0.06	0.12			
		Scenario 11				Scenario 12					

	Agent A									
	1	**2**	**3**	**4**	**1**	**2**	**3**	**4**	***n***	**φ**
4	0.45	0.55	0.75		0.60	0.70	0.80			
3	0.30	0.35	0.60		0.50	0.65	0.70			
2	**0.20**	0.29	0.35		0.35	0.55	0.60			
1	0.12	**0.20**	0.30		**0.20**	0.40	0.50			

Table 2

Simulated sequential trial illustrating each approach using latent toxicity tolerance of 27 patients.

		CDP design			POCRM			BOIN desgin		
k	u_k	d_{ij}	π_{ij}	y_{ij}	d_{ij}	π_{ij}	y_{ij}	d_{ij}	π_{ij}	y_{ij}
1	0.978	d_{11}	0.02	0	d_{11}	0.02	0	d_{11}	0.02	0
2	0.595	d_{12}	0.20	0	d_{21}	0.06	0	d_{12}	0.20	0
3	0.340	d_{22}	0.33	0	d_{22}	0.33	0	d_{22}	0.33	0
4	0.055	d_{32}	0.50	1	d_{23}	0.50	1	d_{23}	0.50	1
5	0.043	d_{23}	0.50	1	d_{31}	0.20	1	d_{22}	0.33	1
6	0.869	d_{22}	0.33	0	d_{22}	0.33	0	d_{12}	0.20	0
7	0.478	d_{22}	0.33	0	d_{13}	0.33	0	d_{22}	0.33	0
8	0.649	d_{22}	0.33	0	d_{13}	0.33	0	d_{22}	0.33	0
9	0.873	d_{22}	0.33	0	d_{22}	0.33	0	d_{22}	0.33	0
10	0.539	d_{22}	0.33	0	d_{31}	0.20	0	d_{32}	0.50	0
11	0.738	d_{22}	0.33	0	d_{31}	0.20	0	d_{33}	0.66	0
12	0.129	d_{22}	0.33	1	d_{23}	0.50	1	d_{33}	0.66	1
13	0.495	d_{22}	0.33	0	d_{13}	0.33	0	d_{32}	0.50	1
14	0.690	d_{22}	0.33	0	d_{31}	0.20	0	d_{22}	0.33	0
15	0.787	d_{22}	0.33	0	d_{13}	0.33	0	d_{32}	0.50	0
16	0.285	d_{22}	0.33	1	d_{32}	0.50	1	d_{32}	0.50	1
17	0.847	d_{22}	0.33	0	d_{31}	0.20	0	d_{22}	0.33	0
18	0.905	d_{22}	0.33	0	d_{31}	0.20	0	d_{32}	0.50	0
19	0.963	d_{22}	0.33	0	d_{22}	0.33	0	d_{22}	0.33	0
20	0.779	d_{22}	0.33	0	d_{23}	0.50	0	d_{32}	0.50	0
21	0.223	d_{22}	0.33	1	d_{23}	0.50	1	d_{32}	0.50	1
22	0.248	d_{22}	0.33	1	d_{32}	0.50	0	d_{22}	0.33	1
23	0.862	d_{22}	0.33	0	d_{31}	0.20	0	d_{32}	0.50	0
24	0.534	d_{22}	0.33	0	d_{31}	0.20	0	d_{22}	0.33	0
25	0.286	d_{22}	0.33	1	d_{13}	0.33	1	d_{32}	0.50	1

		CDP design			POCRM			BOIN desgin		
k	u_k	d_{ij}	π_{ij}	y_{ij}	d_{ij}	π_{ij}	y_{ij}	d_{ij}	π_{ij}	y_{ij}
26	0.440	d_{22}	0.33	0	d_{13}	0.33	0	d_{22}	0.33	0
27	0.237	d_{22}	0.33	1	d_{13}	0.33	1	d_{32}	0.50	1
MTDC		d_{22}			d_{13}			d_{22}		